

# CyberKnife Stereotactic Body Radiation Therapy for Small Hepatocellular Carcinoma Patients with Decompensated Cirrhosis: protocol of study

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## Study protocol

**Keywords:** hepatocellular carcinoma, CyberKnife, stereotactic body radiation therapy, protocol, Child-Pugh B classification, Child-Pugh C classification.

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# Abstract

**Background:** There is a lack of data on the safety and the efficacy of stereotactic body radiotherapy in small hepatocellular carcinoma (HCC) patients with decompensated cirrhosis, and this study was conducted to explore on this field.

**Methods:** This study is designed as a mono-center study. The participants who were diagnosed with HCC and decompensated cirrhosis received Cyberknife stereotactic body radiation therapy (CK-SBRT). The primary outcome measures are to calculate overall survival rates (OS), progression-free survival rates (PFS) and local control rates (LC). The secondary outcome measures are to observe radiation-induced liver injury (RILD) rates after CK-SBRT. Moreover, adverse reactions are also observed.

**Discussion:** HCC patients' options of treatments were limited by poor liver function. CK-SBRT may offer an option for these patients. We propose to conduct a study to explore the efficacy and adverse reactions of CK-SBRT in treating HCC patients with decompensated cirrhosis ( $\leq 5$  cm). The trial protocol has been approved by the Institutional Review Board of 302 Hospital of PLA (People's Liberation Army). The Ethics number is 2020062D.

**Trail registration:** Clinical trails number: NCT04512833. Date of registration: August, 2020.  
<https://clinicaltrials.gov/show/NCT04512833>

## Background

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the fourth most common cause of cancer death[1]. Most HCC patients develop the disease with a history of chronic hepatitis, such as HBV, HCV infection or alcoholic liver diseases. Therefore, when we choose the treatment modality for patients, sufficient hepatic capacity[2] is a prerequisite in HCC patients and needs to be evaluated accurately before treatment. Liver transplantation (LT) is the optimal treatment for HCC patients with decompensated cirrhosis, but it is limited due to a lack of donors and strict criteria. Stereotactic body radiation therapy (SBRT) has been an effective treatment for HCC patients, and our previous study[3] showed SBRT may provide new options for the treatment of decompensated cirrhosis patients. However, because the sample volume of our previous study was small and it was a retrospective study, the result may be biased. Therefore, we propose to conduct a study to explore the efficacy and adverse reactions of SBRT in treating HCC patients with decompensated cirrhosis ( $\leq 5$  cm).

## Method And Design

### Study design

This is a mono-center study to explore the efficacy and adverse reaction in hepatocellular carcinoma patients with decompensated cirrhosis treated by CyberKnife SBRT (CK-SBRT).

## Primary outcome measures

1. Overall survival rate: OS is defined starting from the date of CK-SBRT to the date of final follow-up or demise of patients.
2. Progression-free survival: PFS is estimated starting from the date of CK-SBRT to the date of disease progression or demise of patients.
3. Local control rate: LC is calculated starting from the date of CK-SBRT to progress (the lesion diameter is more than original tumor in contrast-enhanced CT or contrast enhanced MRI).

## Secondary outcome measures

1. Radiation-induced liver injury (RILD) rate:

RILD included classic RILD and non-classic RILD. Classic RILD manifests as symptoms of fatigue, hepatomegaly, and anicteric ascites, etc. Additionally, the serum alkaline phosphatase level in these patients increases to more than twice the normal level, but the serum transaminase and bilirubin levels remain normal[4, 5]. Non-classic RILD usually occurs in patients with hepatitis and cirrhosis who are also with markedly elevated serum transaminases (>5 times the upper limit of normal) rather than elevated alkaline phosphatase or a decline in liver function (measured by a worsening of Child-Pugh score by 2 or more)[6].

RILD was evaluated every three days during CK-SBRT, every month for initial three months and every three months thereafter until 8 months after CK-SBRT.

2. To observe acute and late gastrointestinal toxicities following CK-SBRT[7].

## Inclusion Criteria

The hepatocellular carcinoma patients were diagnosed by image examination and laboratory test or pathology.

1. Primary HCC diagnosed by a surgeon and/or radiologist and oncologist;
2. The diameter of lesion  $\leq 5$ cm.
3. Age of 30-80 years old.
4. Unfeasible or refusing to undergo other treatments, such as resection, liver transplantation, etc.
5. Residual normal liver volume  $\geq 700$  cc;
6. With decompensated cirrhosis (Child-Pugh B or C classification);
7. Without portal vein tumor thrombus;
8. Eastern Cooperative Oncology Group (ECOG) score 0-1;
9. Distances between tumor and normal organs (esophagus, stomach, duodenum, bowel) are more than 5 mm;

10. Platelet count  $\geq 50 \times 10^9/L$ , white blood count  $\geq 1.5 \times 10^9/L$ ;
11. Patients infected with hepatitis B virus who are treated with adefovir or entecavir; patients infected with hepatitis C virus whose HCV DNA are negative.
12. Eastern cooperative oncology group (ECOG) PS score 0 or 1.
13. White blood count  $\geq 2 \times 10^9/L$ , platelets count  $\geq 60 \times 10^9/L$ .
14. A life expectancy of  $\geq 6$  months.
15. All participants understand the research subject and sign a written informed consent document.

### **Exclusion criteria**

1. With previous therapies, such as resection, liver transplantation, radiofrequency ablation, transarterial chemoembolization, etc.
2. The outline of lesion is not confirmed by image examination;
3. With hepatic or any other abdomen radiotherapy history;
4. With severe internal medicine diseases.
5. Pregnant women.
6. Participants who are in another trial while on study.

### **Radiation treatment planning**

All participants are implanted with 3 to 4 fiducial markers one week prior to CT localization. The distance between markers and lesion is less than 6cm. Before CT localization, a vacuum-bag is used for fixing the body, the arms and the legs (both arms are along the body, and both hands are on thighs). The acquired parameters of CT images are as follows: tilted angle of  $0^\circ$ ; slice thickness of 1 mm; voltage of 120 KV tube current of 400 mA; pixel size of  $512 \times 512$ . When the patients received simulation, they need hold their breath with smooth breathing. We adopt contrast-enhanced CT or contrast-enhanced MRI as an auxiliary image for fusion. The radiation oncologists contour gross tumor volume (GTV), planning target volume (PTV) and organs at risk. GTV is defined as the visible lesion based on image examination. PTV expands 3-5mm of GTV. The prescribed doses are 50-54Gy/5-6fx. All CK-SBRT plans are calculated by G4 CyberKnife MultiPlan (Version 4.0.2) and VSI CyberKnife MultiPlan (Version 4.6.1). The plans enclose PTV with 70–90% isodose line of maximum dose equated to the prescribed dose. Normal tissues tolerance doses comply with AAPM TG-101 report[8].

### **Evaluation and follow-up**

The CK-SBRT plan is delivered every day including on weekend. During CK-SBRT, the adverse reaction is evaluated every day. Physical examination and laboratory test are assessed every three days. In case patients present nausea and/or vomiting, they will receive corresponding drug treatment. The treatment schedule will be delayed when patients with uncontrollable vomiting. Moreover, when Child-Pugh score is two points higher than treatment before, the treatment will be also suspended, even be terminated. After

CK-SBRT, the patients are followed up, which includes physical examination, laboratory test and image examination. The follow up period defines as every month for initial three months, and every three months thereafter until 3 years. The trail is planned to begin on August 2020.

### **A quality assurance**

Two radiation oncologists and two physicists form the CyberKnife QA group.

### **Statistical analysis**

LC, OS and PFS are estimated using the Kaplan-Meier method. Uni-variable and multi-variable hazard ratios are calculated using the Cox proportion hazard model. P values<0.05 are considered statistically significant.

## **Discussion**

Most HCC patients were infected with hepatitis B or C virus in China, which resulted in these patients' mortality risks of not only tumors, but also complications from cirrhosis[9-11]. Therefore, the patients' options of treatments were limited by poor liver function. Although liver transplantation is a primary choice for decompensated cirrhosis-HCC patients who meet the Milan criteria, it is limited due to a lack of donors and strict criteria. SBRT has applied to HCC patients for several years and brought a satisfactory effect. However, there was a lack of data on treating small HCC patients with worse liver function with CK-SBRT, especially for the cases with Child-Pugh C classification.

Our previous retrospective study[3] showed that for the HCC patients with decompensated cirrhosis, the overall survival rates of 1-year, 2-year and 3-year were 84.4%, 61.8% and 46.0%, respectively. The local control rates of 1 year, 2 years and 3 years were 92.9%. The progression-free survival rates of the 1-year, 2-year and 3-year treatments were 73.8%, 44.6% and 33.4%, respectively. However, the retrospective study may be biased. We will conduct this prospective study to offer more credible evidence.

The main death causes of HCC patients are complications of cirrhosis. For patients who receive CK-SBRT, adverse reactions are not ignored. Child-Pugh score is a parameter to evaluate liver function, and it is also the clinical metric for diagnosed with RILD[12]. Moreover, gastrointestinal adverse reactions are also needed to evaluate.

## **Conclusion**

CK-SBRT for small HCC patients with decompensated cirrhosis is worth exploring by combining survival rates with adverse reactions.

## **Abbreviations**

CP: Child-Pugh; CT: computed tomography; CK-SBRT: CyberKnife stereotactic body radiation therapy; ECOG: Eastern cooperative oncology group; GTV: Gross target volume; LC: Local control; MRI: Magnetic resonance imaging; OS: Overall survival; PFS: Progression-free survival; PTV: Planning target volume; RILD: Radiation-induced liver disease.

## Declarations

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### Authors' contributions:

XD is the principle investigator and designed the protocol of this study. JS drafted the manuscript. WL participated in clinical protocol. DL and DZ participated in physical protocol. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board of 302 Hospital of PLA (People's Liberation Army). The Ethics number is 2020062D.

### Consent for publication

Not Applicable.

### Availability of data and materials

Materials and methods are available in the [clinicaltrials.gov](http://clinicaltrials.gov).

### Competing Interests

The authors declare no competing financial interests.

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