Protocol

Title: Phase 2 Study of Neoadjuvant Intensity-modulated Radiotherapy for Centrally located Hepatocellular Carcinoma

Principal investigators:

Prof. Jianxiong Wu, MD & Prof. Weihu Wang, MD

Jianxiong Wu, Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli Area, Chaoyang District, Beijing 100021, China

Weihu Wang, Key Laboratory of Carcinogenesis and Translational Research, Department of Radiation Oncology, Peking University Cancer Hospital & Institute, No. 52 Fucheng Road, Haidian District, Beijing, 100142, China.

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1. Definition of centrally located hepatocellular carcinoma

Centrally located hepatocellular carcinoma (HCC) is defined as a carcinoma adjoined hepatic portals, less than 1 cm from major vascular structures (including the main portal branches, the main trunks of the hepatic veins as well as the inferior vena cava) which are usually located in Couinaud segments I, IV, V, VIII, or at the junction of the central segments.[1] All centrally located HCCs should be confirmed through multidisciplinary team (MDT) discussion based on clinical or pathological diagnosis. Physicians participating in the MDT discussion should include senior doctors from department of radiology, radiation oncology, hepatobiliary surgery, and pathology.

2. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, and its incidence is on the rise.[2] For resectable HCC, the primary therapy is resection or liver transplant.[3] Considering a lack of healthy liver donator, liver resection has been considered the first choice for HCC at our center. However, for centrally located HCC, in which the lesions are attached or adjacent to major blood vessels, it's difficult to achieve complete resection. Mesohepatectomy and extended hemihepatectomy are currently the main surgical approaches,[4] yet the risk of incomplete resection or narrow surgical margins (<1 cm) is high, which may result in higher recurrence and decreased overall survival (OS).[5,6] Thus, it is necessary to built new treatment modalities to improve the prognosis of centrally located HCC.

Historically, radiotherapy has not played a significant role in the treatment of liver malignancies because of the low tolerance of the whole liver to radiation. With improvements in 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy, higher doses of radiation can be delivered to target lesions with low doses to the noninvolved liver; thus, experience in the use of radiation for the treatment of focal HCC has increased.[7]

Considering that HCC is a relatively radiation-sensitive tumor,[8] we suppose that by applying neoadjuvant radiotherapy before surgery could potentially improve treatment outcomes. The main

hypotheses of preoperative radiotherapy for centrally located HCC are: (1) to reduce tumor burden so that the difficulty of hepatic resection would be decreased; (2) to increase the distance between the tumors and major vascular vessels, and (3) to improve long-term results of surgery. However, the value of neoadjuvant IMRT for centrally located HCC has not been reported in prospective studies. In this study, we would like to explore the efficacy and safety of neoadjuvant IMRT followed by radical surgery in patients with centrally located HCC.

3. Endpoints

3.1 Primary endpoint

The primary endpoint is 5-year overall survival (OS). OS is calculated as the period from the date of the first radiation to death from any cause or the last follow-up, whichever came first.

3.2 Secondary endpoints

The secondary endpoints are tumor response to intensity-modulated radiotherapy (IMRT), 5-year disease-free survival (DFS), and treatment-related adverse events.

- Radiographic tumor response is evaluated according to the modified Response Evaluation Criteria in Solid Tumors guidelines. Major pathological response (MPR) is defined as the presence of 10% or fewer viable tumor cells in the primary tumor. The MPR includes complete pathological response (pCR), defined as no residual viable tumor cells in the resected liver cancer specimen.

- DFS is defined as the time interval between the date of surgery and that of the first detection of recurrence, death from any cause, or the last follow-up, whichever came first.

- Radiation-related toxicity will be evaluated weekly during RT and monthly after RT and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0.3). Acute toxicity is defined as events occurring during or within the first 3 months after treatment. Late toxicity will be assessed at least 3 months after treatment.

Operative complications will be graded according to the Clavien–Dindo classification system.[12]

4. Study design and sample size

4.1 Study design

This single-center, single-arm, prospective phase 2 study was approved by the Ethical Committee of the Cancer Institute and Hospital of the Chinese Academy of Medical Science.

4.2 Sample size

Based on our previous prospective randomized study, the estimated 5-year OS rate was 37.2% in patients with centrally located HCC who received narrow-margin hepatectomy alone. It was assumed that when treated with neoadjuvant IMRT followed by surgery, the 5-year OS rate of centrally located HCC would be close to that of Barcelona Clinic Liver Cancer Staging Classification (BCLC) 0–A disease, which was approximately 67% at our center. The enrolment period was 4 years. All patients were followed up for at least 2.5 years. The minimum sample size was 35 (two-sided $\alpha = 0.05$; $\beta = 0.10$; power 90%) estimated using the Power Analysis and Sample Size software (version 15.0.5, NCSS, Kaysville, Utah). The dropout rate was assumed to be 5%.

5. Patients

5.1 Inclusion criteria

- Age between 18 and 75 years;
- Eastern Cooperative Oncology Group performance status of 0–1;
- A pathological diagnosis of HCC through percutaneous liver biopsy or clinical diagnosis of HCC based on typical radiographic characteristics;
- At least one measurable lesion;
- Child–Pugh A liver function;

- Serum bilirubin ≤1.5 × the upper limit of normal (ULN), alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN;
- Normal creatinine and urea nitrogen;
- Baseline white blood cell count >4 × 10^9/L, haemoglobin >110 g/L, and platelet count >90 × 10^9/L;
- Patients should be aware of the purpose of the study and the operations required by the study and volunteer to participate in the study before signing the informed consent form.

5.2 Exclusion criteria

- Any previous antitumor treatment of HCC;
- Tumor edges that could not be defined;
- Severe cirrhosis complications;
- A history of other malignancies;
- Inability to reach required IMRT doses;
- pathological type other than HCC;
- tumor thrombosis in the main trunk of the portal vein or inferior vena cava;
- lymph node or remote metastasis.

6. Treatments

6.1 Intensity-modulated Radiotherapy

Liver-directed neoadjuvant IMRT will be delivered to all of the patients. Gross tumor volume (GTV), including primary tumor (GTVp) and tumor thrombosis (GTVt), will be delineated on planning CT scan, referring to pretreatment multiphasic contrast MRI through an image fusion approach. Clinical target volume (CTV) includes the GTVp plus a 0.5 cm margin in all directions and GTVt without a

158 margin. The planning target volume (PTV) includes a 0.5 cm margin in the anterior-posterior and
159 left-right directions and a 1.0 cm margin in the cranial-caudal direction around the CTV. The
160 prescription dose to 95% of the PTV is planned at 50–60 Gy in 25–30 fractions over 5–6 weeks,
161 depending on the dose constraints of organs at risk (OARs).

162 The dose constraints for the OARs are as follows: whole liver, mean dose ≤24 Gy; stomach and
163 duodenum, maximum dose ≤54 Gy, V50 ≤10 mL; colon, maximum dose ≤55 Gy, V52 ≤ 10 mL; spinal
164 cord planning risk volume, maximum dose ≤40 Gy; and left and right kidney, V20 ≤ 30%. To ensure
165 the repeatability of the position of the stomach and duodenum, all patients will be asked to fast 4 hours
166 before simulation or radiotherapy. Cone-beam CT will be performed in the first five fractions and then
167 once a week if the setup errors were <0.5 cm in the first five fractions.

168 **6.2 Surgery**

169 All patients will undergo hepatectomy using a selective and dynamic region-specific vascular occlusion
170 technique. The first step of the procedure is ligating and dividing the ligaments around the liver to
171 make it movable. Then, intraoperative ultrasonography will be used to define the tumor location and
172 display the vessels to be manipulated during resection. The extent of HCC resection is based on tumor
173 location, tumor size, relation of the tumor to the major vascular structures, and the degree of hepatic
174 cirrhosis.

175 A precise hepatic hilar dissection will be performed before resecting the tumor. Depending on the
176 transection area, the left or right portal vein and hepatic artery will be dissected in the hilum and
177 encircled with vessel tapes. When liver parenchymal dissection is performed on the right side of the
178 Cantlie line, the right hepatic artery and portal vein will be occluded intermittently and the left area is
179 free from clamping. When the dissection is performed on the left side of the Cantlie line, similar
180 occlusion will be applied on the left hepatic artery and portal vein and the right area will be free from
181 clamping. A dynamic procedure will be used for hepatic blood flow, such that outflow occlusion is
182 applied only when necessary and the IVC is occluded only in emergency situations. In cases where the
183 tumor is adherent to the major vascular structures, surgeons would carefully dissect and peel the lesions
184 away from the vascular surface using a Cavitron Ultrasonic Surgical Aspirator (CUSA) to avoid cutting

the major vessels and prevent postoperative liver failure. After tumor removal, the specimen will be examined to measure resection margin (the shortest distance from the edge of the tumor to the plane of liver transection).

7. Study procedures

7.1 Screening phase

Screening procedures will be completed within 14 days before treatment:

- Review of eligibility criteria;
- Signed informed consent;
- Review of medical history and demographics;
- Physical examinations;
- Vital signs;
- Pathological diagnosis of HCC through percutaneous liver biopsy;
- ECOG performance status;
- Laboratory tests including hematological, biochemical, endocrinologic, virological, and urine and feces examinations;
- Electrocardiogram/echocardiography;
- Abdominal-pelvic contrast-enhanced CT, abdominal magnetic resonance imaging (MRI) scan, thoracic and brain contrast-enhanced CT scan.

7.2 Treatment phase

Liver-directed neoadjuvant IMRT will be performed in all of the patients. The prescription dose to 95% of the PTV is planned at 50–60 Gy in 25–30 fractions over 5–6 weeks, mainly depending on the dose constraints of OARs. Adverse events should be monitored throughout the treatment period based on

patient report, investigator's observation, and each examination. Surgery will be performed 4–12 weeks post-IMRT. An MDT discussion is necessary before surgery for all patients. All operations would be carried out by the same surgical team to standardize operative quality and safety.

7.3 Post-treatment phase

All patients will be followed up every 3 months during the first 2 years after hepatectomy, then every 6 months during the next 3 years, and every year thereafter. Follow-up tests include alpha-fetoprotein (AFP), liver function, chest CT, and abdominal MRI and/or CT. The patients will be diagnosed with recurrence based on typical imaging findings and/or continually increased serum AFP levels. Patients will be followed until death or the end of study.

8. Efficacy

8.1 Radiographic tumor response to radiation

Radiographic tumor response to radiation is evaluated according to the modified Response Evaluation Criteria in Solid Tumors guidelines. Response will be assessed by the investigator before surgery.

- Complete response (CR) is defined as the disappearance of all viable (enhancement in the arterial phase) target lesions.
- Partial response (PR) is defined as a decrease of at least 30% in the sum of the diameters of the viable target lesions.
- Progressed disease (PD) is defined as the appearance of any new malignant lesions or an increase of 20% in the sum of the diameters of viable target lesions.
- Standard disease (SD) is defined as a tumor response between PR and PD.

8.2 Pathological response

Pathological results are reported by at least two pathologists with expertise in gastrointestinal pathology, according to protocols for examining of specimens from patients with hepatocellular carcinoma by the College of American Pathology.

- A negative margin is defined as the absence of tumor cells at the edge of the specimen.
- Major pathological response is defined as the presence of 10% or fewer viable tumor cells in the primary tumor. Major pathological response includes complete pathological response, which is defined as no residual viable tumor cells in the resected liver cancer specimen, as per current College of American Pathologists synoptic reporting.

9. Safety evaluation

9.1 Adverse event

All adverse symptom or sign, laboratory abnormality, or illnesses that occur from the time patients sign the informed consent until 12 months after surgery will be collected. The investigators should record any adverse event in detail, including adverse events and all associated symptoms description, occurrence time, severity, relationship with the treatment, duration, corresponding treatment, and final outcomes.

Adverse events include the following:

- Exacerbation of the existing medical condition/disease (including symptoms, signs, and laboratory tests) prior to entering the clinical trial;
- Any newly occurring adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
- Abnormal laboratory test values or results of clinical significance;

9.2 Serious adverse event

A serious adverse event is defined as a harmful adverse event that meets the following criteria:

- Results in death or life-threatening;
- Requires hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;

- Congenital anomaly/birth defect.

Important medical events that may require medical or surgical intervention, based upon medical judgment, to prevent one of the outcomes listed in the definition above may be considered a serious adverse experience. All serious adverse events occurring during the study must be reported to Institutional Review Board (IRB) within 24 hours. The initial and follow-up reports of a serious adverse event should be made.

9.3 Safety analysis

NCI-CTCAE 4.0.3 is used to evaluate the grade of adverse events, to observe any adverse events and serious adverse events that occurred in all patients during the clinical study period, including abnormal laboratory examination results, clinical manifestations and vital signs, to record their clinical manifestation characteristics, severity, occurrence time, duration, treatment method and outcomes, and to determine their relationship with the study drug.

10. Statistical analysis

10.1 Study population

All patients who finish per-protocol treatment will be included in the analysis.

10.2 Survival analysis

OS is calculated as the period from the date of the first radiation to death from any cause or the last follow-up, whichever came first.

DFS is defined as the time interval between the date of surgery and that of the first detection of recurrence, death from any cause, or the last follow-up, whichever came first.

10.3 Efficacy analysis

Radiographic tumor response is evaluated according to the modified Response Evaluation Criteria in Solid Tumors guidelines. Major pathological response (MPR) is defined as the presence of 10% or

fewer viable tumor cells in the primary tumor. The MPR includes complete pathological response (pCR), defined as no residual viable tumor cells in the resected liver cancer specimen. Objective response rate is defined as the proportion of patients with complete or partial response.

10.4 Safety analysis

All adverse events, deaths, clinical laboratory results and vital sign measurements will be included in the safety analysis.

10.5 Analysis methods

Continuous variables are expressed as median (range) or mean ± standard deviation (SD), as appropriate. Categorical variables are expressed as n (proportion). The baseline ALBI score is calculated as follows: ALBI score = (log10 bilirubin (μmol/L) × 0.66) + (albumin (g/L) × -0.085). ALBI scores ≤ -2.60 were graded as ALBI grade 1, -2.60 ~ -1.39 as ALBI grade 2 and > –1.39 as ALBI grade 3.

The Kaplan–Meier estimator is performed to calculate the median survival time and survival rates (DFS and OS). All statistical analyses are performed using SPSS Statistics (v24.0, IBM; Armonk, NY) and R (v4.1.0, R Foundation, Vienna, Austria).

11. Regulatory ethics compliance

11.1 Investigator responsibilities

The investigators are responsible for ensuring that the clinical study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guideline on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

11.2 Informed consent

Each patient must give written consent according to local requirements after the nature of the study has been fully explained. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements.

Before enrolment in the study, the investigator must explain to potential patients the aims, methods, reasonably anticipated benefits, and potential hazards of the study, any discomfort participation in the study may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the patient's care for the treatment. The patient will be given the opportunity to ask questions. After the explanation and before entry into the study, consent should be recorded by the patient's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the patient.

11.3 Compensation to research patients

A patient is entitled to compensation if injury or death is due to adverse effect of investigational treatment. Compensation must be consistent with the region's laws, regulations, and guidelines in which the study is conducted.

11.4 Institutional review board

Before the start of the study, the investigator will provide the institutional review board (IRB) with current and complete copies of the documents, which include, but are not limited to, final protocol, informed consent, investigators' curriculum vitae, information regarding funding, and other potential conflicts of interest. The study will be undertaken only after the IRB has given full approval of all the documents. All the protocol amendments must be submitted to the IRB for review and approval before implementation of the changes.

12. Administrative requirements

The investigators should perform the following aspects, which include, but are not limited to, protocol amendments, regulatory documentation, case report form completion, record retention, monitoring, and data quality control.

13. References

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