Randomized Controlled Trial of Transarterial Chemoembolization versus Proton Beam Radiotherapy for The Treatment of Hepatocellular Carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of death in patients with cirrhosis (1). It is the sixth most common neoplasm in the world, with more than a half million newly diagnosed cases annually (2,3). The etiology is unknown but it is reported mainly in patients with cirrhosis and patients with chronic hepatitis B infection (HBV) (2). Surgical resection and liver transplant are potential curative treatments for patients who meet Milan criteria (Appendix 1) or have $\leq$ 2cm solitary lesion (3,4).

CT scan or Magnetic Resonance Imaging (MRI) of the abdomen with/without alpha fetoprotein (AFP) is an important tool for early detection. HCC is diagnosed in patients with cirrhosis by one imaging technique showing a nodule larger than 2 cm with contrast uptake in the arterial phase and washout in venous or late phase, or two imaging techniques showing this radiological behavior for nodules of 1-2 cm in diameter (3). Cytohistological confirmation is required for patients who do not fulfill these criteria (3,4).

Multiple treatments are available. The best appropriate treatment is determined according to hepatic function reserve as represented by Child-Pugh-Turcotte class (Appendix 2), and tumor size and number. Patients who are surgically fit with Child class A and solitary lesion $\leq$ 2 cm are best treated by tumor resection. Liver transplantation is the best treatment for patients with unresectable lesion(s) that meet the Milan criteria (5) (Appendix 1).

Patients with tumor burden that exceeds Milan criteria are considered to receive one of the following locoregional treatments: transarterial chemoembolization (TACE), radiofrequency ablation (RFA), percutaneous ethanol injection and proton beam radiation (6). The goals of these treatments are to control tumor growth, to downstage tumor size to meet Milan criteria, and to improve survival. Patients who exceed the Milan criteria benefit from downstaging, so they can be qualified for liver transplant. Patients who meet Milan criteria benefit from tumor control to bridge them to liver transplantation (6,7). TACE is considered the most common locoregional treatment that is used to treat HCC. Proton beam radiotherapy has been used in treating HCC in a few centers across the globe. Phase I and II trials showed a satisfactory safety and efficacy results. Loma Linda University Medical Center is one of these pioneering centers that use proton beam as a treatment for HCC (ref). This is the first randomized trial in the medical field that will compare head-to-head the efficacy of TACE versus proton beam in treating HCC patients.

Transarterial Chemoembolization (TACE)

Multiple studies have shown contradictory results regarding the efficacy of TACE in improving survival compared to other treatments. The majority of these studies are retrospective studies or used a small sample of patients. These contradictory results have been attributed to the difference in endpoints of these studies and the multiple variables such as tumor size and liver function that usually impact and confound the outcome.

In one large study involving several institutions in Italy, chemoembolization did not improve survival compared to supportive care only. Patients who did not undergo TACE lived as long as patients who received TACE, even though the tumors were more likely to shrink in size in patients who were treated (8). Llovet et al. used TACE as a palliative treatment in a prospective, randomized controlled trial published in 2002 on 112 patients with intermediate stage HCC not felt to be candidates for other therapies. The patients randomized to TACE versus supportive care only. A significant increase in survival for the chemoembolization group was observed when compared with control (82% and 63%, 1-and 2-year survival, respectively, compared with 63% and 27%) (9). A study in Japan has shown that TACE can downstage liver cancer (10). Downstaging created the option for transplant in some of these patients. Otherwise, these patients had tumors that were not operable (eligible for operation) or not qualified for liver transplantation because of the initial large size of their tumors (10). More importantly, this study showed an improvement in survival in patients whose tumors became considerably smaller. In the U.S., trials are underway to see whether doing TACE before liver transplantation increases patient survival as compared to liver transplantation without TACE. Risk and common side effects of TACE include: bleeding, infection, worsening liver function, perforation of the common bile duct, veins or arteries, abdominal pain, nausea, vomiting, and fever.

It is reasonable to conclude that TACE is a procedure with acceptable side effects and a controversial small advantage in improving survival, especially in patients with small tumor and for patients waiting for liver transplantation. TACE can be used only in patients with relatively preserved liver function. The reason for this is that these procedures, as mentioned previously, can lead to liver failure in individuals with poor liver function.

Proton Beam Radiotherapy

Proton beam radiotherapy has physical properties that target the actual tumor mass and spare large portions of nearby normal tissues. Phase I and II trials demonstrated the safety of this treatment modality in decompensated patients with cirrhosis with HCC. Few trials in Southeast Asia and the United States demonstrated that proton beam could be an effective treatment that may improve survival and control tumor progression. Tokuuye et al. treated 79 patients who had HCC with proton beam radiotherapy (12). A median total dose of 72 Cobalt gray equivalents in 16 fractions was delivered. At 5 years, local tumor control and survival rates were 89% and 27% respectively. Kawashima et al. used the same fractionation scheme in 30 patients with HCC with an indocyanine scheme green retention rate at 15 minutes. Complete disappearance of tumors occurred in 24 patients (80%). The 2-year local regression-free rate in that study was 96%, and the 1-year and 3-year survival rates were 77% and 62% respectively (13). Eight patients developed hepatic insufficiency, which presented as ascites, elevated transaminase levels, and/or asterixis from 1 to 4 months after therapy (13). Bush et al., in a phase II trial where 34 patients with HCC completed 15 sessions of total 63 cobalt Gray equivalents, 75% local tumor control rate and overall survival rate of 55%. Six patients underwent liver transplantation 6 to 18 months after proton therapy. In 2 patients, there was no evidence of tumor pathology, demonstrating that proton therapy can eradicate HCC (14). A complete pathologic response was also observed by Merle et al (15). Risks involved in proton treatment include internal bleeding, radiation hepatitis (elevation in liver enzymes), worsening liver function (elevation in

bilirubin and INR) and perforation of the surrounding solid organ such as small bowel and stomach.

Proton bean radiotherapy has been associated with some of the best outcomes in HCC patients; however, further studies are needed to compare proton to other treatments.

In this randomized trial we wish to compare head-to-head the efficacy of proton beam radiotherapy versus TACE in treating patients with unresectable HCC.

Aim of The Study

This study aims to compare the efficacy of TACE versus proton beam radiotherapy in treating cirrhotic patients with HCC who meet San Francisco criteria.

Study Design

This is a randomized controlled trial targeting HCC patients at Loma Linda University Medical Center (LLUMC) and the Inland Empire area. The diagnosis of HCC will be determined according to one abdominal imaging (CT scan or MRI) performed within 3 months of randomization showing characteristics of HCC. These characteristics include including one or more nodules (2 cm) hypervascular or with contrast uptake in the arterial phase and washout in venous or late phase or two imaging techniques showing this radiological behavior for nodules of 1-2 cm in diameter. An independent radiologist at LLUMC will verify the diagnosis of HCC. Patients with cirrhosis with liver tumor that does not fulfill these criteria will need a cytopathological confirmation of HCC.

The diagnosis of cirrhosis will be determined clinically and radiologically in patients with chronic liver disease by the presence of thrombocytopenia with or without coagulopathy, and splenomegaly with irregular liver surface with or without liver biopsy showing bridging fibrosis and regenerative nodules.

Patients

Patients with cirrhosis and HCC who are not candidates for surgical resection will be targeted for enrollment. Patients will be recruited from the liver clinics at the Transplantation Institute and Faculty Medical Office. Patients from the Inland Empire area will be invited to participate as well. Community physicians will be informed of the study via mail and will be encouraged to refer their patients for participation (see attached letter No 1). Patients who are qualified to receive both TACE and proton treatments will be included. CT scan of the chest and bone scan within 6 months is required to exclude the presence of metastasis. Macrovascular invasion will be excluded using MRI or CT scan of the abdomen that will be performed within 3 months of enrollment.

Interventional radiologists and a radiation oncologist at LLUMC will evaluate the patient's case independently prior to randomization if the candidate is qualified to receive both treatments. Contraindications to receive TACE are: Child class C, hypovascular lesion and active sepsis. Contraindications to proton are: tense ascites requiring frequent paracentesis or proximity to a hollow organ such as the stomach or small intestine.

Inclusion Criteria

1. Patients are candidates to receive both proton beam and TACE
2. Patients with no evidence of metastasis or macrovascular invasion
3. Patients with tumor burden that meets San Francisco criteria (Appendix 1)

Exclusion Criteria

1. Patients who are candidates for surgical resection
2. Patients with lesion < 2 cm
3. Patients who have contraindication to receive either TACE or proton
4. Patients with serum alpha fetoprotein > 500
5. Patients with metastasis or macrovascular invasion
6. Patients treated previously for HCC by any locoregional treatment
7. Patients with prior liver transplant
8. Patients with Child class C
9. Patients with MELD score of > 25 (Appendix 5)
10. Patients with other comorbid diseases that may impact survival
11. Patients with ongoing alcohol intake
12. Patients with active sepsis
13. Patients with gastrointestinal bleeding within a week
14. Patients unwilling to sign informed consent form
15. Patients with history of noncompliance

Methods

Patients meeting the inclusion and exclusion criteria will be randomized (1:1) by an individual who is not a study investigator using the random number method. Subjects will be registered and randomized by contacting Roger Grove (ext 44032, rgrove@dominion.llumc.edu). Subjects will be randomly assigned to one of two groups:

Group 1: patients will receive one or more sessions of TACE (Appendix 3).
Group 2: patients will receive 15 consecutive sessions of proton beam radiation (Appendix 4).

Primary Endpoint

The primary end point of the study is to measure ***overall survival*** defined as the time from randomization until death. In order to control for non-cancer death related factors that may compound the survival rate, a competing risk analysis rather than Kaplan-Meier will be used to compare the survival between the two groups.

Secondary Endpoints

1. ***Time to progression***.
   This endpoint reflects the time between randomization and radiological progression as defined by the amendments of the Response Evaluation Criteria in Solid Tumors (RECIST) (16).
   - **A. Complete Response** is defined as the disappearance of any intratumoral arterial enhancement in all target lesions.

B. Partial Response is at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.

C. Progressive Disease is an increase of at least 20% in the sum diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started. Or the appearance of one or more new lesions.

A newly detected hepatic nodule will be classified as HCC- and will be declared as evidence of progression- when its longest diameter is at least 10 mm and the nodule shows the typical vascular pattern of HCC on dynamic imaging. Lesions larger than 10 mm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth in subsequent scans.

D. Stable Disease is any cases that do not qualify for either partial response or progression disease.

MRI or CT-scan of the abdomen will be used to determine the targeted lesions for treatment and its baseline measurements. Target lesions will be measured using a single linear summation of the large diameter of the tumor. The average of two measurements by two independent radiologists will be considered for baseline and follow up assessment.

2. ***Downstaging***

This endpoint will be applied to subjects in whom their tumor burden exceed Milan criteria but meet San Francisco criteria (Appendix 1). The direct measurement of the longest diameter of the viable tumor will be compared pre-and-post treatment. Usually, patients with San Francisco criteria will not be qualified for MELD score exception upgrade on UNOS waiting list unless their tumor burden is down-staged to Milan criteria using one of the locoregional treatments. Measuring this endpoint will help in comparing the efficacy of proton versus TACE in downstaging tumor in patients who meet San Francisco criteria.

Follow Up

Patients with HCC usually require either CT scan or MRI of the abdomen to be performed routinely every three months to monitor tumor progression. Patients undergoing any locoregional treatment usually require a CT scan or MRI of the abdomen to be performed 4-6 weeks after the treatment and then every three months. Follow up imaging will be the same modality used at baseline (CT or MRI). Patients are usually evaluated in the liver clinic 4 weeks after treatment and then every three months. Subjects receiving proton therapy will also be followed in radiation medicine clinic by their treating radiation oncologist every 3 months for the first year then every 6 months. Participants in this study will be followed according to this protocol. No radiological testing will be ordered for the purpose of the study as the recommended assessments follow the current standard of care. Patients will be followed for research purposes until death or transplant, or until which time the study investigators determine the study is complete.

Data and Statistics

Data will be evaluated according to intent to treat analysis. One- and two-year survival will be compared between two groups using competing risk analysis. This analysis will provide an estimate of HCC-related death in the presence of alternate yet plausible outcomes such as death from liver failure or liver transplantation. It is also a better technique in illustrating differential rates of competing outcomes in patients waiting for liver transplantation. This analysis will limit the effects of confounding factors such as death from liver disease. Secondary end points will be compared using Student's *t*-test for quantitative data and chi-squared (χ^2) test or Fisher's exact test for qualitative data. Demographics and standard of care laboratory data between groups will be compared. Logistic regression will be used to determine independent factors affecting survival.

The study is designed and powered to show at least 15% difference in mortality between two groups. Group size is calculated by assuming that patients in the TACE group will have at least 15% improvement in 2-year survival compared to the proton beam group. With 110 patients in each group the study has 80% power to detect a 15% difference in the mortality between two groups. We are not expecting any significant drop out because both treatments are considered crucial for patients' survival; and also based on our experience in treating these patients for many years at LLUMC. The level of significance is 0.05 (2-sided) for all statistical tests. The Statistical Package for the Social Sciences (SPSS 16.0 for window; SPSS, Inc., Chicago, Illinois) was used for all statistical analyses.

We will conduct an interim analysis after randomizing 40 patients in each group. This analysis will determine if there is any early significant difference in survival between two groups. The interim report will be submitted to the Institutional Review Board.

Data will be collected anonymously and subjects will be identified using a numerical code. The code will be stored at the PI and Co-PI office. The study database will be maintained and stored in the department of radiation medicine. Only PI, CO-PI and research coordinators will have access to the data.

Budget

This study will utilize all the routine radiological and biochemical tests that are part of the medical care of these patients. There will be no specific blood or radiological testing that will be performed or ordered only for the purpose of the study. TACE is considered a standard of care for HCC patients and all insurance companies including MediCal and Medicare pay for this treatment. Many insurers will cover proton treatment for HCC This study does not incur any extra expenses that require additional funding.

Appendix 1

Tumor Classification

Milan Criteria

Solitary lesion ≤ 5 cm or ≤ 3 lesions, none of > 3 cm

San Francisco Criteria

Solitary lesion ≤ 6.5 cm or ≤ 3 lesions none > 4.5 cm and total tumor diameter ≤ 8 cm

Appendix 2

Child-Pugh-Turcotte Score and Class

1. Bilirubin (mg/dl)

<2 OR < 4 for patients with primary biliary cirrhosis (1 point)
2-3 OR 4-10 for patients with primary biliary cirrhosis (2 points)
>3 OR > 10 for patients with primary biliary cirrhosis (3 points)

2. Albumin (g/dl)

>3.5 (1 point)
3.5-2.8 (2 points)
<2.8 (3 points)

3. PT prolongation (INR)

<4 seconds (<1.7) (1 point)
4-6 seconds (1.7-2.3) (2 points)
>6 seconds (>2.3) (3 points)

4. Ascites

Absent	(1 point)
Slight	(2 points)
Moderate	(3 points)

5. Encephalopathy

Absent	(1 point)
Mild (I-II)	(2 points)
Severe (III-IV)	(3 points)

Class Interpretation:
Class A: 5-6
Class B: 7-9
Class C: 10-15

Stages of Hepatic Encephalopathy

Stage 1: Euphoria or depression, mild confusion, slurred speed, disordered sleep

Stage 2: Lethargy, moderate confusion

Stage 3: Marked confusion, incoherent speech, sleeping but arousable

Stage 4: Coma, initially responsive to noxious stimuli, but later unresponsive

Appendix 3

Transarterial Chemoembolization Treatment Protocol

This procedure is done with the help of fluoroscopy (type of x-ray) imaging. A catheter (long, narrow tube) is inserted into the femoral artery in the groin and is threaded into the aorta (the main artery of the body). From the aorta, the catheter is advanced into the hepatic artery. Once the branches of the hepatic artery that feed the liver cancer are identified, the chemotherapy is infused and the arterial branch that supply the tumor is embolized using Gel Foam or Lipoid. The whole procedure takes one to two hours, and then the catheter is removed.

The patient generally stays in the hospital overnight for observation. A sandbag is placed over the groin to compress the area where the catheter was inserted into the femoral artery. The nurses periodically check for signs of bleeding from the femoral artery puncture. They also check for the pulse in the foot on the side of the catheter insertion to be sure that the femoral artery is not blocked as a result of the procedure. (Blockage would be signaled by the absence of a pulse).

Generally, the liver tests increase (get worse) during the two to three days after the procedure. This worsening of the liver tests is actually due to death of the tumor (and some non-tumor) cells. The patient may experience some post-procedure abdominal pain and low-grade fever. However, severe abdominal pain and vomiting suggest that a more serious complication has developed. Imaging studies of the liver are repeated in six to 12 weeks to assess the size of the tumor in response to the treatment.

Appendix 4

Proton Beam Radiotherapy Treatment Protocol

Procedures for HCC subjects randomized to proton therapy:

Immobilization and Treatment planning CT Scan

Immobilization

All patients will be fit with a full-body immobilization device to limit day-to-day set up variations and to reduce interfraction alignment errors. This will be accomplished by placing the subject supine within a half cylinder PVC shell then adding two-part foam to create a rigid mold. This device will be used for all subsequent patient treatments to provide reproducible patient alignment.

Treatment Planning CT

Subjects will undergo CT simulation in the department of radiation medicine while lying in their immobilization device. All images will be acquired with IV contrast enhancement during the arterial phase. Image acquisition will take place only when the subject is actively breath holding at end-expiration. Imaging will cover the entire abdomen from above the right hemi-diaphragm through the 5^{th} lumbar vertebral body. Recommended scan spacing is 3x2 mm.

Target Volume and Normal Tissue Definition

Gross Tumor Volume (GTV) – The GTV will be contoured on each CT image and will include all areas of known disease as identified on the planning images and/or seen on diagnostic CT or MRI.

Clinical Target Volume (CTV) – A CTV will be created to extend 1cm beyond the GTV in all dimensions. This volume may be edited if it extends beyond the liver parenchyma. The CTV will be edited so that it will not include organs known not to be involved by the tumor (i.e. abdominal wall, kidney, bowel).

Normal Tissue Definition – All organs and normal tissue regions not targeted for treatment will be contoured for dose-volume-histogram calculations. The entire liver will be contoured in all cases taking care to omit the gallbladder and portal vessels. Bowel that lies near the target volume and the right kidney should also be routinely contoured.

3-Dimensional Treatment Planning, Dose Definitions, and Normal Tissue Constraints

Treatment Planning

A computerized 3-Dimensional treatment plan will be generated utilizing the Odyssey treatment planning system at LLUMC. The target region will be the CTV with the additional margin to account for daily setup variations and energy specific beam penumbra. Beam angles typically used include right lateral, posterior, and posterior oblique beams.
Anterior beams should be used only in selected patients, as these beams will not be within the immobilization device. Beam weighting and custom editing of beams shaping devices may be utilized to optimize the final dose distribution. All computer simulated treatment plans require approval by the treating physician prior to patient treatment.

Proton Dose to CTV

All doses will be prescribed to a point at or near the center of the CTV target region. The total dose delivered will be 70.2 CGE given in 15 fractions over a three-week course. The uniformity of dose across the target region will not vary by more than 10% of the prescribed dose. At least two beams will be treated each day to reduce the dose at the beam entry site.

Normal Tissue Constrains

Liver – Dose constraints for the liver will be based on dose-volume histogram (DVH) analysis from the Odessey treatment planning system. The dose that falls within the GTV will be excluded from the DVH calculation; however dose given to liver tissues outside the GTV but within the CTV will be included. The treatment-planning goal will be to limit the volume of liver receiving more then 30 Gy to 33% or less. If this constraint cannot be met, the additional CTV margin may be changed from 1cm to 5mm. This will be considered a minor protocol violation and will be noted in the patient record for future analysis.

Bowel – If any portion of the bowel falls within the 90% isodose volume field reductions will be required. Full margins will used for the first seven fractions of treatment. The following 8 fractions will be delivered with modifications that limit dose to the bowel surface to 50% of the remaining dose. In these cases the minimum dose to the CTV and GTV will be recorded for future analysis.

Kidney – At least 50% of the right kidney will receive no more then 20 Gy. This constrain assumes complete sparing of the left kidney.

Treatment Delivery

Patients will be treated at the proton treatment center at LLUMC. For each treatment, the patient will be placed in their custom-made immobilization device. Orthogonal diagnostic x-ray images will be taken of the treatment area and registered with the digitally reconstructed radiographs created from the planning CT scan. All misalignments greater then 1mm from the established treatment isocenter will be corrected. All beam shaping devices will be verified each day both by the therapy personnel and with the record and verify system. The initial treatment setup and subsequent new treatment fields will be verified by a physician prior to that day's treatment. At least two fields will be treated daily. Treatment will only be given during an active breath hold at end-expiration to minimize respiratory motion of the liver. Fifteen fractions over 3 weeks will be delivered. All patients will be

clinically evaluated, weekly, by the treatment radiation oncologist to assess treatment tolerance and to monitor for acute toxicities.

Appendix 5

Model For End-Stage Liver Disease (MELD) Score

The MELD score is calculated using the following equation:

3.8 x log (e) (bilirubin mg/dL) + 11.2 x log (e) (INR) + 9.6 log (e) (creatinine mg/dL)

The equation seeks to calculate a patient's likelihood of dying within three months from their liver disease. It is used by UNOS to allocate organ for liver transplant for patient on the list. Scores range from 6-40. A score of six indicates the least ill patient and a score of forty indicates the sickest patient. The priority for organ allocation is given for patients with the highest MELD score.

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