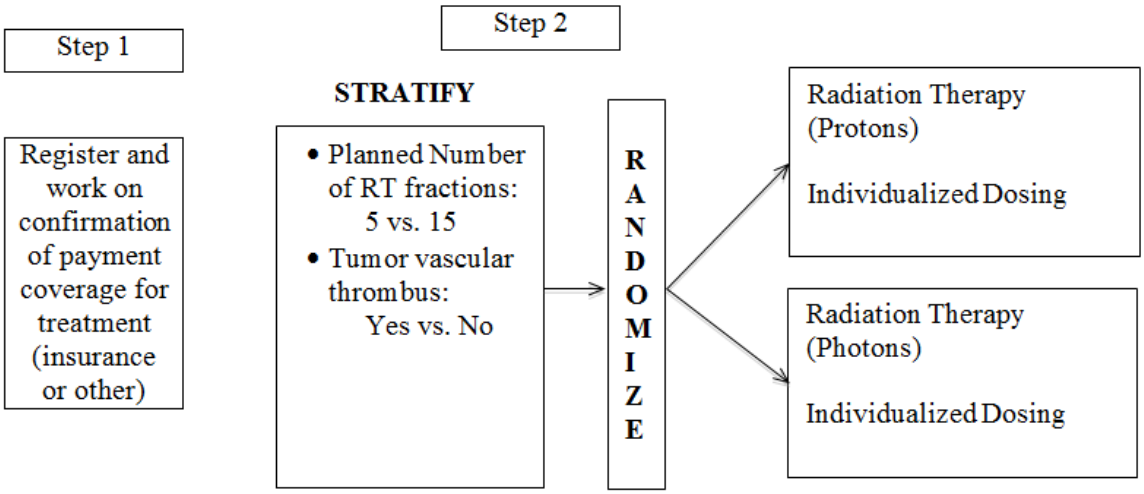
Step 1
Register and work on confirmation of payment coverage for treatment (insurance or other)
Step 2
STRATIFY
• Planned Number of RT fractions: 5 vs. 15
• Tumor vascular thrombus: Yes vs. No
RANDOMIZE
Radiation Therapy (Protons)
Individualized Dosing
Radiation Therapy (Photons)
Individualized Dosing

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active must be willing and able to use medically acceptable forms of contraception during the radiation therapy.

3.1.3 Submission of blood and tumor tissue (if available) is requested for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See details of submissions in Section 10.)

3.2 Eligibility Criteria (30-July-2018)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to STEP ONE Registration

3.2.1 Pathologically (histologically or cytologically) or radiographically-proven (based on the American Association for the Study of Liver Diseases [AALSD] criteria) unresectable or locally recurrent hepatocellular cancer prior to registration;

3.2.2 Appropriate stage for study entry based on the following diagnostic workup:

- All patients must have CT scan chest/abdomen/pelvis with multiphasic liver CT scan prior to registration. If CT contrast is contraindicated, CT chest without contrast and MRI of abdomen is permitted.
- Participants must have measurable disease at study entry, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >2 cm with conventional techniques or as >1 cm with spiral CT scan.
- Patient must have 3 or fewer single or multinodular tumors. For patients with a single lesion, lesion must be 15 cm or less in greatest dimension. For patients with two lesions, no lesion may be greater than 10 cm in greatest dimension. For patients with three lesions, no lesion may be greater than 6 cm in greatest dimension. Portal vein involvement or thrombosis combined with a single lesion that is ≥ 1 cm and ≤ 15 cm in greatest dimension is allowed.

3.2.3 Age ≥ 18

3.2.4 Zubrod Performance Status 0-1 within 30 days prior to registration;

3.2.5 Negative urine or serum pregnancy test for women of childbearing potential within 7 days prior to study entry;

3.2.6 Adequate hematologic function prior to registration defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3;
- Platelets ≥ 50,000 cells/mm^3;
- Hemoglobin ≥ 9.0 g/dl. (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable.)

3.2.7 Adequate renal/hepatic function prior to registration defined as follows:

- Total bilirubin < 4 x institutional upper limit of normal (ULN);
- Transaminases (AST and ALT) < 6 x institutional ULN;
- Albumin ≥ 2.5 g/dl;
- Creatinine < 2 mg/dl.

3.2.8 Prior chemotherapy, targeted biological therapy (e.g. sorafenib), surgery, transarterial chemoembolization (TACE), ablation for present disease is acceptable.

3.2.9 Must have Child-Turcotte-Pugh (CTP) A or B7

3.2.10 The patient or a legally authorized representative must provide study-specific informed consent prior to study registration.

3.3 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

Prior to STEP ONE Registration

3.3.1 Definitive clinical or radiologic documentation of extrahepatic tumor, defined as extrahepatic metastases or malignant nodes (that enhance with typical features of HCC) > 3.0 cm, in sum of maximal diameters (e.g. presence of one 3.4 cm metastatic lymph node or two 2 cm lung lesions). Note that benign non-enhancing periportal lymphadenopathy is not unusual in the presence of hepatitis and is permitted, even if the sum of enlarged nodes is > 2.0 cm.

3.3.2 Uncontrolled prior invasive malignancy, excluding the current diagnosis;

3.3.3 Systemic chemotherapy for the study cancer < 2 weeks prior to registration;

3.3.4 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic;

3.3.5 HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter prior to registration. Note also that HIV testing is not required for eligibility for this protocol. This exclusion criterion is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.3.6 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields (to include Y90).

3.3.7 Prior liver transplant.

Prior to STEP TWO Randomization

3.3.8 Unable to obtain confirmation of payment coverage (insurance or other) for either possible treatment.