Title: **Phase II Study of Proton Beam Irradiation for the Treatment of Unresectable Hepatocellular Cancer and Cholangiocarcinoma**

PROTOCOL: **09-131**

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Title: Phase II Study of Proton Beam Irradiation for the Treatment of Unresectable Hepatocellular Cancer and Cholangiocarcinoma

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Coordinating Center:

MGH will be the coordinating center for this multi-center study. All patients from all participating sites will be registered with QACT before beginning treatment. Data will be coordinated by the MGH Biostatistics Center.

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Funding:
Thomas F. DeLaney, M.D., Principal Investigator; For correlative studies (at MGH only): Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center

Agent(s): *–Proton Beam Irradiation (no IND)*

Protocol Summary

Principal/Overall Investigator

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Protocol Title

A Phase II Study of Proton Beam Irradiation of Unresectable Primary Liver Tumors

Funding

For correlative studies (at MGH only): Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center

Specific Objective

To determine the local control of proton beam radiation for unresectable primary hepatoma (hepatocellular carcinoma or intrahepatic cholangiocarcinoma)

Background and Significance

The efficacy of the current treatment (chemotherapy, arterial embolization) of unresectable hepatocellular cancer, and intrahepatic cholangiocarcinoma is poor. A recent study from Japan demonstrated impressive local control and survival rates for 122 unresectable hepatocellular cancer patients treated with proton beam irradiation.

Protons are a charged form of radiation. Their biology is similar to x-rays, resulting in similar cell killing effects. The advantage of protons lies in their physical dose distribution. Because of the defined range of protons (i.e. the Bragg peak), dose distributions can be designed that conform more closely to the tumor volume. This results in a much greater ability to reduce radiation dose to non-target normal tissues, especially liver, and allows greater dose to be delivered to the tumor.

With protons, high dose irradiation of hepatic lesions is feasible because of the marked reduction in normal hepatic irradiation.

Recruitment

Patients will be recruited from the surgical, medical and radiation oncology practices at Massachusetts General Hospital, Brigham and Women's Hospital, Dana Farber Cancer Institute, MD Anderson Cancer Center and University of Pennsylvania. Patients will not be paid for participating in this study. We expect to recruit approximately 90 patients over a 2-year period. Because DFCI/BWH does not have a proton center, patients from these institutions will be referred to MGH.

Research Design and Methods

This is a phase II research protocol designed to determine the local control with proton beam radiation therapy in the treatment of hepatocellular cancer and intrahepatic cholangiocarcinoma.

Risks and Discomforts

Proton Beam Radiation Therapy

Very likely*:* These symptoms usually recover in the first few weeks following completion of radiation therapy

• Irritation, redness and discoloration of the skin in the radiation area.

• Fatigue (tiredness)

Likely

- Decreased blood counts
- Low platelet count
- Elevated LFTs
- Abdominal pain or cramps
- Nausea

Less likely

- Diarrhea
- Decreased/ loss of appetite
- Vomiting
- Slow wound healing
- Weight loss
- Indigestion
- Gastritis
- Radiation Esophagitis
- Rib microfracture

Rare

- Damage to the liver which could result in inflammation and scarring of the liver. This could lead to jaundice and possibly cirrhosis. Efforts to prevent excessive liver irradiation will be made to minimize the chance of these side effects
- While radiation can cause mucosal ulceration, other tissues may be damaged which may require surgery and may be life-threatening.

- Stomach and bowel are protected well from excessive dose of radiation. However, overdosing the stomach or bowel can lead to ulceration or perforation.
- Pain, inflammation or scarring of your kidneys, stomach and bowel. These organs are protected well from excessive dose of radiation. Therefore, it is unlikely that patients will experience symptoms of injury to these organs
- Nerve damage
- Development of a new cancer resulting from treatment may happen many years after completing treatment
- Spinal cord injury

MRIs use powerful magnets to make images. Therefore, persons with metal implants, such as surgical clips or pacemakers should not have an MRI. However, there are no known health risks associated with this exposure. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at the request of the patient.

CT Scans: The radiation associated with these diagnostic radioactive drug and diagnostic x-ray studies will not adversely affect the treatment of the patient's disease.

Reproductive risks: Because the treatment in this study can affect an unborn baby, female patients should not become pregnant while on this study. Female patients should also not nurse a baby while on this study.

Potential benefits

The potential benefits of this treatment include shrinkage of the tumor, greater control of tumor growth, and possibly longer life.

SCHEMA

- 1. **REGISTER**.

- 2. **TREATMENT:** Proton Beam Irradiation in 15 fractions. Acute toxicity evaluation weekly during study treatment, and at 3 month follow up.

- 3. **FOLLOW-UP:** Evaluation for Tumor Response using RECIST Criteria. Evaluation for acute and late toxicity per CTCAE v. 3.0

Eligibility Criteria:

1. Patients must have a biopsy proven unresectable or locally recurrent cholangiocarcinoma, or a diagnosis of an unresectable or locally recurrent hepatocellular cancer using either pathology of the liver tumor or radiologic imaging and an elevated AFP. For patients with a single tumor, lesion may be up to 12 cm in

size. For patients with two lesions, no lesion may be greater than 10 cm in size. For patients with three lesions, no lesion may be greater than 6cm in size.

2. Patients may have single or multinodular tumors (up to 3).
3. No prior liver directed radiation therapy.
4. Patients are not candidates for surgery on the basis of tumor extent or medical condition.
5. Patients must be 18 years or age older.
6. Patients must have ECOG PS 0-2.
7. If patient has underlying cirrhosis, only Child's classification Group A or Group B patients should be included in this study.
8. Patient must have adequate renal function; serum creatinine </=2 mg / dl.
9. Expected survival must be greater than three months.
10. Signed Informed Consent.

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1. OBJECTIVES

1.1 Study Design

This is a phase II research protocol designed to determine the local control with proton beam radiation therapy in the treatment of unresectable primary hepatocellular carcinoma or intrahepatic cholangiocarcinoma.

1.2 Primary Objectives

To demonstrate 2 yr LC of >80% with proton beam irradiation for unresectable hepatocellular cancer. This will be benchmarked against 2 yr LC of ~55% for tumors > 3cm in size with radiofrequency ablation.

1.3 Secondary Objectives

1.3.1 To determine safety and tolerance of this treatment program.

1.3.2 To evaluate tumor response, patterns of failure, and survival in patients with hepatocellular cancer undergoing proton beam irradiation.

1.3.3 To evaluate 5 yr overall survival and local control in patients with hepatocellular cancer undergoing proton beam irradiation.

1.3.4 To describe the tumor response, patterns of failure, local control and 5 year overall survival in patients with cholangiocarcinoma undergoing proton beam irradiation.

2. BACKGROUND

2.1 Proton Beam Therapy

There have been unprecedented efforts in radiation oncology to develop and use sophisticated, conformal photon techniques in order to improve the outcome for cancer patients. The aim of these new techniques is to concentrate the radiation dose distribution more completely on the disease target, thereby sparing critical normal tissues and increasing the target dose. Toward this end, many advances have been made and examples of new developments include Tomotherapy and intensity modulated photon therapy. At the same time, heavy, charged-particle programs, particularly those for proton therapy, have been developed. Proton therapy dose distributions are superior to those of photon therapy and this provides the potential to further improve clinical outcomes. Several institutions have committed to build dedicated proton therapy centers such as the Francis H. Burr Proton Therapy Center (FHBPTC) at the Massachusetts General Hospital (MGH), the MD Anderson Proton Treatment Center, the Loma Linda University Medical Center proton therapy facility, and others. Several more proton therapy centers are in the final planning stage.

2.1.1 The Advantages of Protons for Delivery of Conformal Therapy

Characteristics of Proton Beams

The basis for the advantages of proton beams lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially whereas protons have a finite range dependent upon the initial proton energy. Therefore, the depth dose characteristics of the two beams are qualitatively different (see Figure O-1). Protons lose their energy in tissue mostly by coulombic interactions with electrons in the constituent atoms; however, a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant as the proton traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance (approximately 0.7 cm in width at 80% of the maximum dose) and the proton comes to rest, resulting in a distinctive sharp rise in the tissue absorbed dose (energy absorbed per unit mass) - known as the Bragg peak (see the curve labeled "unmodulated proton beam" in Figure O-1). In physical terms, the magnitude of the transfer of energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The low dose region between the entrance and the Bragg peak is called the plateau of the dose distribution and the dose there is 30-40 percent of the maximum dose.

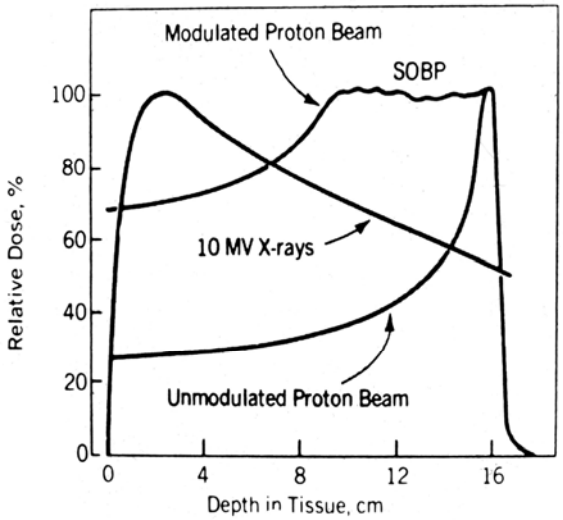

Figure O-1. Proton (Bragg peak and modulated Peak) and 10 MV depth dose curves.

The Bragg peak is too narrow in extent to irradiate any but the smallest of targets, ablation of the pituitary gland for example. For the irradiation of larger targets/tumors the beam energy is modulated -

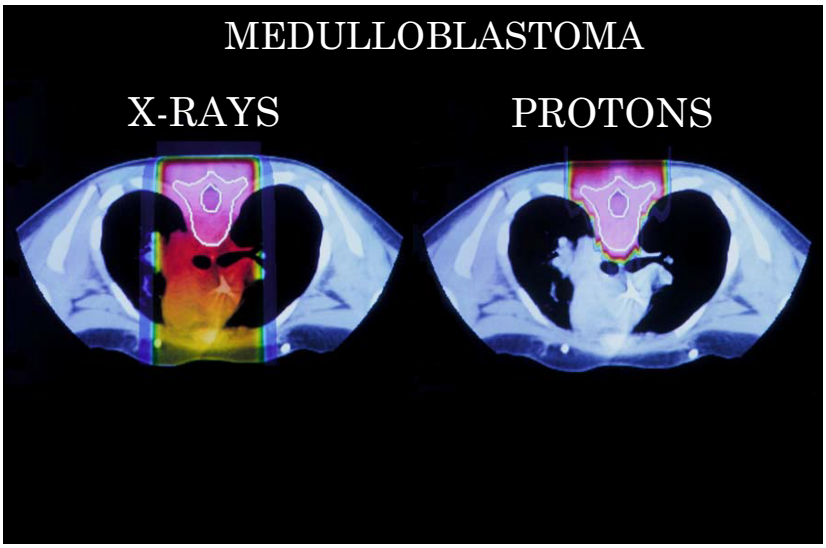

Figure O-2. Posterior, single-beam treatment of the spinal axis.

several beams of closely spaced energies (ranges) are superimposed to create a region of uniform dose over the depth of the target. These extended regions of uniform dose are called "spread-out Bragg peaks" (SOBP). This is shown in Figure O-1 as the “modulated proton beam”. For comparison, Figure O -1 also shows the depth-dose curve for a 10 MV x-ray beam, an x-ray energy commonly used to treat deep seated tumors.

Note that the x-ray beam dose rises to a maximum value at relatively shallow depths, then falls off exponentially to lower doses at the treatment depth. A clinical comparison of single-beam proton and photon beams is shown in Figure O-2 where a single posterior beam is used for the treatment of the spinal axis in the treatment of medulloblastoma. Note that, for the photon treatment, the heart, mediastinum, esophagus, lung and spinal cord are irradiated by the treatment beam whereas for the proton treatment, the beam stops abruptly distal to the target volume and there is no irradiation of the tissues and organs distal to the target volume.
In the usual clinical situation, more than one radiation beam is used in both x-ray and proton treatments.

However, the advantage shown for protons using single beams is present for each and every beam used. Therefore, one cannot overcome the physical disadvantage of x-rays by the use of multiple beams or complex beam arrangements. In modern proton therapy facilities, which have isocentric gantries and sophisticated beam delivery and control systems, proton therapy capabilities are equivalent to those for state-of-the-art, conformal therapy using x-rays with respect to numbers of beams, beam directions and complex delivery techniques such as intensity modulation.

2.2 Study Disease

Hepatocellular carcinoma is the most common primary cancer of the liver. The disease has a dismal five-year survival rate of less than 5%. Hepatocellular carcinoma is an infrequent cancer in developed countries. However, its incidence has substantially increased in Japan during the past three decades and slight increases have been reported in the United Kingdom and France. In the United States, an increase in the number of cases from 1.4 per 100,000 to 2.4 per 100,000 has occurred over the past two decades [1]. The age-specific incidence of this cancer has progressively shifted toward younger patients.

Cholangiocarcinomas are an uncommon malignancy, with an incidence of 1 to 2 cases per 100,000 population in the United States and constituting approximately 2% of all reported cancers [2]. Untreated bile duct cancers are rapidly fatal diseases and majority of patients will die within 6 months to a year of diagnosis. Death usually results from liver failure or biliary sepsis [2]. Long-term survival is highly dependent on the effectiveness of surgical therapy but many patients are not candidates for resection because of the local extent of disease [2].

2.3 Rationale

Unfortunately, many patients with primary hepatobiliary cancer are not surgical candidates due to anatomic location or size of the tumor, concurrent cirrhosis or medical inoperability. Therefore, an important role exists for a treatment that can provide the equivalent of tumor excision, but with minimal morbidity.

The treatment of unresectable hepatocellular or locally recurrent hepatocellular cancer and cholangiocarcinoma has been palliative. Standard treatment modalities have included transarterial chemoarterial embolization (TACE), radiofrequency ablation, or systemic chemotherapy/targeted therapy with few long-term survivors. TACE is useful in patients with multiple lesions, but is not considered an ablative approach. Similarly, systemic therapy is does not produce more than anecdotal complete responses.

Most published data combines hepatocellular cancer and cholangiocarcinoma, including reporting of disease control and survival outcomes for both histologies together. However, emerging data for HCC reported by Bujold and colleagues suggest a difference in overall survival and local control from the combined historical data for this histology[14]. Thus, this study will further investigate outcomes for HCC, while describing the same outcomes for cholangiocarcinoma separately, informing future trials.

Radiofrequency ablation (RFA) is the most commonly employed ablative technique for non-surgical candidates at many institutions. Radiofrequency ablation refers to a method of tumor ablation by which local application of radiofrequency achieves thermal ablation of targeted tissues. Generally, a 14-gauge electrode is placed into the tumor. Delivery of electromagnetic energy in the form of high-frequency (~400 MHz) alternating current causes ionic agitation and the generation of heat due to friction. Coagulative necrosis of hepatic tissue is achieved when temperatures greater than 55 degrees Celsius are maintained for a minimum of 6 minutes. RFA can be performed percutaneously, laparoscopically, endoscopically, or at the time of laporotomy. The exact approach is frequently dictated by the location of the tumor. In spite of these multiple approaches, the use of RFA can be limited by location. An adjacent large vessel can act as a heat sink and limit the efficacy of therapy. Treatment of dome lesions near the diaphragm carries the risk of diaphragmatic perforation and treatment of deep lesions near bowel loops may be associated with bowel perforation. Radiofrequency ablation can be highly effective for small lesions, with local control of 75% or greater. However this local control falls off steeply beyond 3-5 cm in maximum diameter. In one study by Solbiati et al, colorectal metastases less than 2.5 cm had a recurrence risk of 21.6% [4]. This risk increased to 52.8% if the tumor was 2.6-4.0 cm and as high as 68.1% for tumors > 4 cm. Local control for RFA at 2 years was 55%. 2 year overall survival for both groups is. 50%. For radiofrequency ablation to more clearly impact survival, this local control will need to improve. Recurrences after RFA are frequently marginal.

Because of the limited tolerance of the liver to external beam irradiation when the whole liver is irradiated, experience with this modality has been limited. However, several studies have demonstrated that the tolerance of liver significantly increases when smaller volumes of the liver are irradiated. A study from the University of Michigan reported the results of 22 patients with unresectable hepatocellular carcinoma and cholangiocarcinoma treated by high dose irradiation employing conformal 3D techniques using 10 MV X-rays and hepatic artery fluorodeoxyuridine. These patients were observed to have a 4-year survival of 20% and no late hepatic toxicity [5]. Total radiation doses were determined by the fraction of normal liver treated to 50% of the isocenter dose. If 33% of the normal liver received 50% of the dose, the patient was treated to 66 Gy, if 33% to 66% of the liver received 50% of the dose the patient received 48 Gy and if 66% of the liver received 50% of the dose the patient received 36 Gy. Treatment was given daily at 1.8 Gy per fraction five days per week. Several subsequent reports from the University of Michigan group provided more quantitative information regarding both dose-response of liver cancer and dose-volume sparing effects of normal liver tissue[5-9]. They estimated using maximum likelihood analysis that for b.i.d. fractionation with 1.5Gy per fraction the TD_{50} dose for radiation-induced liver disease for primary hepatobiliary cancer is about 40Gy when the whole liver is irradiated. When half of the liver is irradiated the TD_{50} increases to 80Gy, and when less than 1/4 of the liver is irradiated no liver toxicity is predicted regardless of dose level. The tumor response exhibits strong dose dependence with the response rate for tumor doses above 60Gy twice as high as for tumor doses below 50Gy. Similarly encouraging results of dose escalations studies using three-dimensional conformal radiotherapy have recently been reported by groups from Korea (183 patients) and Taiwan (93 patients)[10-12]. These studies demonstrated that the overall median survival could also be significantly improved with higher doses. The chief cause of mortality was progression of underlying severe cirrhosis and not tumor or treatment related causes.

Given these promising results in otherwise incurable malignancies, the MGH group undertook a Phase I study to evaluate the use of high dose conformal proton beam irradiation for selected patients with hepatocellular cancer, cholangiocarcinoma and hepatic metastases. The dose escalation was based on a model based on the amount of radiation that the normal liver received, or equivalent uniform dose (EUD) to the liver. The eligibility criteria were 1-3 lesions, greatest less than 6 cm in size, Childs A/B, and no extrahepatic disease. Patients were treated with gated proton beam therapy using 4D treatment planning techniques. Generally, patients have been treated to a dose of 45-75 Gy (RBE) in 15 fractions. The study was a dose escalation trial based on liver EUD. The dose that each patient was treated to was based not only on the liver EUD at each step but had to comply with protocol defined normal tissue constraints (bowel, chest wall). To date, there have been no local failures or radiation-induced liver disease through 3 of the first 4 dose levels.

Because of the limitations of the EUD based liver concept as a dose escalation platform, as well as the non dose-limiting nature of liver with proton therapy, we have decided to proceed with a modification of the approach taken by the Tsukuba group (13). Investigators at Tsukuba have treated 165 patients (192 tumors) with a similar 15 fraction protocol to a median dose of 72 Gy. Patients with tumor sizes of 10 cm or greater were allowed on the study. Central tumors (within 2 cm of the porta hepatis) were treated to 66 Gy in 22 fractions because of concerns of toxicity. Local control at 5 years was an impressive 86.9%. Local control at 2 years was 90%. However 5 yr OS was only 23%, highlighting the out of field progression and comorbidities in these patients. In this study, we propose a treatment schedule of 15 fractions of proton beam radiation with an expected 2 yr LC of > 85%. Because we anticipate treating large tumors generally greater than 3 cm, we will seek to improve upon a RFA local control rate of ~ 50% to 80% with proton beam therapy.

2.4 Correlative Studies Background

Preclinical and clinical work in the Steele Lab and elsewhere has identified the stromal-derived factor 1 alpha (SDF1α) as an attractive candidate for biomarker of resistance to various therapies, but its role after proton beam radiation therapy is unknown. Based on findings from preliminary studies, we propose here to evaluate the changes in blood circulating SDF1α and circulating myeloid cells before, during and after a three-week schedule of proton beam radiation therapy, and to explore potential associations between the changes in these biomarkers and resistance to treatment. In exploratory studies, we will evaluate several other cytokines using multiplex protein array (Meso-Scale Discovery, Inc.).

Circulating cell populations will be evaluated by fluorescence-based flow cytometry. Protein concentration in plasma will be measured using ELISA kits for SDF1α and MSD multiplex kits for cytokines (IL-1, IL-6, IL-8 and TNF-α) vascular growth factors (VEGF, sVEGFR1, PlGF and bFGF). These techniques have been used in the Steele Lab for over 8 years to evaluate patients' samples.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Patients must have a biopsy proven unresectable or locally recurrent intrahepatic cholangiocarcinoma. Otherwise, patients must have a diagnosis of an unresectable or locally recurrent hepatocellular cancer using either pathology of the liver tumor or radiologic imaging and an elevated AFP. Patients with a single lesion must be 12 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 6cm in greatest dimension. Patients may have

single or multinodular tumors (up to 3). There must be no evidence of extrahepatic tumor. Portal vein involvement or thrombosis is allowed.

3.1.2 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See Section 10 for the evaluation of measurable disease.

3.1.3 Patients may have had prior chemotherapy, targeted biological therapy (ie sorafenib, etc…), surgery, transarterial chemoembolization (TACE), radiofrequency ablation, or cryosurgery for their disease. 5-fluorouracil, capecitabine and sorafenib must be discontinued prior to study entry, with no wash-out period required. Nitrosoureas and mitomycin C must be discontinued at least 6 weeks prior to study entry. All other agents must be discontinued at least 4 weeks prior to study entry. Patients may not have had prior radiation to the affected area.

3.1.4 Patients must be 18 years of age or older.

3.1.5 Expected survival must be greater than three months.

3.1.6 ECOG performance status ≤2.

3.1.7 Participants must have normal organ and marrow function as defined below, all of which must be obtained within two weeks prior to study registration date:

- Absolute neutrophil count ≥ 750/mcL
- Platelets ≥ 25,000/mcL
- Total bilirubin ≤ 4.0 X institutional upper limit of normal
- AST (SGOT)/ALT (SGPT) ≤ 6.0 X institutional upper limit of normal
- Creatinine </= 2mg/dl or creatinine clearance ≥ 60 mL/min/1.73 m^2 (Calculated per Cockroft & Gault formula) for subjects with creatinine levels above institutional normal.

3.1.8 If patient has underlying cirrhosis, only Child-Pugh classification Group A or Group B patients should be included in this study. Clinical assessment of ascites and encephalopathy is required. Child-Pugh classification must be determined for all study participants at the time of eligibility analysis. Note albumin and PT/INR are required for Child-Pugh classification; these labs should be drawn with other labs required for eligibility analysis.

Table 1: Child-Pugh classification of liver function

Score	**1**	**2**	**3**
Acites	Absent	Slight to moderate	Severe
Encephalopathy	Absent	Slight to moderate	Severe
Serum albumin	>3.5 g/dl	3-3.5 g/dl	<3 g/dl
Serum bilirubin	<2 mg/dl	2-3 mg/dl	>3 mg/dl
Prolongation of prothrombin time	<4 seconds	4-6 seconds	>6 seconds

Score of 5 to 6 corresponds to Child-Pugh class A

Score of 7 to 11 corresponds to Child-Pugh class B

Score of 12 to 15 corresponds to Child-Pugh class C

3.1.9 The effects of radiation on the developing human fetus are known to be teratogenic. Therefore, male and female patients of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Female patients of child bearing potential must also have a negative serum pregnancy test.

Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.10 Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1. Women who are pregnant or lactating.

3.2.2. Patients with evidence of non-hepatic metastatic disease.

3.2.3. Local conditions or systemic illnesses which would reduce the local tolerance to radiation treatment, such as serious local injuries, active collagen vascular disease, etc.

3.2.4 Prior liver directed radiation treatment.

3.2.5 Patients may have no serious medical illness, which may limit survival to less than 3 months.

3.2.6 Patient may have no serious psychiatric illness/social situations which would limit compliance with study requirements.

3.2.7 Patients who have had chemotherapy (other than 5-fluorouracil, capecitabine, or sorafenib) or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events (with the exception of anticipated chronic late effects from chemotherapy not expected to be exacerbated by radiation) due to agents administered within the timeframes described in 3.1.3 above.

3.2.8 Patients may not be receiving any other study agents.

3.2.9 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia,

3.2.10 Individuals with a history of a different malignancy are ineligible except for the following circumstances; They have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy.

3.2.11 Because no dosing or adverse event data are currently available on the use of high dose liver radiation participants <18 years of age are excluded from this study.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

We do not expect the inclusion and exclusion criteria to either over or under-represent women, minorities, or underrepresented populations.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Patient Entry

Patients must be registered with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) ([redacted] prior to the start of treatment. Any patient not registered to the protocol prior to the start of treatment will be ineligible. The following information will be provided to the QACT:

- Registering physician (PI or coI) name, telephone number, and pager number
- Protocol name and number, and Date treatment begins
- Patient name, Date of birth, Patient ID number, Primary physician, Primary treatment institution, Confirmation of eligibility
- Copy of signed consent form.
- Patient must start treatment within 1 month of registration

DF/HCC institutions will register eligible participants with the QACT central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must be registered during off-hours or holidays, call the QACT registration line at [redacted] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at [redacted]

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 General Guidelines for Other Participating Institutions

Please see section 5.7 of the Data Safety Monitoring Plan.

4.4 Registration Process for Other Participating Institutions

Please see section 5.7 of the Data Safety Monitoring Plan.

5. TREATMENT PLAN

5.1 Treatment Program

5.1.1 Assessments During Treatment

- Vital Signs: Pulse, Blood Pressure, Temperature obtained weekly
- Lab tests: CBC with diff (WBC, HGB, PLT, ANC, ALC), Liver and renal function tests (SGOT, SGPT, Total Bilirubin, Alkaline Phosphatase, Creatinine, BUN and Creatinine Clearance calculated with Cockroft and Gault formula), LDH and Tumor markers (CEA, CA 19-9, alpha fetal protein) will be obtained weekly during treatment on study days 1, 8, 15 and the day of the last radiation treatment.

Patients will be seen at least once per week by a physician and a radiation oncology nurse while undergoing radiation treatment and will be assessed for acute toxicity.

5.1.2 Radiation Therapy

5.1.2.1 Pre-planning and Simulation Procedures

Prior to radiation planning, patients will undergo placement of fiducial seeds according to institutional procedures. If placement of fiducials is contraindicated in a patient, or if a patient is deemed too high risk for implanting procedure, the patient may proceed with study participation without fiducials at the discretion of the treating investigator.

5.1.2.2 Treatment Planning

Patients will undergo an abdominal 4D CT scan in the treatment position. Treatment planning will be done on a 4D CT-based planning system. If the motion of the GTV is less than or equal to 10mm, an ITV will be defined. If the motion is greater than 10mm, gating or deep inspiration breath hold (DIBH) will be used. For proton treatments, the patient will be in a customized immobilization device in the appropriate position. The treatment planning CT is to be performed with the patient in this device. The radiation oncologist will define the target and the non-target tissues/structures of interest on each section and specify the radiation dose constraints for each of the sensitive structures (uninvolved liver, kidney, large and small bowel, stomach, spinal cord). The treatment

volume is defined as the tumor, visualized on the CT and/or MRI. Clinical Target Volume (CTV) expansion will be 0.5-1 cm at treating physician's discretion. The PTV shall be defined relative to the CTV on the basis of lateral uncertainties alone in the range of 0.5 to 1.0 cm. (Adjustments shall be made within the beam-design algorithm to take into account differences, if any, between the margins needed to account for uncertainties along the beam direction (range uncertainties) and those included in the lateral uncertainty defined PTV.)

5.1.2.3 Dose Fractionation and Specification

Proton treatments will be delivered at the Francis H. Burr Proton Therapy Center at the Massachusetts General Hospital using a 240 MeV cyclotron. At MDACC, proton treatments will be delivered at the MDACC Proton Therapy Center using a 250 MeV synchrotron. At the Roberts Proton Facility at the University of Pennsylvania, proton treatments will be delivered using a 230 MeV cyclotron. All treatments will be administered as one daily fraction, 5 days per week over 3 weeks. The RBE for proton irradiation is set at 1. 1. Thus, the dose unit, Gy (RBE), is proton dose in Gy X RBE of 1. 1. Based on the analysis of the results of the University of Michigan liver protocol there were no cases of liver toxicity for the average liver dose less than 30 Gy delivered in 1.5 Gy per fraction. In our protocol we intend to use **15 fractions, 5 daily fractions per week**.

For peripheral tumors the total dose will be as follows:
67.5 Gy (RBE) (NTD 81 Gy10, 101 Gy3) in 15 fractions

For central tumors (within 2 cm of porta hepatis), fractionation will be as follows:
58 Gy (RBE) (NTD 67 Gy10, 79.6 Gy3)

Underdosing of the PTV will be permitted to maintain normal tissue constraints as described below. However 90% of the PTV should receive the prescription dose. Dose de-escalation will be permitted to maintain a liver EUD below 20 Gy (RBE) and a mean liver dose $\leq$ 24 Gy (RBE). If dose is de-escalated to below 45 Gy (RBE), the patient will be removed from study and referred as appropriate for further management.

Normal Tissue Constraints:
Spinal cord max dose: 30 Gy (RBE)
Stomach max dose: 42 Gy (RBE)
Bowel (including duodenum, small bowel, large bowel) max dose: 45 Gy (RBE)

Kidney V14 (volume receiving 14 Gy (RBE) < 30%)
Liver-GTV: EUD $\leq$ 20 Gy (RBE), mean dose $\leq$ 24 Gy (RBE)- whichever is lower.
Heart Max dose: 45 Gy (RBE), V40<10%
Chest Wall: no more than 2ccs may receive >60 Gy (RBE)

The deviations in dose constraints described above are considered planning deviations only and will not constitute protocol deviations. Treatment plans that include minor planning deviations may be delivered as part of this protocol. Treatment plans that include major planning deviations may be delivered on this protocol with the review and approval of the PI prior to treatment start. All relevant DVH data regarding doses to critical structures will be maintained in the study database for analysis.

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Pre-treatment Criteria

Baseline staging requirements:

All assessments must be completed within 6 weeks of study entry, unless otherwise noted.

5.2.1 Complete history and physical examination by radiation oncologist and responsible medical oncologist or surgeon.

5.2.2 Laboratory evaluation: CBC with diff (WBC, HGB, PLT, ANC, ALC), Liver and renal function tests (SGOT, SGPT, Total Bilirubin, Alkaline Phosphatase, Creatinine, BUN and Creatinine Clearance calculated with Cockroft and Gault formula), LDH and Tumor markers (CEA, CA 19-9, alpha fetal protein) sodium, potassium, chloride, carbon dioxide, , calcium, phosphorous,PT/INR, Albumin, Child-Pugh classification, and tumor markers (CEA, CA 19-9, alpha fetal protein). Lab tests must be completed within 2 weeks of study entry.

5.2.3 Thoracic CT scan to exclude lung and mediastinal metastases.

5.2.4 Abdominal and Pelvic CT scan to exclude non-hepatic disease or metastases. **5.2.5** Hepatic MRI is required if any lesion is difficult to visualize and/or measure on the Abdominal/Pelvic CT scan.

5.3 Proton Beam Delivery

All charged particle treatment will be given with the patient at the Francis H. Burr Proton Therapy Center, MD Anderson Proton Therapy Center, or the University of Pennsylvania Roberts Proton Facility. Film or digital images will be taken prior to each treatment in accordance with the proton center's standard practice

for all patients. These images are used to verify the position of the patient and the aperture. These images are permanently stored electronically for each patient. Respiratory gating or deep inspiration breath hold (DIBH) is recommended to account for respiratory excursion if tumor motion is > 10mm. Treatment may start any day of the week except Friday.

5.4 General Concomitant Medication and Supportive Care Guidelines

There are no required concomitant medications in this study. No other cytotoxic therapy or radiotherapy may be used during study treatment. Patients may receive all concomitant therapy deemed necessary to provide optimal support.

5.5 Duration of Therapy

Proton radiation therapy will in most instances be completed within 3 weeks of the start of treatment (15 consecutive hospital business days). This may be extended if patients require a break from treatment. Criteria for break would include any G3 or G4 toxicity. All labs will be assessed by the treating physician to determine whether they are considered clinically significant or not clinically significant and treatment will be held at their discretion. All patients experiencing any of the following events will be taken off treatment:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.6 Duration of Follow Up

Study participants will be followed for five years from the completion of study treatment or until death, whichever occurs first. Participants will be removed from follow-up when any of the criteria listed in Section 5.5 apply. Participants removed from treatment or follow-up will be followed for survival outcomes and a 2 years analysis of local control.

5.7 Criteria for Removal from Study

Participants will be removed from study upon death or withdrawal of consent. The reason for study removal and the date the participant was removed must be documented in the medical record and recorded in the study-specific case report form (CRF). Alternative care options will be discussed with the participant, if applicable.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Ted Hong, MD at [redacted]

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

6.1 Potential Toxicity

Radiation side effects are typically divided into those that occur acutely (during radiation and up to 3 months after radiation) and those that occur later (>3 months post-radiation). Common acute radiation side effects include fatigue, skin irritation or erythema, elevated liver function tests, nausea, low platelet count, decreased blood counts, abdominal pain or cramps, decreased/ loss of appetite, vomiting, slow wound healing, weight loss, indigestion, gastritis, radiation esophagitis, and diarrhea. Typically, these side effects can be controlled with medication.

Late side effects that are unlikely to occur but would include rib microfracture, nerve damage, inflammation and scarring of liver, mucosal ulceration and tissue damage, ulceration or perforation of stomach/ bowel, pain, inflammation, or scarring of kidneys, stomach and bowel, development of new cancer, hepatic injury (hepatitis), renal injury, gastric, bowel obstruction and spinal cord injury. Another rare but serious late side effect is the development of second tumors. It is hoped that proton radiation will substantially reduce both acute and late side effects by reducing the amount of normal tissue that is irradiated.

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v3.0) which is available at http://ctep.cancer.gov/reporting//ctc html).

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All toxicities that are Grade 2 or higher and determined to be possibly, probably or definitely related to the study intervention or study procedures will be collected on the Toxicity case report forms from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.2 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

CAEPRs for Proton Beam Radiotherapy to the Liver

Very likely*:* These symptoms usually recover in the first few weeks following completion of radiation therapy

• Irritation, redness and discoloration of the skin in the radiation area.

• Fatigue (tiredness)

Likely

- Decreased blood counts
- Low platelet count
- Elevated LFTs
- Abdominal pain or cramps
- Nausea

Less likely

- Diarrhea
- Decreased/ loss of appetite
- Vomiting
- Slow wound healing
- Weight loss
- Indigestion
- Gastritis
- Radiation Esophagitis
- Rib microfracture

Rare

- Damage to the liver which could result in inflammation and scarring of the liver. This could lead to jaundice and possibly cirrhosis. Efforts to prevent excessive liver irradiation will be made to minimize the chance of these side effects
- While radiation can cause mucosal ulceration, other tissues may be damaged which may require surgery and may be life-threatening.
- Stomach and bowel are protected well from excessive dose of radiation. However, overdosing the stomach or bowel can lead to ulceration or perforation.

- Pain, inflammation or scarring of your kidneys, stomach and bowel. These organs are protected well from excessive dose of radiation. Therefore, it is unlikely that patients will experience symptoms of injury to these organs
- Nerve damage
- Development of a new cancer resulting from treatment may happen many years after completing treatment
- Spinal cord injury

6.3 Toxicity Management

Most radiation toxicities during the course of treatment are self-limited and resolve with a treatment break. Therefore, any Grade 3 or 4 acute toxicity will result in a treatment break until it resolves to Grade 2 or less, with the exception of labs. All labs will be assessed by the treating physician to determine whether they are considered clinically significant or not clinically significant and treatment will be held at their discretion. If a participant experiences a Grade 3 or 4 hematological toxicity, the participant is allowed to receive a colony stimulating factor to aid in the resolution.

6.4 Dose Modifications/Delays

Grade 3 or 4 acute toxicity will result in a treatment break until it resolves to Grade 2 or less, with the exception of any Grade 3 Baseline labs that fit the eligibility criteria. Thrombocytopenia will only result in a treatment break if it becomes a Grade 4. All labs will be assessed by the treating physician to determine whether they are considered clinically significant or not clinically significant and treatment will be held at their discretion. If a treatment break of > 14 days is needed, the patient will be removed from study.

7. DRUG FORMULATION AND ADMINISTRATION: Not applicable

8. CORRELATIVE/SPECIAL STUDIES

8.1 Circulating Biomarkers

Participation in the correlative blood sample studies will be offered to study participants at MGH only.

Based on findings from preliminary studies, we propose here to evaluate the changes in blood circulating SDF1α and circulating myeloid cells before, during, and after a three-week schedule of proton beam radiation therapy, and to explore potential associations between the changes in these biomarkers and resistance to treatment. In exploratory studies, we will evaluate several other cytokines using multiplex protein array (Meso-Scale Discovery, Inc.).

8.1.1 Experimental Design

Blood will be drawn by venipuncture, and the first 7-10 ml blood will be excluded or used for other analysis. The following 8 ml will be collected in an EDTA tube. The EDTA tube with the blood sample will be shipped in wet ice within 2 hours of drawing for further processing at Steele Laboratory at MGH. We will analyze the correlation between plasma SDF1α and circulating myeloid cells with multiple measures of outcome (ORR, TTP, OS) in advanced liver cancer patients after proton beam radiation therapy.

8.1.2 Collection

To this end we will measure circulating biomarkers

(i) pretreatment

(ii) during proton beam radiation therapy at days 1, 8, 15 and the last day of radiation treatment

(iii) one month post-completion of the proton beam radiation treatment; and

(iv) at the time of disease progression

Samples will be collected at the following time points-

a. Prior to the start of therapy

b. Within 72 hours of start of therapy.

c. Day 8, 15 and the day of the last radiation treatment.

d. 1 month after completion of therapy.

e. following radiologic progression

8.1.3 Shipping Instructions

The tube containing the blood should be shipped with the following information

1. Study Number at the DF/HCC
2. Patient number on the study
3. Patient's initials
4. Treating physician's name
5. Date of collection
6. Date of shipping

The tube of blood should be placed in a sealable container and placed in a box with the necessary information. The box should be marked Biohazard.

[redacted]

[redacted]

8.2 Genotype Testing

Next generation sequencing and tissue-based testing on specimens of patients at MGH will assess exploratory tissue markers in relation to worsening local control and will potentially inform future trials.

Next generation sequencing assays have been developed by the Massachusetts General Hospital Center for Integrated Diagnostics (MGH CID) to detect a wide variety of alterations in cancer genes that could alter response to therapy. The 1K Cancer Panel provides for the evaluation of small nucleotide variants (SNVs) and insertion/deletions (indels) across ~800 cancer genes using tumor DNA. The Solid Tumor Fusion Panel can detect gene fusions across ~50 gene targets using complimentary DNA (cDNA). Both of these approaches generate target-enriched libraries that undergo next-generation sequencing on an Illumina platform. A blood sample is used as a control to identify alterations that occur specifically in the tumor tissue. All testing and sequence analysis will be performed in the MGH Translational Research Laboratory (MGH TRL) within the MGH CID.

8.2.1 Sample Shipment

a) Formalin-fixed, paraffin-embedded (FFPE) intrahepatic cholangiocarcinoma and hepatocellular carcinoma tissue samples will be submitted for genotype testing as either the FFPE block or as 15 sections of tissue (5 microns) that have been cut from the block and mounted onto plus microscope slides.

b) Slides must be sent secured in appropriate slide holders and FFPE blocks in a crush-proof container to the following address by overnight courier, under ambient conditions:

Massachusetts General Hospital
[redacted]

c) A whole blood sample collected on protocol will also be sent to the same address above, on cold packs by overnight carrier. Appropriate IATA shipping of dangerous goods regulations must be followed. Patients at external sites will have a one-time blood sample drawn and sent to the same address above.

d) Quality assurance measures require that each patient sample is submitted with the protocol number and two unique identifiers (i.e. surgical number, patient ID number, patient initials). An email must also be sent to the MGH TRL centralized mailbox [redacted] indicating intent to submit the sample, the trial number, and the relevant sample identifiers. The MGH TRL program coordinator will verify receipt of the sample, whether the sample was received in acceptable condition and specified amount, and will confirm the identifiers before initiating the testing process.

9. STUDY CALENDAR

9.1 Required Data

Lab evaluations must be completed within 2 weeks of study entry. All other baseline assessments must be completed within 6 weeks of study entry. All study assessments should be administered +/- 3 days of the protocol-specified date, unless otherwise noted.

Data Set	**Prior to Study Entry**	**Weekly Visit During Radiation Therapy**	**At Follow-Up (3)**
Age	X		
Sex	X		
H&P (including clinical assessment of ascites and encephalopathy at baseline and follow up)	X	X	X
Toxicity Assessment	X	X	X
Vital Signs (pulse, blood pressure, temperature)		X	
CBC with diff (WBC, HGB, PLT, ANC, ALC)	X	X	
PT/INR, Albumin, Child-Pugh classification	X		X
Renal Function Tests (BUN, creatinine, calculated creatinine clearance per Cockroft & Gault)	X	X	
Liver Function Tests (SGOT, SGPT, T bili, Alk Phos) & LDH	X	X	X
Tumor markers (CEA, CA 19-9) Alpha Fetal Protein	X	X	X
Beta-HCG (women of child-bearing potential)	X		
Tumor Measurement	X		twice yearly (1)
Abdominal and Pelvic CTand/or hepatic MRI	X		twice yearly (1)
Thoracic CT	X		twice yearly
Peripheral Blood for correlative studies (optional)	X	X (2)	X (2)

Notes:

(1) Imaging and tumor measurements in follow up are required for study data twice yearly. Additional imaging studies may be obtained for clinical follow up at the discretion of the treating clinicians. For study participants who receive follow up care at institutions other than the treating institution, imaging reports and scans must be sent to the treating institution to be included in the study data set.

(2) Peripheral blood will be obtained with clinical labs at pretreatment, during proton beam radiation therapy at days 1, 8, 15 and the last day of radiation treatment. (this blood draw is optional and will be offered to study participants at MGH only)

(3) Follow up assessments will be due at 1, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months post treatment, with a visit window of +/- 3 weeks for the 1 month follow up and+/- 6 weeks for all other follow up dates.

9.2 Data Collection

Weekly on-study labs are to be drawn on study days 1, 8, 15 and the day of the last radiation treatment. All patients will be evaluated initially, and at 1, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, and 60 months post treatment. Each follow-up examination will consist of interval history and physical examination, toxicity assessment, liver function tests, LDH, PT INR, albumin, Child-Pugh classification and tumor markers (CEA , CA 19-9,alpha feta protein). Baseline and follow up physical examination will include clinical assessment of encephalopathy and ascites for calculation of Child-Pugh Score. Assessment of the liver tumor by CT and/ or MRI will be performed at time of abdominal imaging twice yearly for two years and then yearly for three years. Chest CT will be obtained twice yearly for two years and then yearly for three years. Additional imaging studies may be obtained for clinical follow up at the discretion of the treating clinicians. For study participants who receive follow up care at institutions other than the treating institution, imaging reports and scans must be sent to the treating institution to be included in the study data set.

10. MEASUREMENT OF EFFECT

10.1 Toxicity and Complications

Acute and late morbidity of radiation treatment will be scored using the Common Terminology Criteria for Adverse Events 3.0 (CTCAE 3.0; see Appendix 11)

10.2 Tumor Response: RECIST Criteria

Complete Response (CR): Disappearance of entire lesion, with no additional evidence of disease Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of the primary lesion, taken as reference the baseline sum LD.

Progressive Disease (PD): At least a 20% increase in the LD of the lesion, taken as the reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

10.3 Local Failure

Local failure is defined as: evidence of tumor growth/regrowth in any direction beyond that present of the pre-treatment imaging studies in the treated lesion(s). Intrahepatic recurrence elsewhere in the liver is defined as any new lesion in the liver. The imaging studies are to be comparable in technical factors.

10.4 Marginal failure

Marginal failure is defined as appearance of tumor growth at the margin of the target volume

10.5 Nodal failure

Failure in regional lymph nodes: porta-hepatis, para-aortic, diaphragmatic.

10.6 Distant Failure

Defined as appearance of tumor at sites beyond regional nodal and marginal site.

10.7 Overall Survival

Duration measured from registration until death or censored at date of last follow-up for patients still alive.

11. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse Events

As above, the CTCAE 3.0 will be used to grade all acute and late radiation effects and Adverse Events.

Report of Adverse Events to the IRB

Adverse events will be reported to each site's IRB in accordance with the local IRB guidelines. All adverse events will also be reported to the Coordinating Center and all participating sited as described in the attached Data and Safety Monitoring Plan (Appendix III).

11.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) that is available at http://ctep.cancer.gov/reporting//ctc.html

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study intervention, throughout the study, and within 30 days of the last study treatment. Participants who experience an ongoing adverse event or related to a study procedures and/or study treatment beyond 30

days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB, the Coordinating Center and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11.2 Definitions

11.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.2.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected’.

11.2.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the treatment. For the purposes of this study, an adverse event is considered expected when it appears in the protocol and/or informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study treatment.

11.2.3.2. Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the protocol and/or informed consent document as a potential risk.

11.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.3 Recording Adverse Events

Adverse event information will be obtained at each contact with the participant. All adverse events will be recorded on the appropriate study-specific case report forms (CRFs).

11.4 Reporting Adverse Events

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements and reporting requirements of the principal investigator.

Each adverse event will be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local policies, and federal guidelines and regulations as appropriate.

It is the responsibility of the participating investigator to notify the Principal Investigator, and the local IRB of all serious adverse events as required in the protocol.

The Principal Investigator will provide information with respect to adverse events and safe use of the study treatment (e.g., safety reports, Action Letters) to all participating investigators as described in the attached Data and Safety Monitoring Plan (DSMP) as soon as the information becomes available.

11.5 Coordinating Center Notification by Investigator

11.5.1 Serious Adverse Event Reporting Requirements

All events meeting the criteria for Serious Adverse Event (see Section 11.2.2) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator as serious adverse events. This includes events meeting criteria outlined in Section 11.2 as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long-term follow-up, report death at the time of continuing review.

The participating investigator must report each serious adverse event, regardless attribution, to the DF/HCC Principal Investigator within 1 business day of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 1 business day after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by email or fax to the Coordinating Center at:

[redacted]

Within the following 1-2 business days, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.5.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events will be reported to the Principal Investigator on the toxicity Case Report Forms.

11.6 Institutional Review Board (IRB) Notification by Investigator

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator (or Protocol Chair) and to the local IRB according to the local IRB's policies and procedures in reporting adverse events.

The Principal Investigator (or Protocol Chair) will report adverse events and serious adverse events from all participating sites to the DFCI IRB according to the IRB's policies and procedures in reporting adverse events.

11.7 Hospital Risk Management Notification by Investigator

The participating investigator will report to the Principal Investigator (or Protocol Chair) and to local Risk Management any subject safety reports or sentinel events that require reporting according to institutional policy.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

Data for this study will be collected and managed by the MGH Biostatistics Center. Electronic Case Report Forms will be posted for use by all participating sites in TrialDB, and study staff at each site will be given access to enter CRF data electronically. Data will be monitored by the MGH FHBPTC Senior Clinical Research Program Manager or designee.

12.1.2 Data Submission

The schedule for completion and submission of electronic case report forms to the MGH Biostatistics Center can be found in section 5.10 in the Data Safety Monitoring Plan.

12.1.3 DICOM Data

De-identified DICOM data from the proton plans for each study subject will be transmitted to the Advanced Technology Consortium QA Center at Washington University, St. Louis (ATC). ATC will maintain the de-identified image data for analysis by investigators at all participating sites. Treatment plans for all patients will be sent electronically to the ATC .The treatment planner or the physicist who performs the initial review of the plan will be responsible for transmitting these data. Please see section 12.3.1 for more information.

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

12.3.1 Quality Assurance and Rapid Review of Treatment Plans

To ensure protocol compliance, the treatment plans for the first three patients treated at each site will be reviewed by the Principal Investigator and Participating Site's PI. As described above, plans will be submitted to the ATC for this protocol. The plans will be sent to the ATC upon approval by the treating physician, and the PI and/or Participating Site PI will review and confirm protocol compliance within three working days of the start of treatment.

13. REGULATORY CONSIDERATIONS

13.1 Declaration of Helsinki

The PI will ensure that this study will be conducted in full conformity with the current version of the declaration of Helsinki and with U.S. FDA requirements

13.2 Patient Confidentiality

The investigators will ensure that patient anonymity is maintained.

13.3 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the lead site (DF/HCC) IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.4 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study, including an adequate explanation of the aims methods, anticipated benefits and potential hazards of the study to the patient. The formal consent of a participant, using the IRB approved consent form, must be obtained by the Principal investigator or physician co-investigator before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. If the patient does not speak English, an interpreter will be made available and the treating institution's policy for obtaining research consent from non-English speaking patients will be followed. The informed consent process will be documented in the patient's medical record. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.5 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- ICH Consolidated Good Clinical Practice: Guidelines (E6)
  www fda.gov/cder/guidance/iche6 htm

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- Institutional research policies and procedures www.dfhcc harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the Principal Investigator and the IRB according to the local reporting policy.

13.6 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.7 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.8 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix II).

- The Principal Investigator/Coordinating Center is responsible for distributing all Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

14. STATISTICAL CONSIDERATIONS

The primary objective is to demonstrate proton beam radiation of unresectable primary hepatocellular cancer is associated with local control of at least 80% at 2 years. The null hypothesis is based on a 2-year local control rate of 55% following treatment of tumors >3cm with radiofrequency ablation (RFA), as discussed in **2.3**. However, the local control tends to much poorer in certain subgroups, including tumors unable to be treated by RFA and the largest tumors, thus 55% is used as an upper bound for the sample size considerations.

14.1 Study Design/Endpoints

The primary endpoint is local control at 2 years, or equivalently, the absence of local failure as defined in **10.3**. Starting with a total of 60 patients with unresectable primary hepatocellular cancer, we project 30 of them will be alive at 2 years for the evaluation of local control assuming a 2-year overall survival of 50%. The number of evaluable patients is a conservative assumption based on the historical RFA data and the Tsukuba proton data (13) showing a 2-year overall survival in the range of 50-70%. Analysis of 30 patients alive at 2 years will achieve 94% power to detect a local control rate of 80% if at least 21 of them were free of local failure. The decision rule is associated with 7% probability for accepting the proton protocol is associated with improved local control when the true rate is only 55% at 2 years.

The rate of local control will be based on actuarial estimates, primarily at 2 years, using the Kaplan-Meier method. Time to local failure will be measured from the start of radiation therapy to the date of local failure, as defined in 10.3. Patients who have not failed locally will be censored at the time of last follow-up. A minimum follow-up of 2 years will be required, while patients who die or drop out of the protocol prior to 2 years will be censored at that date.

14.2 Sample Size/Accrual Rate

The accrual goal was previously revised to 60 patients in order to preserve high power for detecting a slightly smaller but clinically significant increase in local control to 80% at 2 years. Recently, emerging data suggest unresectable liver tumors represent clinically heterogeneous groups, in particular, intrahepatic cholangiocarcinomas are associated with a more favorable prognosis than primary hepatocellular cancers. Thus we propose to restrict the primary hypothesis in **14.1** to the major tumor group, namely patients with unresectable primary hepatocellular cancer. As intrahepatic cholangiocarcinomas constitute one-third of the present enrollment, we propose to continue with their accrual in order to estimate their failure and survival endpoints with reasonable precision for planning future studies for the specific population. Based on the observed distribution of the tumor groups, the target accrual is increased to a total of 90 patients in order to obtain 60 patients with unresectable primary hepatocellular cancer for testing the primary hypothesis in **14.1.**

Since the protocol was activated by MD Anderson Cancer Center at the end of September 2010, 47 patients have been enrolled by two participating institutions over a period of 13 months. As of March 2013, their combined accrual has reached 57 patients. We project the increased sample size will be reached within the next year and a half, as the protocol has expanded recently to a third institution. **If a patient is found to be ineligible once registered and therefore taken off study and excluded from analysis, an additional patient may be enrolled and included in analysis.** As specified in **5.6,** the patients will be followed for at least 5 years from the completion of protocol treatment or until death, whichever occurs first.

14.3 Stratification Factors

Not applicable.

14.4 Analysis of Secondary Endpoints

The secondary endpoints of acute and late toxicity, tumor response, failure patterns and overall survival are defined in the modality review of **10.1-10.7**. Toxicity and response data will be summarized in tables, with the exact binomial confidence interval reported for their rates. Time to failure and survival will be analyzed using standard methods for failure time data, primarily the Kaplan-Meier estimate, while differences between patient subgroups may be explored using the log-rank test. In particular, the increase in sample size will provide high precision for estimating the failure and survival endpoints separately for patients with hepatocellular cancer and cholangiocarcinoma.

14.5 Reporting and Exclusions

Not Applicable

15. PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection. A report may be published in a peer-reviewed journal, or an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of data collection.

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17. APPENDICES

Appendix I: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.