**AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK**

**ACRIN 6673**

# MULTICENTER FEASIBILITY STUDY OF PERCUTANEOUS RADIOFREQUENCY ABLATION OF HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS


**Study Chair**
Gerald D. Dodd, III, M.D.
Department of Radiology
Univ. of Texas Health Science Ctr. at SA
7703 Floyd Curl Drive
San Antonio, TX 78229
(210) 567-5558
FAX # (210) 567-5556
*dodd@uthscsa.edu*

**Statistician**
Dawei Liu, Ph.D.
Center for Statistical Sciences
Brown University, Box G-S121
121 South Main Street, 7th Floor
Providence, RI 02912
(401) 863-2175
FAX # (401) 863-9182
*daweiliu@alexander.stat.brown.edu*

**Surgical Oncologist**
Glenn Halff, M.D.
Department of Surgery
Univ. of Texas Health Science Ctr. at SA
7703 Floyd Curl Drive
San Antonio, TX 78229
(210) 567-5777
FAX # (210) 567-6608
*halff@uthscsa.edu*

**Medical Oncologist**
Anthony Shields, M.D.
Department of Medicine
Harper Hospital, 5 Hudson
3990 John R. Street
Detroit, MI 48201
(313) 745-6258
FAX # (313) 993-0559
*shieldsa@karmanos.org*

**Radiologists**
Damian E. Dupuy, M.D
Brown University School of Medicine
Rhode Island Hospital
Department of Diagnostic Imaging
593 Eddy St.
Providence, RI 02903
(401) 444-5184
FAX # (401) 444-5017
*ddupuy@lifespan.org*

David Lu, M.D
1828 Elm Ave
Manhattan Beach, CA 90266-5005
(310) 794-7952
FAX # (310) 825-6066
*dlu@mail.rad.ucla.edu*

**Pathologist**
Shahla Masood, M.D.
University of Florida
655 West 8th Street
Jacksonville, FL 32209-6511
(904) 244-4387
FAX # (904) 244-4060
*shahla.masood@jax.ufl.edu*


***PARTIAL PROTOCOL—CONTACT ACRIN PROTOCOL DEVELOPMENT AND REGULATORY COMPLIANCE FOR A COMPLETE PROTOCOL***


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**CONFIDENTIAL**

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## AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

## MULTICENTER FEASIBILITY STUDY OF PERCUTANEOUS RADIOFREQUENCY ABLATION OF HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS

### SCHEMA

| **ELIGIBILITY** | **REGISTRATION** | **TREATMENT** | **FOLLOW UP** |
|---|---|---|---|
| Cirrhosis<br>1-3 HCC ≤ 3.0 cm<br>or<br>A single tumor >3.0 cm but ≤ 5cm | | Percutaneous RFA (Repeat RFA permitted for 15 months after initial ablation session)* | CT scans within 1st week after initial RFA and every 3 months post ablation for 18 months** |

*Last allowable per protocol repeat RFA must occur within 1 month from the 15-month CT scan.

**Initial post RFA CT scan must be done within one week after initial treatment to check for adequacy of ablation. If residual or recurrent tumor is detected at the site of the treated tumor(s) or elsewhere in the liver, re-ablation will be performed as long as the size of the recurrence does not exceed 5.0 cm, the recurrence is not adjacent to vital structures and there is no evidence of extrahepatic tumor. The re-ablation strategy will follow the same ablation strategy used for primary tumors.

### SPECIFIC AIMS/OBJECTIVES

The primary aim for this trial is to estimate the proportion of patients undergoing solitary or repetitive percutaneous RFA treatment sessions whose livers have no identifiable tumor by CT scan at 18 months following initiation of therapy.

### METHODS/METHODOLOGY

Forty participants will be stratified into 1 of 3 strata groups per the MELD score. [1-3] Elapsed time from registration to RFA should not be more than two (2) weeks. Timeline: 1-1.5 years for participant accrual, 1.5 year follow-up after ablation to determine local ablation success, total study period 2.5 to 3 years.

**Note:** Per DSMC review and recommendations on May 17, 2007, the decision has been made that the two groups with MELD scores >15 will be closed for accrual. The study will only enroll participants with MELD score <15. Therefore, the study design is not stratified anymore and the total sample size is 40.

### ELIGIBILITY *(see Section 5.0 for details)*

1. Biopsy proven cirrhosis, or typical findings of cirrhosis by CT scan and or MRI scan.
2. Biopsy proven hepatocellular carcinoma (HCC), or a discrete hepatic tumor(s) as defined by the Barcelona[4] criteria (2 imaging studies showing hypervascular tumor > 2cm, or single imaging study showing hypervascular tumor > 2cm with AFP ≥ 400 ng/mL), or a discrete hypervascular

tumor present on two consecutive imaging studies (CT or MRI) with documented growth of > 1cm in diameter.

3. Hepatic tumor burden meeting the Milan Criteria[5]: 3 or fewer tumors ≤ 3.0 cm, or a single tumor > 3.0 cm but ≤ 5 cm in diameter. (Note: Vague hypervascular nodules ≤ 1cm and less than 3 lesions in number will not be included in tumor count, but will not preclude enrollment.)
4. Not a candidate for surgical resection. (See 5.3.2 & Appendix VIII, Definition #13)
5. No previous or current treatment for HCC by any method.
6. All identified tumors > 1 cm are treatable by percutaneous RFA.
7. All tumors ≥ 1 cm from the main, right and left portal veins (hepatic veins not included).
8. All tumors ≥ 1 cm from any hollow viscera.
9. Serum creatinine ≤ 2.0 mg/dl.
10. Chest and abdominal CT scan and/or abdominal MRI scan within 60 days prior to initial RFA treatment.

**REQUIRED SAMPLE SIZE:** 120 participants.

## 1.0 ABSTRACT

This protocol for human research study is conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonisation (ICH) Guidelines), applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations) and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

Patients with small hepatocellular carcinoma (HCC) and compensated cirrhosis have a marked decrease in survival relative to similar patients without HCC. [6-10] However, with effective treatment, survival can be significantly improved. Surgical resection and hepatic transplantation are considered the standard of care, but, few patients are good surgical candidates and the availability of organ donors is limited.[6-11] Furthermore, surgical resection has associated morbidity, potential mortality, a 35-50% 5-year survival, and a high risk of recurrent intra-hepatic HCC. [17-20] For these reasons there is clearly a need for a less invasive therapeutic technique that can eradicate treated tumors as effectively as resection, that can be used in a greater number of patients, and that can be used to treat the intrahepatic tumor recurrences that occur in the majority of patients.

Several single institution studies of radiofrequency ablation (RFA) of HCC have reported high local tumor eradication rates and extended patient survival.[12,14,21,22] These results combined with many attractive features of the technique (minimal invasiveness, few side effects, minimal complications, and the ability to be repeated as necessary to treat recurrent hepatic tumor) have resulted in RFA becoming the preferred treatment technique for HCC at many medical centers. [12,23,24] This adoption has occurred despite the absence of randomized trials with other therapeutic techniques, the existence of considerable variation in outcomes between studies, and the lack of a standardized RFA technique. Indeed, many important questions remain poorly defined including the true local tumor eradication rate, the impact of tumor size and location on the local success rate, and the impact of RFA on patient survival.

This protocol is a multi-center feasibility trial of the use of percutaneous RFA to treat HCC in patients with cirrhosis. The primary objective of the study is to estimate the proportion of patients undergoing solitary or repetitive RFA treatment sessions in whom all hepatic tumors can be controlled with no identifiable intrahepatic tumor present by CT scan at 18 months following initiation of therapy. The potential advantage of the repeat use of RFA to treat intra-hepatic tumor recurrences has been specifically incorporated into the design of this protocol. Repeat RFA will be allowed throughout the study (for 15 months after initial treatment, including ablation of lesions found at the 15-month follow-up as long as those re-ablations occur within 1 month from the 15-month CT scan) in an attempt to control all hepatic tumors. We are assuming that the control of all hepatic tumors with no identifiable tumor by CT scan at 18 months after the initiation of therapy may yield an increase in survival. If this use of RFA yields hepatic tumor control rates equivalent to or greater than the hepatic tumor free rates achieved with hepatic resection (65% @ 18 months)[25], the results will be considered interesting and adequate justification to pursue future studies of the technique. Results significantly worse than those reported for hepatic resection would be expected to temper the current clinical enthusiasm for RFA, prompt technical improvements in RFA, fuel the investigation of combining RFA with other therapies, or lead to the abandonment of RFA in favor of newer and more promising therapeutic techniques.

Adult patients with cirrhosis and HCC in whom surgical resection is contraindicated will be potential candidates for this study. All participants will undergo an extent-of-disease work-up that includes a chest CT scan and abdominal CT scan and/or abdominal MRI scan Patient population heterogeneity

will be controlled by limiting study enrollment to patients with minimal intrahepatic hepatic tumor burden, no evidence of extra-hepatic tumor, and by categorizing enrolled participants on the basis of the severity of their hepatic dysfunction. The extent of hepatic tumor burden must comply with the Milan Criteria, 3 or fewer tumors ≤ 3.0 cm, or a single tumor > 3.0 cm but ≤ 5 cm in diameter. Hepatic dysfunction will be defined using the MELD Score with one third of the participants enrolled into each of the three following groups: MELD Score >25, 15-25, and <15.[1] These participant discriminators have been chosen as they are strong predictors of the risk of mortality in these patients and although survival is not the primary endpoint in our study, this sub-categorization will allow a more accurate comparison of our data to other studies. Furthermore, these criteria are clinically useful and are used currently in clinical decision-making. As such, describing our results on this basis will translate into the clinical domain. As this is a feasibility study the enrollment in each of the three cohorts will be limited to a total of 40 enrolled participants for a total study enrollment of 120 participants. By design each of the participant cohorts will be individually closed as the target enrollment for each is achieved.

Participants will be followed after the initial ablation session by serial CT scans for 18 months. Any evidence of residual or recurrent tumor at a treated site on or after the first 3-month follow-up CT scan will be classified as a primary failure. However, because of the potential clinical benefit of re-ablating primary failures, secondary success rates following re-ablation will be followed. Likewise, because of the potential impact that continued control of all hepatic tumors (baseline, recurrent, and new) may have on survival, for all intrahepatic tumor(s) detected at the site of the treated tumor(s) or elsewhere in the liver, re-ablation will be performed as long as the size of the recurrence does not exceed 5.0 cm, the recurrence is not adjacent to vital structures and there is no evidence of extrahepatic tumor. The re-ablation strategy will follow the same ablation strategy used for primary tumors.

The primary objective is to estimate the proportion of participants undergoing solitary or repetitive RFA treatment sessions whose livers have no identifiable tumor by CT scan at 18 months following initiation of ablative therapy. Secondary objectives include exploration of the impact of solitary versus repetitive RFA and tumor size on the main objective, evaluation of a possible correlation between the MELD Score and the main objective, estimation of the local and remote intrahepatic, as well as the extra-hepatic tumor recurrence rates and their impact on the main objective, exploration of the impact of tumor size on the local tumor control rates, and exploration of the impact of solitary or repetitive RFA with or without local/regional control on the development of extra-hepatic tumor. [1]

## 2.0 BACKGROUND AND SIGNIFICANCE

### 2.1 Background

The overall incidence of cirrhosis in the United States has increased dramatically over the last two decades.[11,26,27] The survival rate of these patients is directly related to the severity of their cirrhosis. In patients with well compensated cirrhosis the one, two, and six year survival is 90-100%, 87%, and 54%,[6,12,26] respectively, versus 45% at one year and 23-40% at five years in patients with cirrhosis and hepatic failure.[13,27,28] Approximately 10-16% of patients with cirrhosis will develop HCC over their lifetime.[6,11,27] The survival of these patients is dependent

[1] Per DSMC review and recommendations on May 17, 2007, the decision has been made that the two groups with MELD scores >15 will be closed for accrual. The study will only enroll participants with MELD score <15. Therefore, the study design is not stratified anymore and the total sample size is 40.

on the severity of their cirrhosis and the stage of their tumor at the time of diagnosis. In patients with advanced HCC survival is dismal (4-8 months) almost irrespective of the severity of cirrhosis. In patients with compensated cirrhosis and small untreated HCC survival is diminished with the one, two, and three year survival rates being 81%, 56%, and 21%, respectively.[7-10] The survival of these patients can be improved with effective therapy; however, not all therapies work.

## 2.2 Conventional Treatment

Systemic chemotherapy has very little impact on HCC and is thus reserved for patients with advanced HCC who are not candidates for other forms of therapy.[14] Leung et al[29] reported that patients with HCC randomized to a combination of cisplatin, doxorubicin, 5-fluorouracil and α-IFN had a median survival of only 8.9 months. Multiple other chemotherapy trials have shown similarly poor results.[15,17,30]

Because cirrhosis predisposes patients to both solitary and multifocal HCC, a cure can only be affected if the entire liver is treated or replaced. Thus, the only truly curative therapy for patients with HCC and cirrhosis is hepatic transplantation.[31] However, not all patients are acceptable transplant recipients, and a chronic shortage of organ donors limits the number of qualified patients who undergo transplantation.

Surgical resection of HCC in patients with compensated cirrhosis yields a significant increase in survival with five year survival rates ranging from 50-83%.[14,17,21,32,33] Unfortunately, only 20% of patients with HCC are considered resectable.[34] Contraindications to tumor resection include too many tumors, tumors in unresectable locations, impaired clinical condition, advanced liver disease, and patient refusal.[13,16] For those patients who undergo hepatic resection, there is considerable postoperative morbidity, a small but real risk of peri-operative death, significant monetary expense, and a high rate of intrahepatic tumor recurrence.[18-20,35,36] The five year survival rate for patients undergoing resection of HCC varies with the size and number of tumors.[12,13,26,30] Zhou et al[36] in a study of a 1000 patients with small HCC (< 5 cm) who underwent resection had an 80.5% local cure rate. Five year survival was reported as 82.5% for patients with tumors less than 2.1cm, 66.3% for patients with tumors between 2.1 cm and 3.0 cm, and 61.2% for patients with tumors between 3.1 cm and 5.0 cm. However, other studies have reported a 43-78% rate of intrahepatic recurrence of HCC at five years following resection with the recurrences being the cause death in the majority of patients. Repeat hepatic resection is considered an effective treatment for recurrent intrahepatic HCC; unfortunately, most recurrent tumors are unresectable.[19,35]

## 2.3 Alternative Therapies

There are a number of alternative therapies that have been used for the treatment of HCC. These include chemoembolization, hepatic artery infusion chemotherapy, ethanol injection therapy, and thermal ablation techniques.[7,15,17,38,39,40]

Chemoembolization has been studied extensively and in most instances has been proven to be palliative only.[14,15,17,30] However, a trial performed by Llovet et al, yielded promising results. Patients in this trial had cancer that was confined to the liver and had preserved liver function. Patients were treated with either chemoembolization utilizing Adriamycin® (doxorubicin) embolization only or treatment to relieve symptoms from the cancer (conservative therapy).

When an analysis was performed partway through the trial, researchers discovered that death was reduced by 53% in patients treated with chemoembolization compared to conservative therapy, which resulted in a decision to stop the trial early. Survival at one year following therapy was 82% for patients treated chemoembolization, 75% for patients treated with embolization only and 63% for patients treated with conservative therapy. Survival at two years following therapy was 63% for patients treated with chemoembolization, 50% for patients treated with embolization only and 27% for patients treated with conservative therapy).[41]

Intra-arterial chemotherapy appears to have some anti-tumor effect and may aid in downstaging of tumors prior to resection or ablation in selected patients with advanced HCC, although it has been associated with considerable hepatotoxicity.[42-44] Sangro et al[42] treated 26 patients with hepatic artery infusion of cisplatin and etoposide, and reported a median survival of 10 months with overall survival rates at 12 and 24 months of 33% and 24%, respectively. Treatment-related deaths occurred in four cirrhotic patients participating in the study.

Ethanol injection therapy has gained fair international acceptance as a safe, inexpensive, and effective therapy for small HCC.[45-48] However, the eradication of individual tumors typically takes multiple therapeutic sessions and the technique is ineffective for the treatment of larger HCC.[22,45,46] Livraghi et al[46] compared the effectiveness of percutaneous ethanol injection therapy to that of radiofrequency thermal ablation (RFA). In the treatment of 112 HCCs less than 3 cm, the authors reported that complete necrosis of the tumors was achieved in 80% of the tumors treated by ethanol injection therapy versus 90% of the tumors treated by RFA. Most importantly, they found that RFA required fewer treatment sessions than ethanol injection therapy to affect the same degree of tumor necrosis, 1.2 versus 4.8 sessions, respectively. In multiple centers, ethanol injection therapy has been discarded in favor of thermal ablation techniques.

## 2.4 Thermal Ablation Techniques

Thermal ablation techniques have been used for the treatment of HCC. The techniques include both freezing (cryoablation) and heating (radiofrequency, microwave, and laser) procedures.[34,39,40,49-52]

### 2.4.1 *Cryoablation*

Cryoablation can be used to treat primary malignant hepatic tumors that by number or location are not surgically resectable. Overall, it is associated with diminished morbidity and mortality relative to resection, and yields a prognosis approximate to that of hepatic resection.[34,40,49] Zhou et al[49] reported 1, 3, and 5 year survival rates of 78 patients undergoing cryoablation of HCC of 63.9%, 40.3%, and 26.9%, respectively. The 5-year survival rate for patients with tumors less than 5 cm was 55% versus 32% for patients with larger tumors. However, the majority of these patients were treated with other treatment techniques including hepatic artery ligation and resection of the frozen tumor. Although cryoablation may offer some advantages over surgical resection it is still an invasive technique that requires a laparotomy in most instances. Miniature probes have been developed recently that may allow the migration to a percutaneous approach.[51]

### 2.4.2 *Heating Ablative Techniques*

Over the last ten years, considerable interest has developed in the thermal ablation techniques that produce heat. Three methods are currently being investigated; microwave, laser, and radiofrequency ablation.[34,39,40,49-54] The majority of the research on microwave ablation has been performed in Japan on small HCCs with minimal experience or knowledge of the technique outside of that country.[40,55-57] Laser ablation has been tested most rigorously in Germany and England. One German researcher, Vogl, has claimed that the technique is highly effective for the treatment of HCC.[55,56] However, Lees[40,58], one of the primary investigators of laser ablation in England, has essentially abandoned the technique in favor of radiofrequency ablation. Overall, the interest and enthusiasm for radiofrequency thermal ablation has far exceeded that for either microwave or laser ablation.

**2.4.2.1** *Radiofrequency Thermal Ablation*

McGahan reported the first use of an interstitial electrode and radiofrequency generator to ablate liver tissue in 1990.[59] The first clinical study detailing the use of RF ablation for the treatment of malignant hepatic tumors was published in 1993.[60] Since then there has been an almost exponential rise in the number of studies published on the subject. All of the studies have shown that RF ablation can be performed safely via a percutaneous needle puncture in an outpatient setting. The morbidity of the procedure is low with few complications and a return to normal physical activity within days of the procedure.[21,22,37,61,62] The reported success rates for local tumor eradication *(analogous to surgical tumor resection with negative margins)* have varied with the type and size of tumor treated. HCC has shown the best response with the range for local tumor eradication of treated tumors varying from 67-98%.[14,21,22,63,64] The size of a tumor has been shown to have a significant effect on outcome. The eradication rate for tumors less than 3 cm appears to be greater than it is for larger tumors.[21,64] An early RFA study by Rossi et al. that included both large and small HCC reported a local recurrence rate of 33% at 6 months[22]. A later study by Solbiati et al[65] that was limited to HCC less than 3cm reported a local recurrence rate at 14 months after RFA of only 13%. The impact of size on outcome has been supported by studies of RFA of colorectal hepatic metastases.[44,64]

## 2.5 Justification for Multi-Institutional Feasibility Trial of RFA of HCC

This protocol is a multi-institutional feasibility trial of percutaneous RFA of HCC, rather than a randomized trial of RFA versus hepatic resection of HCC because of the paucity of definitive information on the efficacy of RFA. To date, almost all studies of RFA of HCC are from individual institutions with minimal standardization of patient and therapeutic variables between studies. Furthermore, the outcome of the individual studies has varied considerably. The goal of this feasibility study is to generate sufficient observational data upon which to base and direct future investigations. The study will be multi-institutional with standardization of eligibility, treatment technique, and method of assessing outcome.

# 3.0 SPECIFIC AIMS/OBJECTIVES

## 3.1 Primary Objective

To estimate the proportion of participants undergoing solitary or repetitive percutaneous RFA treatment sessions whose livers have no identifiable tumor by CT scan at 18 months following initiation of therapy.

## 3.2 Secondary Objectives

**3.2.1** Explore the impact of solitary versus repetitive RFA on the primary objective;

**3.2.2** Explore the impact of tumor size on the primary objective;

**3.2.3** Evaluate for a possible correlation between the MELD Score and the primary objective;

**Note:** Per DSMC review and recommendations on May 17, 2007, the decision has been made that the two groups with MELD scores >15 will be closed for accrual. The study will only enroll participants with MELD score <15. Therefore, this objective will not be pursued.

**3.2.4** Estimate the local and remote intrahepatic and extrahepatic tumor recurrence rates and their impact on the primary objective;

**3.2.5** Explore the impact of tumor size on the local control rates;

**3.2.6** Explore the impact of solitary or repetitive RFA with or without local/regional control on the development of extra-hepatic tumor;

**3.2.7** Estimate the local tumor eradication rate as determined by examination of whole liver specimens obtained via autopsy or explanation versus that determined by CT scan.

## 4.0 STUDY OVERVIEW

At least ten (10) participating clinical sites will be enrolling a total of 120 study participants with HCC and cirrhosis. Forty (40) eligible participants will be stratified, for a total of 120 enrolled participants, to each 3 strata based on the MELD Score. MELD Scores falling within one of 3-groups: MELD Score >25, 15-25, and <15. Forty participants will be recruited into each group for a total of 120 enrolled participants. Enrollment period for this trial will be 1.5 years with an average enrollment of 10 participants at each site per year.

**Note:** Per DSMC review and recommendations on May 17, 2007, the decision has been made that the two groups with MELD scores >15 will be closed for accrual. The study will only enroll participants with MELD score <15. Therefore, the study design is not stratified anymore and the total sample size is 40.

Each participant will be evaluated to determine eligibility. Eligible participants will have no previous or current treatment(s) for HCC by any methods (no radiation therapy, chemotherapy, chemoembolization, and cryo-ablation). All participants will be consented with an IRB approved, site-specific informed consent form prior to conducting any study related procedures and must not be treated by any other methods while on this study.

Once the initial RFA treatment has been performed, abdominal CT scan will be obtained either during recovery or within one week of the initial RFA. CT scans will be conducted every 3 months after the initial RFA treatment. Participants will be contacted via telephone after each

RFA ablation per protocol (section 9.5.5). Final CT scan of the abdomen and chest to determine efficacy of the RFA treatment and for the presence or absence of intrahepatic and extrahepatic tumor will be conducted at 18 months.

## 5.0 PARTICIPANT SELECTION

### 5.1 Inclusion Criteria

**5.1.1** Participants 18 years and older;

**5.1.2** Biopsy proven cirrhosis, or typical findings of cirrhosis by CT scan and/or MRI scan;

**5.1.3** Biopsy proven hepatocellular carcinoma (HCC), or a discrete hepatic tumor(s) as defined by the Barcelona criteria (2 imaging studies showing hypervascular tumor > 2cm, or single imaging study showing hypervascular tumor > 2cm with AFP ≥ 400 ng/mL), or a discrete hypervascular tumor present on two consecutive imaging studies (CT or MRI) with documented growth of > 1cm in diameter;

**5.1.4** Hepatic tumor burden meeting the Milan Criteria: 3 or fewer tumors ≤ 3.0 cm, or a single tumor > 3.0 cm but ≤ 5 cm in diameter. (Note: Vague hypervascular nodules ≤ 1cm and less than 3 lesions in number will not be included in tumor count, but will not preclude enrollment.);

**5.1.5** All identified tumors > 1cm are deemed treatable by percutaneous RFA by the site PI;

**5.1.6** All tumors ≥ 1 cm from the main, right and left portal veins (hepatic veins not included);

**5.1.7** All tumors ≥ 1 cm from hollow viscera;

**5.1.8** Performance status 0-2 on Zubrod Performance Scale (see Appendix V);

**5.1.9** Serum creatinine ≤ 2.0 mg/dl;

**5.1.10** Study-specific signed informed consent;

**5.1.11** Not a candidate for surgical resection (See 5.3.2 & Appendix VIII, Definition #13);

**5.1.12** No previous or current treatment for HCC by any method (no radiation therapy, chemotherapy, chemoembolization, and cryo-ablation) and agrees not to be treated by these therapies while on this study.

**5.1.13** Chest CT and abdominal CT scan and/or abdominal MRI scan within 60 days prior to initial RFA treatment. Outside CT scans or MRI scans performed greater than 60 days prior to treatment or deemed unacceptable, only CT scans will be repeated per the imaging protocol found either on the ACRIN website or in the section 13.0 of the protocol.

### 5.2 Exclusion Criteria

**5.2.1** Prior treatment for HCC by any method;

**5.2.2** Pregnant women are ineligible because it is unknown what effect RF ablation may have on the developing fetus;

**5.2.3** Surgical candidate(See 5.3.2 & Appendix VIII, Definition #13);

**5.2.4** Unbiopsied tumor(s) failing Barcelona or interval growth criteria;

**5.2.5** Tumor(s) < 1cm from main, right , or left portal veins, or hollow viscera;

**5.2.6** Hepatic or portal vein tumor invasion;

**5.2.7** Excessive intrahepatic tumor burden (> 3 hepatic tumors or a tumor > 5cm, or more than 3 vague hypervascular nodules greater than 1 cm);

**5.2.8** Tumors untreatable by percutaneous ablation as determined by site PI;

**5.2.9** Extrahepatic tumor;

**5.2.10** Uncorrectable coagulopathy;

**5.2.11** Serum creatinine > 2 mg/dl;

**5.2.12** Active infection (Symptomatic bacterial and fungal infection – newly diagnosed and/or requiring treatment);

**5.2.13** Choledochoenteric anastomosis;

**5.2.14** Sphincterotomy of duodenal papilla;

**5.2.15** Absolute contraindication to intravenous iodinated contrast (Hx of significant previous contrast reaction, not mitigated by appropriate pre-medication).

## 5.3 Evaluation of Potential Participants for Eligibility

**5.3.1** To be completed within 60 days prior to initial RFA treatment: Chest CT and abdominal CT and/or abdominal MRI scan per protocol. Outside CT scans or MRI scans will be accepted provided that they meet the quality control guidelines in ACRIN website, http://www.acrin.org/6673_protocol.html. Outside CT scans or MRI scans performed greater than 60 days prior to treatment or deemed unacceptable, only CT scans will be repeated per the imaging protocol found either on the ACRIN website or in the section 13.0 of the protocol.

**5.3.2** The surgical oncologist will assess the potential participant to determine if the potential participant is or is not a surgical candidate for liver resection. Non-surgical candidate is defined as a patient who is not appropriate for a liver resection for reasons that include: tumor in an unresectable location, co-morbid disease, insufficient hepatic reserve. (See Appendix IX: Assessment of Tumor Resectability Form)

**5.3.3** Laboratory tests to be completed within 14 days prior to RFA treatment: CBC with platelets, PT, PTT (an INR may be done in place of a PT and PTT), Comprehensive Metabolic Profile (Chem12: Sodium, Potassium, Chloride, Glucose, BUN, Creatinine, Calcium, Phosphorus, Total Protein, Albumin, SGOT, SGPT, Total Bilirubin), Ammonia, GGT, LDH, AFP. Laboratory tests may be repeated just prior to ablation session if clinically indicated or per sites standard of care.

**5.3.4** Medical history obtained within 14 days prior to RFA treatment. (Hx includes absence or presence of pacemaker, no previous or current treatment for HCC, etc.)

**5.3.5** Physical exam within 14 days prior to RFA treatment.

**5.3.6** Assessment of performance status on the Zubrod Performance Scale within 14 days prior to RFA treatment.

**5.3.7** Pregnancy test within 24-hours prior to RFA treatment for women of childbearing potential.

**5.3.8** Aspirin and nonsteroidal anti-inflammatory medications, antiplatelet medications, or warfarin must be discontinued prior to the procedure for a time period that is appropriate given the drug half life and the drugs known antiplatelet activity (e.g., aspirin for 7 days and ibuprofen 24 hours).

**5.3.9** Low molecular weight heparin preparations must be discontinued 12 hours prior to procedures.

## 5.4 Recruitment and Screening

Medical and surgical oncologists and their staff who agree to support the trial will identify participants for the trial. Participants also may be identified by personnel involved in the institution's liver transplant program, site radiologists, imaging staff, or by a research associate.

The Protocol Specific Application (PSA) will require site investigators to record:

1. A lead medical and surgical oncologist from their practice who agree to support the trial by identifying, informing and referring potential participants.
2. Historical data for the past two years from each designated oncology practices and transplant programs regarding the number of participants who would have met the protocol's eligibility criteria.
3. A strategy for educating potential referrers and their staff about the trial and the process for participant identification and consent.

The PSA also will gather information about materials sites would find helpful for participant recruitment such as brochures, posters, and letters. ACRIN will use this information to develop a trial communications plan and other related materials. All materials used for participant recruitment must be reviewed and approved by each institution's IRB.

## 5.5 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. Institutions that wish to join the ACRIN 6673 trial are required to complete the PSA as found on the ACRIN web site, www.acrin.org/6673_protocol.html. ACRIN Institutional Participants Committee (IPC) reviews all PSAs to ensure the participating sites can perform the protocol requirements that relate to the study's primary aims. In addition, sites will be required to answer questions in the PSA about the institution's ability to enroll minority participants to help ACRIN establish and implement minority and gender recruitment strategies. ACRIN's goal is to establish minority and gender recruitment goals that reflect as closely as possible the most recent national census.

- **Demographic Information Obtained:** The PSA application will request documentation of minority and female patient encounters for the most recent two years for the institution, and (if available) for the oncology department.

- **Clinician Diversity:** It is well documented that people are much more likely to trust and want to be a part of programs in which the representatives look like them and come from their culture. As such, institutions will record information about the minority representation of the study team, including information about minority clinicians who could potentially refer patients into the study.

- **Institutional Minority Recruitment Efforts:** Institutions will be asked to provide information about institutional programs that work to recruit minority participants into clinical trails.

## 6.0 SITE SELECTION

### 6.1 Institution Requirements

**6.1.1** Site must have completed and sent in the ACRIN general and protocol specific applications for approval. (See Appendix IV for protocol specific application information)

**6.1.2** Oncology practice and transplant program support sufficient to allow adequate participant enrollment as documented in the protocol specific application.

**6.1.3** An interventional radiologist who:

**6.1.3.1** has prior experience in performing percutaneous RF ablation of hepatic tumors (minimum experience = 15 patients, 5 of which must have been treated with the ValleyLab's device).

**6.1.3.2** agrees to follow RF ablation treatment protocol, imaging protocols, and follow-up timetable.

**6.1.3.3** will identify key medical and surgical oncologists to support the trial.

**6.1.3.4** will develop and implement a strategy to educate the medical and surgical oncologists and their staff about the trial.

**6.1.4** A helical CT scanner with power injector.

**6.1.5** ValleyLab's ablation equipment.

### 6.2 IRB Approval and Informed Consent

All institutions must have site-specific Institutional Review Board (IRB) approval for the ACRIN 6673 protocol and informed consent form. (See Appendix I for ACRIN 6673 informed consent form template.) The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. A copy of the IRB approval letter and a copy of the IRB approved, site-specific consent form must be on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: Protocol Development and Regulatory Compliance Department) prior to registering the first participant.

### 6.3 Accrual Goals and Monitoring

Each institution is expected to enroll slightly less than one participant per month on to the trial on average, so that 10 sites would collectively enroll an average of 8 participants per month. However, it is anticipated that the accrual rate at each institution will vary relative to the local participant mix and in particular relative to the size of a site's liver transplant program. Thus individual site accrual rates may range from 4 to more than 15 per year. Key personnel (medical oncologist, surgical oncologist, or head of liver transplant program) at each participating site must sign a letter agreeing to facilitate participant recruitment. The ACRIN Biostatistics and Data Management Center (BDMC) will monitor and report on participant accrual. Accrual reports will be reviewed bi-weekly for the first six months with the intention of discovering and

resolving any recruitment barriers. The trial PI and his designees will comprise the "Participant Enrollment Support Committee." Committee members will be responsible for monitoring the accrual rates for individual institutions. Should an institution fall below 50% of the expected accrual reported on the Protocol Specific Application after a three months from the time the site is open for enrollment, the Participant Enrollment Support Committee will work with the institution to identify accrual barriers and develop strategies for meeting accrual goals.

## 7.0 ONLINE REGISTRATION SYSTEM

### 7.1 Using the Online Registration System

Once the investigator-designated research staff (i.e. the Research Associate [RA]) has determined the participant to be eligible (see Eligibility Criteria and/or Appendix II), the participant may be consented. Upon obtaining a signed informed consent form, the information of the study participant will be registered by logging onto the ACRIN web site **(www.acrin.org),** which is available 24 hours a day, 7 days a week**.** Please refer to the **ACRIN Procedure Manual**, Section 7.1, **Participant Registration** for instructions. Time elapsed from registration to RFA should not be more than two (2) weeks.

### 7.2 Unsuccessful Registrations

**7.2.1** ACRIN and protocol-specific requirements for Institution participation are maintained within the Administrative database. The protocol specific attributes are then interfaced with the web application for on-line verification of site participation acceptance. If the institution has not met all the regulatory requirements based on the required attributions within the database, a screen that includes a brief explanation of the failure to gain access to the registration screens is projected. If during the completion of the eligibility questions a participant is deemed ineligible based on a response, a message box appears to instruct the research staff to contact the Data Management Center.

**7.2.2** In the unlikely event that the ACR web registration site is not accessible, participating sites may still register a participant by faxing the completed eligibility checklist to the DMC at the ACR (215-717-0936, ATTN: PARTICIPANT REGISTRATION). ACR staff will fax a response to the registering site with the confirmation of registration and participant case number as soon as possible.

## 8.0 STUDY PROCEDURES

### 8.1 Pre-Registration Visit – Determine Eligibility

- Prior medical history reviewed;
- Prior abdominal CT and/or abdominal MRI scans and chest CT scan reviewed. **NOTE**: prior abdominal MRI images can be used to determine eligibility for enrollment in this trial, but not as part of the protocol follow-up imaging scans;
- Chest and abdominal CT scans, if protocol criteria are not met, are ordered;
- The surgical oncologist will review Assessment of Tumor Resectability to determine if the potential participant is **or** is not a liver resection candidate (See Appendix IX);
- Laboratory tests are ordered: CBC with platelets, PT, PTT (an INR may be done in place of a PT and PTT), Comprehensive Metabolic Profile (Chem12: Sodium, Potassium, Chloride,

Glucose, BUN, Creatinine, Calcium, Phosphorus, Total Protein, Albumin, SGOT, SGPT, Total Bilirubin), Ammonia, GGT, LDH, AFP.

- Patients failing to meet the Barcelona Criteria or growth criteria for the diagnosis of HCC must be biopsied and positive diagnosis of HCC must be confirmed prior to registration.

## 8.2 VISIT 1 – Baseline: Within two (2) weeks prior to registration/ablation

**NOTE:** Eligible participants must agree to not being treated for HCC by any methods, such as chemotherapy, radiation therapy, chemoembolization, cryoablation while on this study.

- Participant provided a signed informed consent form (prior to implementation of any study-related procedures);
- Pre-RFA targeted hepatic sonogram performed, if ultrasound is to be used as the guidance technique for ablation;
- Medical history: Participant self-report conducted;
- Physical examination performed;
- Laboratory tests conducted;
- Beta hCG blood test for Pregnancy conducted within 24-hours of RFA treatment (Must have a negative pregnancy result to become eligible);
- Chest CT and abdominal CT scans and/or abdominal MRI scans are performed. Outside CT scans or MRI scans performed greater than 60 days prior to treatment or deemed unacceptable, only CT scans will be repeated per the imaging protocol found either on the ACRIN website or in the section 13.0 of the protocol.
- Assessment of performance status on the Zubrod Performance Scale;
- EKG to be conducted.

## 8.3 VISIT 2 - Registration/Ablation Visit

- Eligible participant is registered. **Note:** Registration of the participant can occur within 14 days prior to the ablation if all the eligibility criteria have been met and continue to meet the criteria; and the participant has signed the informed consent form;
- Percutaneous ablation performed on one or more hepatic HCC percutaneously;
- Recovery after ablation for participant per PI discretion and/or institution's standard of care practice;
- Post-ablation laboratory tests performed: CBC with platelets, Comprehensive Metabolic Profile (Chem12: Sodium, Potassium, Chloride, Glucose, BUN, Creatinine, Calcium, Phosphorus, Total Protein, Albumin, SGOT, SGPT, Total Bilirubin), Ammonia, GGT, LDH. Laboratory tests must be performed within 2 hours after ablation treatment to identify any acute changes;
- Baseline CT scan of liver performed during recovery or within 1-week after ablation treatment.

## 8.4 VISIT 3 – First Week After RFA

- Telephone contact/follow-up with participant to assess for adverse events to be performed per section 15.0;

- Baseline abdominal CT scan obtained within 1-week of the RFA session if it was not performed during recovery.

## 8.5 VISIT 4 – 3 Months After Initial RFA Treatment

- Laboratory tests performed: Comprehensive Metabolic Profile (Chem12: Sodium, Potassium, Chloride, Glucose, BUN, Creatinine, Calcium, Phosphorus, Total Protein, Albumin, SGOT, SGPT, Total Bilirubin), Ammonia, GGT, LDH, AFP;
- Abdominal CT scan performed 3 months (+/- 1-week) following the initial RFA treatment;
- Assess for protocol-specific adverse events per section 15.0.

## 8.6 VISITS 5 Through 8, Every 3 Months After Visit 4

- Laboratory tests performed: AFP
- Abdominal CT scan performed every 3 months (+/- 1-week) following the initial RFA treatment;
- Assess for protocol-specific adverse events per section 15.0.

## 8.7 VISIT 9 – 18 Months After Initial RFA Treatment

- Final abdominal and chest CT scan performed as a final evaluation to determine efficacy of RFA treatment;
- Laboratory tests performed: AFP;
- Assess for protocol-specific adverse events per section 15.0.

## 8.8 Repeat Ablation Visits

- All laboratory tests as noted in section 5.3.3 and 8.3 will be repeated at each repeat ablation treatment;
- Beta hCG blood test for pregnancy conducted with 24-hours prior to each repeat ablation treatment;
- Abdominal CT during recovery or within one (1) week of the re-ablation treatment;
- If residual or recurrent tumor is detected at the site of the treated tumor(s) or elsewhere in the liver, re-ablation will be performed as long as the size of the recurrence does not exceed 5.0 cm, the recurrence is not adjacent to vital structures and there is no evidence of extrahepatic tumor. The re-ablation strategy will follow the same ablation strategy used for primary tumors. Repeat ablation will be allowed throughout the study (for 15 months after initial treatment, including ablation of lesions found at the 15-month follow-up as long as those re-ablations occur within 1 month from the 15-month CT scan);
- Assess for protocol-specific adverse events per section 15.0.

## 8.9 Telephone Contact/Follow-up Visit

- Contact will occur to assess protocol-specific adverse events (AEs) after initial RFA treatment and after each repeat ablation per section 15.0.
- After the initial RFA treatment, participant will be contacted at Day 1, Week 1 and 1 Month. Month 3 follow-up data will be collected at Visit 4 (3 Months after Initial RFA ablation);

- After each repeat ablation, participants will be contacted at Day 1, Week 1, 1 Month, and 3 Months.

  **Note**: Either the participant should be contacted via telephone or an interview should occur in person during a clinic visit. Medical record reviews can be used to assess the participant's status **only** when direct patient contact attempts have been exhausted and have failed.

## 8.10 Study Parameters

| Study Procedure | Pre-Registration Visit | VISIT 1: Baseline/Within 2 weeks Prior to RFA | VISIT 2: Day of Initial RFA Treatment | Day 1 after RFA Treatment | VISIT 3: First Week After Ablation | VISIT 4: 3 Months After Initial Ablation | VISIT 5 – 8: Every 3 Months After Initial Ablation | VISIT 9: At 18 Months | Re-ablation Visit(s)[g] Possible for 15 Months After Initial Ablation[n] |
|---|---|---|---|---|---|---|---|---|---|
| Signed Informed Consent | | X | | | | | | | |
| ACRIN Web Registration | | X[j] | X[j] | | | | | | |
| Medical History | X | X[b] | | | | | X | X | |
| Physical Examination | | X[b] | | | | | | | |
| Chest CT Scan | X[a, m] | X[a, m] | | | | | | X[l] | |
| Abdominal CT | X[a, m] | X[a, m] | X | | X[h] | X | X[c] | X | X[h] |
| General Anesthesia/ conscious sedation/local sedation | | | X | | | | | | X |
| I.V. contrast agent(s) | | | X | | X | X | X | X | X |
| Image Guidance (US, CT, or MR) | | | X | | | | | | X |
| Tumor Biopsy Results/Findings | X[d] | | | | | X[d] | X[d] | X[d] | X[d] |
| Targeted Hepatic Sonogram | | X[e] | | | | | | | |
| PT, PTT (INR may be done in place of PT and PTT) | | X[b] | | | | | | | X[b,i] |
| CBC with platelets | | X[b] | X[j] | | | X | | | X[b,i] |
| Chem 12,GGT,LDH, NH3 | | X[b] | X[j] | | | X | | | X[b,i] |
| EKG | | X[b] | | | | | | | |
| Alpha-fetoprotein (AFP) | | X[b] | | | | X | X | X | X[b] |
| Pregnancy Test | | | X[k] | | | | | | X |
| Performance Status | | X | | | | X | X | X | |
| Telephone Follow up | | | | X[f] | X[f] | X[f] | | | X[f] |

a. Within 60 days prior to initial RFA. **NOTE** – abdominal MRI will be allowed to determine eligibility for enrollment in this trial, but not for f/u imaging.
b. Within 2 weeks prior to initial and repeat RFA.
c. Abdominal CT performed every 3 months (+/- 1 week) following the initial RFA treatment.
d. Biopsy performed as necessary to resolve equivocal CT scan findings.
e. If ablation is to be performed under sonographic guidance.
f. Telephone follow-up will be completed at 1 day, 1 week, 1 month and 3 months post ablation (3 months phone contact will occur only for repeat ablations, since the 3 Month follow-up data will be collected at the 3 Month Visit after Initial RFA ablation). This follow-up scheme will be repeated after each ablation session.
g. Laboratory studies to be repeated prior to repeat ablation sessions.
h. Abdominal CT may be deferred for up to one week after initial and repeat ablations.
i. Post-ablation laboratory test performed within 2 hours of RFA ablation procedure to identify any acute changes.
j. Registration of the participant can occur within 14 days prior to the ablation if all eligibility criteria have been met and continue to be met; and participant has signed the informed consent form.
k. Beta hCG blood test for pregnancy conducted within 24-hours of ablation for women in childbearing potential.
l. Chest CT performed at 18 months after initial ablative session to assess for possible metastases.
m. If outside of 60 day window a repeat CT scan must be performed.
n. Final re-ablation, if indicated, must occur within 1 month from the 15-month follow-up CT scan.

# 9.0 RFA TREATMENT PLAN

## 9.1 Ablation Strategy

**9.1.1** Per the eligibility criteria, participants will have 1-3 tumors (the primary tumors) at the time of enrollment. Treatment of all primary tumors may take one or more ablations performed during one or more ablation sessions to achieve complete treatment as determined by follow-up CT scans. All ablative sessions performed on the primary tumors prior to the first 3-month follow-up CT scan will be deemed the "primary therapeutic effort". The efficacy of the primary therapeutic effort will be judged based on the findings present on the 3-month CT scan. If residual or recurrent tumor is detected at the site of the treated tumor(s) or elsewhere in the liver, re-ablation will be performed as long as the size of the recurrence does not exceed 5.0 cm, the recurrence is not adjacent to vital structures and there is no evidence of extrahepatic tumor. In participants who require additional ablative sessions after the 3-month CT scan, the tumor status as determined by subsequent CT scans will be deemed the "secondary or assisted outcome". The overarching ablative strategy throughout the study is to render each participant free from intra-hepatic tumor (as determined by the CT scan) at 18 months after the first ablative session.

**9.1.2 Ablation Strategy for individual tumors:** The following are the minimum requirements for ablating tumors of a given size. The recommended ablation needles are the smallest that can be used for the specified tumor. The recommended number of ablations is the minimum that can be performed for the specified tumor; however, more ablations may be performed at the operator's discretion. Since all tumors are not perfect spheres, the operator should use the maximum diameter to choose the appropriate ablation strategy. All tumors should be treated with the goal of ablating the tumor as well as a $360^{o}$ 5-10mm tumor free margin around each tumor (see diagram in Appendix VII and Reference Number 37).

**9.1.2.1** Tumors ≤ 1cm = 1 ablation with 2cm tip single needle.

**9.1.2.2** Tumors >1 but ≤ 2cm = 1 ablation with 3cm tip single needle.

**9.1.2.3** Tumors >2 but ≤ 3.0cm = 1 ablation with cluster needle or 2 or more ablations with the 3cm tip single needle used independently or with the switchbox.

**9.1.2.4** Tumors >3 but ≤ 5.0cm = 2 or more ablations with cluster needle or 3 or more ablations with the 3cm tip single needle used independently or with the switchbox.

**9.1.3** The ValleyLab's generator must be operated in the automated mode whereby the power is adjusted relative to the impedance. The beginning impedance and the 1-minute post ablation temperature are to be recorded on the RFA Treatment Forms. If the 1-minute post ablation temperature is less than 60ºC a repeat ablation cycle (12 minute cycle without switchbox, and 16 minute with switchbox) with the needle in the same position must be performed.

## 9.2 Ablation Equipment

The same brand RF ablation device will be used for all participants to limit performance variability between devices. The ValleyLab's RF ablation system was chosen, as it is the device most commonly used for percutaneous RF ablation.

**9.2.1** ValleyLab 500-KHz, monopolar RF ablation generator, Model CC-1, with automated ablation algorithm.

**9.2.2** ValleyLab Cooled Tip RF ablation needles:
Single, 2 cm tip (Model No. CT 2020),
Single, 3 cm tip (Model No. CT 2030),
Cluster 3-prong, 2.5 cm tip (Model No. CTC 2025).

**9.2.3** ValleyLab Generator SwitchBox.

## 9.3 Procedure

**9.3.1** Performed under conscious sedation, local sedation, or general anesthesia per site standard of care.

**9.3.2** Imaging (US, CT, or MR) performed to plan and guide ablation.

**9.3.3** Two or four RF ground pads placed on participant. For single needle electrodes 2 ground pads are used with 1 ground pad applied anteriorly to each of the participant's thighs. For cluster needle electrodes 4 ground pads are applied, 2 to each of the participant's thighs with one placed anteriorly and the other placed posteriorly. All ground pads are to be applied perpendicular to the length of the thigh.

**9.3.4** Skin at puncture site anesthetized (conscious sedation only) and small skin incision(s) made as necessary to facilitate passage of RF ablation electrode.

**9.3.5** Ablation electrode placed percutaneously into tumor under image guidance.

**9.3.6** Baseline impedance recorded on RFA Treatment Form.

**9.3.7** 12-minute ablation performed on each tumor without switchbox (number of ablations performed per tumor as per ablation strategy, Section 9.1). Sixteen-(16) minute ablation cycle is to be used with switchbox and multiple probes. When the switchbox is being used, the 16-minute ablation cycle should be initiated by driving each probe to impedance independently. If an ablation cycle is terminated prior to the specified time (12 minutes without switchbox / 16 minutes with switchbox), the actual time of the ablation and the reason the ablation was prematurely terminated must be documented on the RFA Treatment Form.

**9.3.8** One-minute post-ablation temperature obtained after each ablation.

**9.3.9** Needle track cauterized as deemed necessary by the physician performing the procedure.

**9.3.10** Additional needle insertions performed as necessary to ablate all targeted tumors.

**9.3.11** After all tumors are ablated, participant observed for 4-6 hours or admitted for overnight observation per site PI's discretion and/or the institution's standard of care practice.

**NOTE:** Participants may have non-protocol liver tumor(s) ablated if indicated per site's standard of care. ACRIN data regarding RFA treatment of non-protocol tumors (ACRIN TF and RA forms) will not be collected.

**9.3.12** RFA Treatment Form and the Liver Diagram completed, including location and size of tumors, number of ablations per tumor, baseline impedance prior to each ablation, length of time of each ablation, one-minute post-ablation temperature after each ablation, number and location of cauterizations performed, and complications encountered.

**9.3.13** Abdominal CT scan can be either obtained while participant is in recovery to check for complications and assess adequacy of ablation or be deferred for up to one week after ablation.

**9.3.14** Post-ablation laboratory tests must be performed within 2 hours of RFA ablation procedure (Section 8.3) to identify any acute changes.

## 9.4 Procedural Documentation

**9.4.1** RFA Treatment Form filled out.

**9.4.2** Ablated tumors numbered in accordance with numeric assignment established on Initial Evaluation Form.

**9.4.3** Tumors located by Couinaud hepatic segment.

**9.4.3.1** Couinaud hepatic segment for each tumor recorded on RFA Treatment Form.

**9.4.3.2** Location of each tumor drawn on the liver diagram and numbered per Initial Evaluation Form and RFA Treatment Form.

**9.4.4** Location of each cauterization recorded on Treatment Form and on the Liver Diagram.

## 9.5 Evaluation And Follow-up

**9.5.1** Abdominal CT scan within one (1) week following the initial ablation session and every three (3) months thereafter for 18 months. A chest CT scan will be performed to evaluate for extrahepatic metastases at 18 months. Additional abdominal CT scans may be performed following repeat ablation sessions to assess the adequacy of the treatment; however, the established 3-month interval from the initial RFA ablation for follow-up abdominal CT scans will be maintained.

**9.5.2** The findings on follow-up abdominal CT scans will be recorded on the IM Form.

**9.5.2.1** All abdominal CT scans performed after the initial enrollment CT scan will be interpreted using the numeric tumor assignment established on the Initial Imaging Form and the RFA Treatment Forms.

**9.5.2.2** Each tumor will be evaluated for local success or failure using criteria specified in section 10.0.

**9.5.2.3** All abdominal CT scans will be evaluated for intrahepatic tumor as well as extrahepatic metastases.

**9.5.3** If residual or recurrent tumor is detected at the site of the treated tumor(s) or elsewhere in the liver, re-ablation will be performed as long as the size of the recurrence does not exceed 5.0 cm, the recurrence is not adjacent to vital structures and there is no evidence of extrahepatic tumor. The re-ablation strategy will follow the same ablation strategy used for primary tumors. Final re-ablation, if indicated, must occur within 1 month from the 15-month CT scan.

**9.5.4** AFP will be drawn within 1 week of the abdominal CT examinations to help interpret equivocal findings of tumor recurrence. If AFP is elevated over baseline (Baseline AFP is the lowest level of AFP before or after RFA treatment) any suspicious area should be biopsied or followed by CT scans to detect evidence of tumor growth. For the purpose of the study, pathologic proof and unequivocal abdominal CT findings will be used to determine the presence or absence of tumor.

**9.5.5** Telephone follow-up to assess for adverse events will be administered at 1 day, 1 week, 1 month and 3 months post ablation (3 months phone contact will occur only for repeat ablations, since the 3 Month follow-up data will be collected at the 3 Month Visit after Initial RFA ablation) by a research assistant or nurse coordinator. All participants should be followed at least 3 months post ablation and after each ablation session.

**Note**: Either the participant should be contacted via telephone or an interview should occur in person during a clinic visit. Medical record reviews can be used to assess the participant's status **only** when direct patient contact attempts have been exhausted and have failed.

**9.5.6** All pathology slides from tumor biopsies performed before or after ablation will be sent to ACRIN central pathologist(s) for review.

**9.5.7** If a participant undergoes hepatic resection of ablated tumors, hepatic transplantation, or autopsy, the pathology specimens will be evaluated both locally and by ACRIN designated pathologist(s) for the presence or absence of tumor at the ablated sites or elsewhere in the liver.

## 9.6 Off-Study Criteria

If a participant undergoes another treatment for HCC by any method other than RFA, and if there is evidence of extrahepatic tumor on the follow-up abdominal CT scan, the participant will discontinue the serial CT scans which occur after the initial ablation session at every 3 months for 18 months. In addition, protocol re-ablation of tumors or ablation of new tumor(s) will not be allowed.

The following information will be collected for any participants that meet the off-study criteria:

1. Date of Off-study: the start date of other treatment for hcc, or the date of abdominal scan CT scan with evidence of any extrahepatic disease;
2. Reason for the off-study;
3. Type of non-protocol treatment, if applicable;
4. Participant status: Living, deceased, unknown, or unable to contact;
5. Performance status.

## 10.0 Outcome Criteria

## 10.1 CT Criteria

The primary outcome is to estimate the proportion of participants undergoing solitary or repetitive percutaneous RFA treatment sessions whose livers have no identifiable tumor by CT scan at 18 months following initiation of therapy.

**10.1.1** The RECIST criteria **will not** be used in this study to determine local tumor response to therapy as the goal of ablation is to create a zone of coagulative necrosis that is substantially larger than the original tumor. Once accomplished, the ablated tumor and ablated cuff of "normal" liver become indistinguishable by existing imaging techniques. Thus, if the RECIST criteria were used to evaluate RF ablations, effective ablations would be erroneously classified as local failures on the basis of enlargement. Given this significant limitation of the RECIST criteria the CT findings for local recurrence as reported by Chopra et al[61] will be used.

**10.1.2 Local intra-hepatic tumor**

The status of each ablated tumor will be assessed per CT scan and classified as tumor present, absent, or indeterminate using the criteria published by Chopra et al. If residual or recurrent tumor is detected at the site of the treated tumor(s) or elsewhere in the liver, re-ablation will be performed as long as the size of the tumor does not exceed 5.0 cm, not adjacent to vital structures, and no evidence of extrahepatic tumor. Final re-ablation, if indicated, must occur within 1 month from the 15-month CT scan.

**10.1.2.1** Tumor absent: homogeneous avascular sharply marginated ablation site that is unchanged in size or smaller than the immediate post-ablation thermal injury.

**10.1.2.2** Tumor present:

a. growth of ablated tumor (excluding growth due to biloma or abscess formation),

b. residual or new enhancement of ablated tumor (excluding benign peri-ablational enhancement),

c. contiguous viable tumor.

**10.1.2.3** Indeterminate: imaging findings that do not clearly fulfill the CT criteria for success or failure.

**10.1.3 Remote intra-hepatic tumor**: The presence of new tumor remote from previously ablated tumor sites will be interpreted based on the standard CT criteria for the diagnosis of HCC and recorded. If residual or recurrent tumor is detected at the site of the treated tumor(s) or elsewhere in the liver, re-ablation will be performed as long as the size of the tumor does not exceed 5.0 cm, not adjacent to vital structures, and no evidence of extrahepatic tumor. Final re-ablation, if indicated, must occur within 1 month from the 15-month CT scan.

Once ablated, the status of each tumor will be assessed using the same criteria as previously stated.

**10.1.4 Extrahepatic tumor**: All of the CT scans will be evaluated for the presence of extrahepatic tumor.

### 10.1.5 Reader Evaluation

Scans from each institution will be read centrally to determine the presence or absence of tumor with results recorded on the CX Form. If the central reader disagrees with the interpretation from the enrolling institution's local reader, the CT scan will be read by a second central reader with the majority opinion of the three interpretations being used as the official interpretation. A specific attempt will be made to resolve indeterminate results by majority rule; however, it is anticipated that a small number of tumors will remain unresolved by imaging or biopsy at the conclusion of the study. Sites with incorrect reports or disproportionately poorer local success rates relative to other institutions will be contacted by the Protocol PI to seek a potential remedy to the problem.

## 10.2 Pathology Criteria

In participants whom undergo resection of their ablated hepatic tumors, transplantation of their native livers, or who expire and undergo autopsy, the result of the pathological evaluation of the specimens will be used to determine the condition of tumor in the liver or the presence of extra-hepatic metastases. Each hepatic specimen will be assigned the following:

**10.2.1 Local intra-hepatic tumor**: The status of each ablated tumor will be assessed and classified as tumor present or absent in or contiguous to ablated tumor;

**10.2.2 Remote intra-hepatic tumor**: The presence of new tumor remote from previously ablated tumor sites will be documented.

## 10.3 Survival Data

**10.3.1** Alive and free from tumor

**10.3.2** Alive with residual or recurrent tumor

**10.3.3** Dead and free from tumor

**10.3.4** Dead with residual or recurrent tumor

# 11.0 PATHOLOGY INFORMATION

## 11.1 Diagnosis of Cirrhosis

The nature of proof of cirrhosis can be by hepatic biopsy or clinical history with typical CT and/or MRI findings of cirrhosis (nodular liver, splenomegaly, varices, and ascites). If available, pathology reports from liver biopsies should be sent to ACRIN pathologists.

## 11.2 Diagnosis of HCC

**11.2.1** All tumors failing to meet the Barcelona Criteria or growth criteria for the diagnosis of HCC must be biopsied and those specimens must be submitted to the ACRIN core pathologist for review. The type of the biopsy will be dictated by the enrolling site and may either be a core biopsy or a fine needle aspiration (FNA). All biopsies will be interpreted by both the local pathologist and an ACRIN pathologist(s).

A central pathologist will review the available FNA or core biopsy and the report of the local pathologist. The local pathologist's interpretations of the material will be recorded on form PL, and the ACRIN pathologist's interpretations will be recorded on form P4. If there is disagreement with the local pathologist's diagnosis of the presence or absence of hepatocellular carcinoma, then the pathologic material will be sent to a second ACRIN

central pathologist or designee for another interpretation. The true pathologic diagnosis will be considered the diagnosis that is agreed upon by two out of three interpreters. This final interpretation will be recorded.

**11.2.2** All hepatic resection, hepatectomy specimens, or autopsy specimens will be evaluated for the presence or absence of HCC at ablated sites or elsewhere in the liver. The gross pathology procedure will consist of cutting the specimen in the same plane as the CT scan at a maximum of 1cm slice thickness. The imaging forms will be used to correlate tumor and ablation sites according to the original tumor number assignment scheme. Representative specimens from each ablation site and any other site suspicious for HCC will be submitted for H&E staining. The results of the pathology evaluation will be recorded following the original tumor number assignment scheme. The histology slides will be interpreted by both the local pathologist and one ACRIN pathologist. The ACRIN pathologist will review the available slides and the report of the local pathologist. The ACRIN central pathologist's interpretations of the material will be recorded on the P4 form. If there is disagreement with the local pathologist's diagnosis of the presence or absence of hepatocellular carcinoma at one or more sites, then the slides will be sent to a second ACRIN pathologist or designee for another interpretation. The true pathologic diagnosis will be considered the diagnosis that is agreed upon by two out of three interpreters.

The results of the pathological evaluation of each hepatic resection or hepatectomy specimen will be classified in the following manner:

- Local tumor absent: **no** tumor contiguous with an ablated site;
- Local tumor present: tumor contiguous with an ablated site;
- Remote tumor absent: **no** viable tumor remote to an ablated site;
- Remote tumor present: viable tumor remote to an ablated site.

## 11.3 Pathology Submission

All HCC pathology specimens will be sent to an ACRIN central pathology site within 15 working days of case submission to ACRIN. All specimens will be returned within 30 days to the facility where the participant underwent biopsy after review by the central pathologist(s). A copy of the pathology report will be attached to the data collection form. Slides will be prepared according to the standard histology procedure (i.e. hematoxylin and eosin stained).

For the diagnosis and post ablation biopsies, the following should be sent for review to the ACRIN pathologist(s). If only one of the following is available [histology or cytology], the one specimen can be sent:

- Histology: A re-cut of the representative slides of the original core biopsy **or** the original glass slides should be sent to the ACRIN pathologist listed below.
- Cytology: The original glass slides of the core biopsy **or** fine needle aspiration biopsy should be sent to the ACRIN pathologist.

For hepatic specimens from transplant, resection, or autopsy, the following should be sent to the ACRIN pathologist:

- A standard representative slides that were prepared for local site diagnosis and review: This could be either the original glass slides **or** a re-cut of the entire representative slides.

Pathology specimens can be labeled with the ACRIN study and case number of the participant. The pathology report can have the participant personal identifiers replaced with the study and case numbers. Samples should be sent via express mail. The following should be sent with the specimens to ACRIN central pathologist(s): the pathology specimen's return address information, the Central Pathology Form (P4), the Pathology Transmittal Form (PC), and the pathology report (P1) to the following address:

**Shahla Masood, M.D.**
**Attn: Stephanie Crawford**
**ACRIN RFA Study 6673**
**University of Florida**
**655 West 8th Street**
**Jacksonville, FL 32209-6511**
**(904) 244-4387**
**FAX # (904) 549-4060**
Shahla.masood@jax.ufl.edu

At the same time that the specimen and forms are being shipped to the central pathologist, copies of the P4 form, the PC form and the pathology report (P1) should be faxed to ACRIN 6673 Data Management at 215-717-0936 or mailed to ACRIN 6673 Data Management.

## 12.0 DATA COLLECTION AND MANAGEMENT

### 12.1 General

**12.1.1** The ACRIN web address is **www.acrin.org.**

**12.1.2** Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at the American College of Radiology's Data Management Department in Philadelphia.

**12.1.3** Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the Data Management Center before attempting a re-registration.

### 12.2 Clinical Data Submission

**12.2.1** Upon successful participant registration, a confirmation e-mail containing the registration and case specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply deadlines for queries

about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN website. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling.

**12.2.2** The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as open/alive or until the study is terminated. The case is closed when all data have been received, reviewed and no outstanding data query exists for the case.

**12.2.3** To submit data via the ACRIN website, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for missing data, data that are out of range, and data that are in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form Submission" button is depressed.

**12.2.4** Once data entry of a form is complete, and the summary form reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form Submission" button on the form summary screen and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data completed and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the Data Management Center for resolution of the submission.

**12.2.5** If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

## 12.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

## 12.4 Electronic Data Management

**12.4.1** Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complimentary validation programs are initiated at the Brown Biostatistics Center and the Data Management Center. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC research associate. The validation program generated by BC produces a log of errors, which is sent to the DMC Research Associate (RA) for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC RA at the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution. All BDMC communication with the participating sites is normally done through the Data Management Center.

**12.4.2** If checks at DMC or BC detect missing or problematic data, the DMC RA sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC RA updates the participant's data submission calendar with the due date for the site RA or investigator's response.

## 12.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or research associate may use the Forms Due and Future Due Reports as a case management tool.

## 12.6 Data Quality Assurance

**12.6.1** The Biostatistical Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the Data Management Center (DMC). The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

**12.6.2** A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites.

If patterns are discovered in the data that appear to arise from causes specific to an institution, the Biostatistical and Data Management Center (BDMC) will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance Department (PDRC), until the problem has been resolved. If the BDMC, along with the ACRIN PDRC, cannot find a resolution to the problem, it will be brought to the Steering Committee for further discussion and resolution.

**12.6.3** In addition, the ACRIN Quality Assurance Monitor will review case report forms and source documents at several different time points during accrual period on selected study participants enrolled at each site. In addition, the QA Monitor will review the initial regulatory documents and any revised regulatory documents. This monitoring process is to ensure protocol and regulatory compliance and to provide clarification in completion of the case report forms in order to minimize any inconsistencies or misunderstandings.

## 12.7 Data Collection Forms

Case report forms for data collection for this study are available on the ACRIN 6673 protocol web site, http://www.acrin.org/6673_protocol.html#main. Refer to the individual form Instructions for information regarding form completion and form submission.

# 13.0 IMAGING INFORMATION

## 13.1 Imaging Schedule

**13.1.1** An abdominal CT and/or abdominal MRI scan(s) will be done at screening (within 60 days prior to participant enrollment-if MRI falls outside of 60 days the CT is required). Abdominal CT scan will be done within one week following the ablation (this will be the post-ablation baseline scan). In addition, an abdominal CT scan will be performed every 3 months for 18 months following the initial ablative session.

**13.1.2** A chest CT scan will be done at screening (within 60 days prior to participant enrollment) and at 18 months (± one week) after the initial ablation session to assess for pulmonary metastases.

## 13.2 CT Protocols

**13.2.1 3-Phase Abdominal CT Scan:** Helical non-contrast liver, followed by i.v. contrast injection of 120-150 cc 60% contrast (≥ *20G angiocath, 3-5cc/sec injection rate),* followed by helical scans through the liver during the hepatic arterial phase and portal venous phase. Pitch 1-1.5. Slice thickness 5-8mm. Arterial phase scan delay time 20-30 seconds. Portal venous scan delay time 60-75 seconds. Each vascular phase scan of the liver must be obtained in a single helical acquisition.

**13.2.2 Chest CT Scan:** Helical chest CT scan with slice thickness 5-8mm with or without the use of intravenous contrast material.

## 13.3 MRI Requirements

Abdominal MRI Scan: 1.5 Tesla, Axial T1 GRE, T2 SE non-contrast liver sequences, followed by axial T1 dynamic gadolinium enhanced scans of the liver in hepatic arterial phase and portal venous phase.

## 14.0 IMAGE SUBMISSION

All images for this protocol are requested to be provided in digital format. ACRIN has developed software that allows for electronic transmission to the IMC image archive of images that have been scrubbed of all participant identifiers. This software will be made available for installation to an already existing PC at your site, or an individual PC computers with this software installed will be supplied on a site-by-site basis. ACRIN will be contacting each site individually to determine their readiness and ability to work with this system. Once readiness has been determined, imaging personnel from ACRIN will coordinate the installation and training of this software.

**14.1** In the event the pre ablation CT images are obtained at an outside institution and are unable to be sent to the IMC electronically, they should be burnt to a CD and sent to ACRIN. The information label on the CD should include: the study number, site number, case number, and the date of the exam. They can be mailed to:

ACRIN Image Archive
ACRIN Protocol 6673 Images
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103

**14.2** If the protocol requires secondary review, images maintained at ACRIN Headquarters Image Archive may be distributed to secondary reviewer by using FTP, MOD, or CD-ROM, where appropriate.

### 14.3 Image Quality Review

An ongoing review will be performed by the ACRIN Imaging Specialist to ensure images meet the study specific parameters. Additional three (3) CT exams will be reviewed in the same fashion when the CT scanner is upgraded or a new CT scanner is installed.

## 15.0 ADVERSE EVENTS REPORTING

### 15.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

### 15.2 Definition of Serious Adverse Event

A Serious Adverse Event **(SAE)** is defined as any untoward medical occurrence that is:

- Death;

- Life-threatening (refers to any adverse event that places the subject at immediate risk of death from the event as it occurred; life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death);
- Inpatient hospitalization and/or prolongation of an existing hospitalization (hospitalization refers to an overnight admission). Emergency room visits are not considered serious until one of the above criteria is met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE;
- Results in persistent or significant disability or incapacity (substantial disruption in a person's ability to conduct normal daily living activities);
- A congenital anomaly or birth defect; or
- Other medically important event.

Important medical events are those based upon appropriate medical judgment that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

## 15.3 Adverse Event Grading

Grade is used to denote the severity of the adverse event. An AE is graded using the following categories (provided the term does NOT appear in the current version of the Common Toxicity Criteria for Adverse Events [CTCAE 3.0]):

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

(For terms listed in the CTCAE, the grade is still recorded as 1, 2, 3, 4, or 5; however, the definition of the various grades will be specific to the term being used.)

## 15.4 Adverse Event Attribution

Attribution is the determination of whether an adverse event is related to a study treatment or procedure.

Attribution categories are:

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

## 15.5 Potential Expected and Unexpected Adverse Events

Adverse events may be *expected* or *unexpected*.

- An **expected AE** is one that is described in the protocol, the consent form, or the investigator's clinical brochure.
- An **unexpected AE** is one that has not been described.

## 15.6 Expected Adverse Events

The overall risk of major complications with RFA of liver tumors is less than 3% [36]. The most common risks of the procedure are bleeding (<1%), infection (<1%) and tissue damage (<1%) related to the ablation needle placement. Bleeding is a rare complication using this technique since the procedure involves tissue thermo-coagulation. Pre-procedural coagulation studies are required to identify and allow for correction of coagulopathies that would increase the risk of post-procedural hemorrhage.

*Radiofrequency Ablation:*

Likely to occur:

- Local pain
- Referred pain
- Nausea
- Vomiting

Rarely occur:

- Bleeding
- Significant drop in blood pressure (<90mmHg systolic)
- Infection (RFA site or blood culture)
- Tissue damage
- Ground pad burn
- Tumor seeding
- Post Ablation syndrome: fever, fatigue, and pain at the treated site

Very rarely occur:

- Acute sepsis
- Cardiac arrest
- Renal failure
- Peritonitis
- Pneumothorax

Approximately 30% of participants may experience self-limited fever, fatigue, and arthralgias 3 to 5 days post treatment that may last 5 to 10 days as reported by Dodd et al.[66]

*General anesthesia:*

- Allergic reaction to anesthesia
- Adverse interaction with other medications
- Suppression of airway reflexes
- Respiratory depression/arrest
- Cardiovascular decompensation
- Reduction of gross motor skills
- Death

*Phlebotomy:*

- Syncope
- Dizziness
- Hyperventilation

- Bruising from needles
- Vasovagal reaction
- Wound infection

*IV Contrast agents:*

- Hives
- Breathing difficulties
- Swelling of the throat
- Swelling of other body parts

## 15.7 Recording of Adverse Events

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on adverse events through discussion and, as appropriate, by examination. Information on all expected and unexpected adverse events considered **possibly**, **probably**, or **definitely** related to the RFA study procedures (RFA treatment; laboratory tests; abdominal CT; and general anesthesia) with grades 1, 2, 3, 4, 5 must be recorded immediately into the source document, e.g. adverse event log and/or progress notes of the study participant's chart, and retained at the site. These adverse events must also be recorded in the ACRIN 6673 AE Form (CRF). The site principal investigator must determine grade and attribution of the event in real time.

A **pre-existing condition** is one that is present at the start of the study. A pre-existing medical condition is defined as an adverse event if the frequency, intensity, or character of the medical condition worsens during the study period. At screening visit, any clinically significant findings/abnormalities should be recorded as a pre-existing condition. At the end of study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be documented as adverse events.

All serious adverse events must be recorded in AdEERS single agent template for AE expedited report, in addition to the source document and ACRIN 6673 AE Form (CRF). All serious adverse events (SAEs) must be reviewed by the investigator in real time and reported to the ACRIN, NCI/CIP (via TRI), and the local IRB (per local IRB policy).

All protocol-specific adverse events occurring during the study period must be recorded. The adverse event reporting period for this protocol is defined as the period from the initiation of any study procedures and up to 30 days after the last RFA study procedure (RFA treatment; laboratory tests; abdominal CT; and general anesthesia). Each adverse event must be followed until resolution, stabilization, or until it has been determined that the study procedures or study participation is not the cause. All serious adverse events that are still ongoing at the end of the study must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be **possibly, probably**, or **definitely related** to the study procedures or study participation must be recorded in the source document and ACRIN 6673 AE Form (CRF) and reported immediately.

## 15.8 Regulatory and Reporting Requirements of Adverse Events

**Routine reporting** is defined as documentation of adverse events on source documents and ACRIN 6673 AE Form (CRF), and submission to ACRIN for preparation of a report for Data

and Safety Monitoring Committee (DSMC) review, quarterly reports to CDUS, and the final study report.

**Expedited reporting** is defined as immediate notification of NCI and ACRIN within the specified timeframe outlined in the protocol and the ACRIN Adverse Event Reporting Manual. Routine reporting requirements also apply.

Serious Adverse Events meeting the criteria for expedited reporting, as specified in the protocol, require (a) telephone notification to both NCI and ACRIN within 24 hours of first knowledge of death (ONLY), (b) completed AdEERS report faxed to both NCI/CIP (via TRI) and ACRIN within 10 days of knowledge along with an email confirming fax submission of the AdEERS report, and (c) documentation of event on ACRIN 6673 AE Form (CRF) for submission to ACRIN. Adverse Events meeting the criteria for routine reporting, as specified in the protocol, must be reported using the ACRIN 6673 AE Form (CRF) and submitted to ACRIN.

**15.8.1** Adverse events must be reported for the period of the protocol in which participants undergo primary study procedures (RFA treatment; laboratory tests; abdominal CT; and general anesthesia). The reporting of AEs in this protocol will conform to the following:

1. Grade 1 Expected with an attribution of **possible, probable,** or **definite** must be reported by **routine reporting procedures**.
2. Grade 1 Unexpected AEs with an attribution of possible, probable, or definite must be reported within ten (10) days of first knowledge of the event. Routine reporting procedures also apply.
3. Grade 2 Expected with an attribution of **possible**, **probable**, or **definite** must be reported by **routine reporting procedures.**
4. Grade 2 Unexpected AEs with an attribution of **possible**, **probable**, or **definite** must be reported within ten (10) days of first knowledge of the event. Routine reporting procedures also apply.
5. All hospitalization (or prolongation of existing hospitalization) for medical events equivalent to CTC Grade 3, 4, 5 with an attribution of **possible**, **probable**, or **definite** which precipitated hospitalization must be reported within ten (10) working days of first knowledge of the event.
6. Grade 3 Expected with an attribution of **possible**, **probable**, or **definite** must be reported by **routine reporting procedures.**
7. Grade 3 Unexpected AEs with an attribution of **possible**, **probable**, or **definite** must be reported ten (10) days of first knowledge of the event. Routine reporting procedures also apply.
8. Grade 4 Expected AEs with an attribution of **possible**, **probable**, or **definite** must be reported by **routine reporting procedures.**
9. Grade 4 Unexpected AEs with an attribution of **possible**, **probable**, or **definite** must be reported within ten (10) days of first knowledge of the event by Expedited Written Report. Routine reporting procedures also apply.
10. Grade 5 AEs, or **Deaths** with an attribution of **possible**, **probable**, or **definite** must be reported within 24 hours of first knowledge of the event by Telephone Report to

ACRIN and NCI-CIP (via TRI) and followed by Expedited Written Report within ten (10) days of first knowledge of the event. Routine reporting procedures also apply.

**11.** Assignment of grades (severity level) and attribution for each AE is to be completed at the site by the Site Principal Investigator. Routine reporting procedures also apply.

**15.8.2** All adverse events must be documented in the study participant's chart and case report forms. For expedited adverse events, a copy of the report must be kept on file at the study site. Significant new information on ongoing serious adverse events should be promptly reported to ACRIN.

## 15.9 Expedited Reporting to NCI and ACRIN

**15.9.1** Any serious adverse event (SAE) with an attribution of possible, probable or definite must be reported. Adverse event (AE) of lesser severity and an attribution of possible, probable or definite is reported on ACRIN AE case report forms and submitted with routine data submission. However, the following guidelines require a written report submitted within ten (10) days of the serious adverse event.

**15.9.2** Any **increased** incidence of a **known or expected** AE that has been reported in the literature, in package inserts or in the consent form must be reported with either routine or expedited reporting per ACRIN 6673 protocol.

**15.9.3** All **deaths** with an attribution of **possible**, **probable**, or **definite** while **on study and up to 30 days after the last primary study procedure**, must be reported within 24 hours of first knowledge of the event by Telephone Report to ACRIN and NCI-CIP (via TRI) and followed by Expedited Written Report within ten (10) days of first knowledge of the event.

## 15.10 How to Report

**15.10.1** An expedited adverse event report requires submission to the NCI/CIP (via TRI) and ACRIN using the paper template, "Adverse Event Expedited Report—Single Agent" on the CTEP home page, http://ctep.info.nih.gov (CTCAE/CTC Archive) or ACRIN website for ACRIN 6673 protocol, http://www.acrin.org/6673_protocol.html. Protocols involving only imaging procedures must be submitted using a paper version. Investigators following those protocols should omit the Course Information section and the Protocol Agent section, even though the template indicates those as mandatory. (Do not try to send the form via the web site; it will not accept a form without those fields filled in.)

General questions regarding completion of the AdEERS report or submission can be sent to CIPSAEReporting@tech-res.com. The AdEERSMD phone helpline is available for any questions at 301-897-7497.

**15.10.2** To make an expedited telephone report to NCI/CIP, contact TRI staff at 301-897-1704 24 hours a day (recorder available Monday through Friday from 7:30 PM to 7:30 AM Eastern Time and on weekends).

Expedited adverse event reports must be sent within the above-mentioned timeframe to NCI/CIP via TRI by fax at 301-897-7402, followed by an e-mail to CIPSAEReporting@tech-res.com confirming that the AdEERS report was faxed. All fatal adverse events should be reported by telephone within 24 hours of the event.

**15.10.3** All fatal adverse events should be reported by telephone within 24-hours of the event. To make a telephone report to ACRIN, call (215) 717-2763, available 24 hours a day (recorder available Monday through Friday from 5:00 PM to 8:30 AM Eastern Time and on weekends).

A copy of all expedited adverse event reports must be sent to ACRIN by fax at 215-940-8819. The original signed and dated report must be sent to ACRIN at:

ACRIN 6673 Adverse Event

Attn: ACRIN AE Coordinator

1818 Market Street, 16th Floor

Philadelphia, PA 19103

**15.10.4** All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Adverse events not requiring expedited reporting are normally reported to the local IRB in an annual report and/or continuing review report.
**Please refer to your local IRB's policies regarding AEs/SAEs and safety reports.**

## 16.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice [International conference of Harmonisation (ICH) guidelines], applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB) for a formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study. The investigator will provide ACRIN with the institution's assurance number, along with the IRB approval letter and a copy of IRB approved, site-specific informed consent form.

All study participants in this study will be provided a consent form describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for a copy of the sample informed consent form). This consent form will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB approved consent form before the participant is subjected to any study procedures. The approved consent form MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent.

## 17.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN policies and applicable federal, state, and local laws and regulations.

## 18.0 PUBLICATION POLICY

Neither complete nor partial study results will be published or passed on to any third party without the formal consent of the ACRIN Publication Committee. Investigators will follow the ACRIN Publication Policy (ACRIN website at http://www.acrin.org/pubpolicy.html).

## 19.0 INSTITUTIONAL AUDITS

The investigator will permit study-related auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. The investigator will ensure the capability for inspection of all participating site's study-related facilities (e.g. imaging center, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

Institutional on-site audits will be completed within 18 months after each site's enrollment of its first ACRIN participant. The audits will be conducted per procedures established by the Cancer Imaging Program (CIP) of the NCI. Subsequent audits will be scheduled per the outcome of the initial audit. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN and NCI/CIP. IRB procedures, approvals, and consent forms will also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org.

To help sites prepare for audits and assure that the investigator and the research staff maintain records appropriately, the ACRIN data management and auditing departments will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial. **Please refer to the study-specific protocol audit guidelines for details.**

## 19.1 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN.

Source documents must verify the eligibility criteria and data submitted on all case report forms (CRFs). If an item is not mentioned (e.g., history and physical with no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data reported to ACRIN. If data is abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. However, every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol at the time of the audit visit. This will prevent any discrepancies and the inability to verify the document and the data reported.

## 19.2 Case Report Forms

Case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case "N/A" must be noted. All entries must be printed legibly in black ink on the paper case report forms. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the correction, recording the date** when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the case report forms (CRFs) will be audited against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires may be documented on the CRF. The image interpretation data required by the study that is a more detailed extraction of information from the image and is not typically documented in the standard radiology report may be recorded on the CRF and is accepted as source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date on which the exam took place from the medical record. **Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (participant questionnaire, CT, MR, etc.).**

Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a deficiency.

## 19.3 Institutional Review Board

Sites must obtain local IRB initial approval. Prior to subject registration, a copy of the IRB approval letter for the protocol and the informed consent form must be sent to ACRIN, along with a copy of the IRB approved informed consent form. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

## 19.4 Audit/Source Documentation

| Form | Data Collection/Timeline | Source Documentation |
|---|---|---|
| **AT** | Assessment of Tumor Resectability | • AT: Surgeon signed, dated;<br>• Medical History: Physician signed, dated; RA signed, dated |
| **TL** | Treatment Labs | • TL: Interventional Radiologist signed, dated;<br>• Hospital or Clinic Chart<br>• Medical History<br>• Laboratory Report |
| **A0** | Participant registration form<br><br>Completed at registration via ACRIN web site | • A0: RA signed, dated; Participant signed, dated<br>• All Consent Forms: PT signed, dated; other signatures as required by local IRB |

| | | |
|---|---|---|
| **I1** | Initial Evaluation Form | • I1: Physician signed, dated or RA signed, dated<br>• Hospital or Clinic Chart<br>• Pathology Reports<br>• Abdominal CT Scan Report<br>• Physical Examination<br>• Medical History |
| **C2** | Initial Imaging Form | • C2: Interventional Radiologist signed, dated;<br>• Abdominal CT Scan Report (C3)<br>• Chest CT Scan Report (C3)<br>• Image Guidance Report (US or MRI if used as guidance technique) (C3) |
| **AT** | Assessment of Tumor Resectability | • AT: Surgeon signed, dated;<br>• Medical History: Physician signed, dated; RA signed, dated |
| **TF** | Primary RFA Treatment Form | • RA: Physician signed, dated; RA signed, dated<br>• Hospital or Clinic Chart<br>• Laboratory Report<br>• Pregnancy Report<br>• Pathology Report<br>• RFA Procedural Report |
| **RA** | Additional RFA Treatment Form | • TF: Physician signed, dated; RA signed, dated<br>• Hospital or Clinic Chart<br>• Laboratory Report<br>• Pregnancy Report<br>• RFA Procedural Report |
| **IM** | Imaging Follow-up Form | • IM: Physician signed, dated; RA signed, dated<br>• Hospital or Clinic Chart<br>• Laboratory Report<br>• Abdominal CT Scan Report |
| **F1** | Follow-up Form-3 month only | • F1: RA signed, dated<br>• Hospital or Clinic Chart<br>• For re-ablation: RA form and its source verification |
| **F2** | Follow-up Form – 6, 9, 12, 15 & 18 months | • F2: RA signed, dated<br>• Hospital or Clinic Chart<br>• For re-ablation: F2 form and its source verification |
| **PL** | Local Pathology Interpretation | • PL: Radiologist/Pathologist signed, dated; RA signed, dated<br>• Pathology Report |
| **P4** | RFA-HCC Central Pathology Interpretation | • P4: Pathologist signed, dated; RA signed, dated<br>• Pathology Report |
| **PC** | RFA-HCC Pathology Submission Form | • PC:RA signed, dated<br>• Pathology Report |
| **QA** | Local Site Pre-ablation Imaging Form | • QA: Site PI signed, dated; RA signed, dated |
| **NT** | New Tumor Imaging Form | • NT: Physician signed, dated; RA signed, dated<br>• Hospital or Clinic Chart; Progress Notes<br>• CT Imaging Report |

| | | |
|---|---|---|
| **TC** | Telephone Contact Form | • Form: RA signed, dated<br>• Hospital or Clinic Chart<br>• Completed per section 8.9 and 9.5.5 |
| **NP** | Non-Participation Form | • NP: PI signed, dated; RA signed dated<br>• Hospital or Clinic Chart; Progress Notes |
| **PR** | Protocol Variation Form | • PR: PI signed, dated; RA signed dated<br>• Hospital or Clinic Chart; Progress Notes |
| **AE** | Adverse Event Form | • AE: PI signed, dated; RA signed dated<br>• Hospital or Clinic Chart; Progress Notes |

## 20.0 STATISTICAL CONSIDERATIONS

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# APPENDIX I

## ACRIN 6673

## SAMPLE CONSENT FOR RESEARCH STUDY

**STUDY TITLE**:

**MULTICENTER FEASIBILITY STUDY OF PERCUTANEOUS RADIOFREQUENCY ABLATION OF HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS**

*[Note: ACRIN does not monitor compliance with the Health Insurance Portability and Accountability Act (HIPAA); that is the responsibility of local IRBs. Local IRBs may choose to combine the authorization elements in the informed consent. Information on ACRIN's HIPAA policy, as well as a template for HIPAA authorization, can be found at www.acrin.org.]*

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to be in this study because you have liver cancer.

## WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) the procedure, radiofrequency ablation, has on you and your cancer.

Radiofrequency Ablation is a procedure that uses electrical energy to create radiofrequency waves that produce heat in tissues and can therefore destroy cells, both cancer and normal cells. The procedure involves placing a special needle (electrode) into the tumor under guidance by CT, ultrasound or sometimes magnetic resonance imaging (MRI). This electrode is then heated to a sufficiently high temperature that cells can be destroyed. Small masses may be destroyed in one treatment but larger ones may require several placements of the needle (electrode). Each heating cycle takes about 12 minutes. The entire procedure may take about 1 to 3 hours. This procedure may be repeated if the cancer re-grows.

This research is being done to see if radiofrequency ablation is able to kill the cancer that is in your liver.

## HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 40 people with certain type of liver cancer will be asked to take part in this study.

## WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

***Before you begin the study …***

Your study doctor will determine whether or not you are eligible by reviewing your prior medical history and chest and abdominal CT or abdominal MRI scan. In addition, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Ultrasound, if your study doctor will use ultrasound during your RFA treatment;
- Medical history;
- Laboratory tests;
- Pregnancy blood test, if you are a female;
- Chest and abdominal CT or abdominal MRI scan, only if your prior CT scans are not appropriate;
- Performance status on the Zubrod Performance Scale;
- EKG.

***During the study …***

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Physical examination;
- Laboratory tests;
- EKG;
- Biopsies.

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Laboratory tests;
- RFA treatment, especially if the cancer cells re-grow;
- Abdominal CT scan.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- General anesthesia, conscious sedation or local sedation with your RFA treatment;
- I.V. contrast material solution with the necessary CT scans;
- RFA ablation treatment;
- Ultrasound, CT, or MR during the RFA treatment to help your study doctor with the RFA treatment;

When you are finished with your RFA treatment, you will have a CT scan of your liver either during your recovery or within one (1) week after the initial ablation. If you do not have the liver CT scan completed during your recovery, you will be asked to come back within the first week to have your liver scanned.

After your RFA treatment, a study staff will call you on the phone to see how you are doing at the following times:

- Day 1;
- Week 1;
- 1 Month;
- 3 Months.

You will need to come back for the following tests and procedures every 3 months for up to 18 months:

- Laboratory tests;
- Abdominal CT scan.

If you need to have a repeat ablation treatment, you will need to have the following tests and procedures:

- Laboratory tests;
- Pregnancy blood test, if appropriate;
- Abdominal CT scan.

If any tumor is found in your liver on the CT scan after the first treatment, the tumor may be treated again as part of this study. Repeat ablation may occur for approximately 15 months following your first RFA treatment if your study doctor feels that it would be in your best interest. The study staff will also contact you at the above-mentioned time periods after each repeat RFA treatment.

## Study Chart

***What you do:***

| | |
|---|---|
| **Within 2 Weeks before the RFA treatment** | • Get chest and abdominal CT and/or abdominal MRI scans, if it was determined necessary;<br>• At least 7 days before the RFA, stop using any aspirin and non-steroidal anti-inflammatory, low molecular weight heparin or antiplatelet medications;<br>• Get routine blood tests;<br>• Get an ultrasound, if your study doctor is using ultrasound during your treatment;<br>• Get a tumor biopsy, if necessary;<br>• Get a physical examination;<br>• Get an EKG;<br>• Within 24-hours prior to RFA, get a pregnancy blood test, if appropriate. |
| **Day of RFA treatment** | • Check-in at out-patient registration or be admitted to the hospital;<br>• Get an RFA treatment;<br>• Get routine blood tests after the RFA treatment;<br>• Get an abdominal CT. |
| **Day 1** | • Telephone contact from study staff. |
| **Week 1** | • Abdominal CT, if not completed on the day of RFA recovery;<br>• Telephone contact from study staff. |

| | |
|---|---|
| **Month 1** | • Telephone contact from study staff. |
| **Month 3** | • Get routine blood tests and tumor blood test (within 1 week before the abdominal CT);<br>• Get an abdominal CT;<br>• Telephone contact from study staff. |
| **Month 6** | • Get tumor blood test (within 1 week before the abdominal CT);<br>• Get an abdominal CT. |
| **Month 9** | • Get tumor blood test (within 1 week before the abdominal CT);<br>• Get an abdominal CT. |
| **Month 12** | • Get tumor blood test (within 1 week before the abdominal CT);<br>• Get an abdominal CT. |
| **Month 15** | • Get tumor blood test (within 1 week before the abdominal CT);<br>• Get an abdominal CT. |
| **Month 18** | • Get tumor blood test (within 1 week before the abdominal CT);<br>• Get an abdominal and chest CT. |

**Repeat RFA treatments:**

***What you do:***

| | |
|---|---|
| **Within 1 Week before the Repeat RFA treatment** | • Get routine blood tests. |
| **Day of Repeat RFA treatment** | • Get a pregnancy blood test, if appropriate within 24-hours of the RFA;<br>• Check-in at out-patient registration or be admitted to the hospital;<br>• Get routine CT scans, sonograms or MRIs;<br>• Get repeat RFA. |
| **After ablation** | • Get abdominal CT during recovery or within 1 week, if necessary;<br>• Get routine blood tests;<br>• Telephone contact by study staff at Day 1, Week 1, Month 1, and Month 3;<br>• Continue with CT scans every 3-month from the initial ablation. |

**Radiofrequency Ablation Procedure**

The Radiofrequency Ablation will be done as an outpatient or overnight inpatient procedure at your institution. Your doctor will discuss with you how your cancer will be treated, depending on its size, location, and your symptoms.

On the day of your radiofrequency treatment, a needle will be inserted into one of your arm veins and attached to a tube. You will be given sedation and medicines through your I.V. to lessen any pain you may have during the procedure. We will connect you to a machine to constantly monitor your pulse and blood pressure.

You will be required to lie still on your back or on your side for approximately 1-3 hours during the treatment. During this time, the following procedures will be done:

- Adhesive ground pads, used to disperse the radiofrequency waves will be placed on your thighs.
- A CT scan machine (a specialized X-ray machine that takes computerized images of the body), an MRI (a specialized magnet that takes computerized images of the body) or an ultrasound may be used to see and find your tumor(s).
- At the site of your cancer, your skin will be cleaned and draped with sterile towels and sheets to lower the chance of an infection.
- You may be given injections of a "numbing" medicine at the place where the needle goes in to lessen any pain you may have with the needle placement, if general anesthesia is given.
- If the tumor in your liver has not been biopsied, it may need to be biopsied using a needle just prior to the ablation
- With CT scan, MRI or ultrasound guidance, a needle electrode will be placed directly into the cancer.
- The needle electrode will be attached to a radiofrequency electrical box. The cancer will be treated with radiofrequency waves for 12 minutes. A large cancer tumor may need more than one 12 minute treatment, so additional 12 minute ablations will be done until the tumor is completely burned. It will take 1 to 3 hours to finish the procedure, depending upon how many tumors in your liver are being treated and the size of each tumor.

After the radiofrequency treatment is completed, you will be kept in the hospital for 4-6 hours for observation or you may be required to stay in the hospital for one night. You will be monitored for pain and recovery from the sedation that you received during the procedure. After about 4-6 hours and it has been determined that you have recovered from the sedation, you may be allowed to leave the hospital. If you have significant side-effects from the procedure you may be admitted overnight for observation if your study doctor decides it is better for you. Immediately following the procedure or within one week, an abdominal CT scan will be done to see the effect of the ablation.

## HOW LONG WILL I BE IN THE STUDY?

You will be in the study for about three (3) years. Your follow-up appointments will be every three months for a total of eighteen (18) months after the first radiofrequency ablation procedure was performed.

## CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the your study doctor if you are thinking about stopping so any risks from the RFA treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if your condition worsens; if you do not follow the study rules; if new information becomes available and this information suggests the treatment will be ineffective or unsafe for you; or if the study is stopped. It is unlikely, but the study may be stopped due to lack of funding or participation.

## WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THIS STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Medications may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiofrequency is stopped, but in some cases side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

### Radiofrequency Ablation Treatment:

***The following risks are likely to occur:***

- *Pain* at the injection and ablation sites as well as in your right shoulder, chest, or abdomen. "Numbing" medicine may be used around the area to be treated. I.V. and oral medicines will be used for additional pain control. After you go home oral pain medications may be used to treat for any continuing pain.
- *Nausea and vomiting* immediately following the treatment. You may be given medicine in the IV or by mouth to help control this.

***The following risks rarely occur:***

- *Infection* related to the needle and ablation site. An immediate infection is very uncommon; however, a delayed infection of the ablated tumor(s) may develop 2-4 weeks after the treatment in less than 3% of patients. If an infection occurs you will be given antibiotics or a drainage tube may need to be placed in the infected tissue in your liver.
- *Tissue damage* related to the ablation needle placement. Tissue damage, nerve damage, or damage to organs near the liver is lowered by using image (CT, MRI ,or sonogram) guidance to ensure that the needle and RF electrode are in the correct position.
- *Ground pad burn* is a rare complication caused by a "hot spot" under the pads used to disperse the radiofrequency waves.
- *Tumor seeding* (cancer cells growing in the place where the needle is inserted and removed) is a rare complication, which may occur when the needle electrode is removed from the tumor.
- *Post-ablation syndrome* occurs in about 30% of patients. This may include fever, fatigue (tiredness), and pain in the joints 3 to 5 days after the treatment and may last 5 to 10 days. It is usually treated by taking over the counter pain medications such as acetaminophen or ibuprophen.

- *Other risks*, which are rare, include *cardiac arrest* (sudden stopping of the heart), *renal failure* (kidneys stop working), *peritonitis* (inflammation of the lining of the wall of the abdomen and pelvis), *pneumothorax* (air around the lungs), bleeding, and a significant drop in blood pressure.

Sedation:

- *Rare:* Allergic reaction to the anesthesia, adverse interaction with other medications, suppression of airway reflexes, cardiovascular decompensation, reduction of gross motor skills, and death.

Radiation:

- You will be exposed to radiation in this research study.
- The amount of radiation you will receive has a low risk of harmful effects.
- The risk from radiation exposure is equivalent or slightly more than the exposure from a x-ray of your chest or belly.
- Radiation dose from a CT scan (100-300 mrem), which is less than or equal to the average annual dose from natural sources of radiation (300 mrem).

Laboratory Tests:

Your blood will be drawn from a vein in your arm by a needle at the time-points the table above indicates.

Likely:

- Discomfort when the needle is placed in your vein.

Less Likely:

- Bruising or bleeding at the site of the blood draw.
- Dizziness and hyperventilation.

Rare:

- Loss of consciousness due to sudden fall of blood pressure.
- Infection at the site of the blood draw.

Reproductive Risk:

This study may be harmful to an unborn child. There is not enough medical information to know what the risks might be to an unborn child in a woman who takes part in this study. Women who can become pregnant must have a negative pregnancy test before taking part in this study. It is important you understand that you need to use birth control while on this study. Ask your study doctor about what kind of birth control methods to use and how long to use them. If you are a woman who can become pregnant, you must agree to a pregnancy test (blood test) before each RFA treatment. You will be told the results of the pregnancy test. If the pregnancy test shows that you are pregnant, you will not be able to take part in the study.

For more information about risks and side effects, ask your study doctor.

## ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. While doctors hope RFA treatment will be useful against liver cancer, there is no proof of this yet. We do know that the information from this study will help doctors learn more about RFA treatment as a treatment for liver cancer and benefit other patients with liver cancer in the future.

## WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition, if you choose not to participate, may include the following: (1) chemotherapy, (2) chemoembolization: (3) cryoablation, (4) radiation therapy, or (5) no treatment except medication to make you feel better. These treatments could be given alone or in combination with each other.

Your doctor can tell you more and the possible benefits of the different available treatments. If you decide to participate in this study, you will not be allowed to have any of the above-mentioned treatments while you are on the study. Please talk to your doctor about your choices before you decide if you will take part in this study.

## WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN). Copies of your CT films will be permanently kept on file at ACRIN. This information will be used for research purposes only. All identifying information will be taken off of the films to maintain confidentiality. Research studies may be conducted on other aspects of the data collected during the study. At this time it is not known what type of studies may be conducted. Some possibilities may be issues affecting patient care or future studies of a medical or non-medical nature.

I agree to the use of my medical records/data/images for other research studies.

☐ YES: INITIALS _____ ☐ NO: INITIALS _____

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study.
- **O**ther groups or organizations that have a role in this study.

If you have a biopsy, your pathology slides will be requested for the study. The slides will be sent for review to pathologists at the University of Florida and then returned to this institution.

## WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Please ask about any expected added costs or insurance problems. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

## WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will receive emergency medical treatment in the case of injury or illness resulting from this study at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

## WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health, welfare, or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

## WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

***(This section must be completed)***

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[investigator's name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of the institutions]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). (OHRP suggests that this person not be the investigator or anyone else directly involved with the research)*

## WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/ or the American College of Radiology Imaging Network's website www.acrin.org.

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a signed copy of this form. If you want more information about this study, ask your study doctor.

## SIGNATURE

**I have read all the above or it has been read to me. I have had the opportunity to ask questions. I understand the information and have had my questions answered concerning areas I did not understand.**

**I willingly give my consent to participate in this study. Upon signing this form, I will receive a copy.**

_____ _____

Participant Signature *(or legal Representative)* Date

# APPENDIX II

**REGISTRATION/ELIGIBILITY CHECK** **(Page 1 of 3)**
**ACRIN 6673**

**ACRIN Institution # _____** **ACRIN Case #_____**

**Eligibility Requirements: Inclusion Criteria -** a response coded other than what is prompted renders a participant ineligible for enrollment.

_____(Y) 1. Biopsy proven cirrhosis, or typical findings of cirrhosis by CT scan and/or MRI scan.

2. Hepatocellular carcinoma (HCC) proven by: (Check all that apply)

(☐ 1 = No, ☒ 2 = Yes)

☐ Biopsy

☐ Barcelona imaging criteria [see Appendix VIII, #3]

☐ Barcelona combined criteria [see Appendix VIII, #3]

☐ Tumor growth criteria [see Appendix VIII, #4]

3. Hepatic tumor burden meeting the Milan Criteria.

- 3 or fewer tumors ≤ 3.0 cm

or

- a single tumor > 3.0 cm but ≤ 5 cm in diameter

_____(Y) 4. All identified tumors are treatable by percutaneous RFA: all tumors are ≥ 1 cm from the main, right and left portal veins and all tumors are ≥ 1cm from hollow viscera.

_____(0-2) 5. Record performance scale as defined by the Zubrod Performance Scale. [see Appendix V and 5.3.6]

_____(Y) 6. Serum creatinine ≤ 2.0 mg/dl.

_____(Y) 7. Chest CT and abdominal CT scan and/or abdominal MRI within 60 days of initial RFA treatment. If any scans are outside the 60-day window, only CT scans will be repeated per the imaging protocol found either on the ACRIN website or in the section 13.0 of the protocol.

_____(Y) 8. Aspirin and nonsteroidal anti-inflammatory medications, anti-platelet medications, or wafarin has been discontinued for a time period that is appropriate given the drug half-life or its known anti-platelet activity (e.g., aspirin for 7 days and ibuprofen 24 hours) prior to the scheduled RFA.

_____(Y) 9. All laboratory requirements as described in section 5.3.3 of the protocol have been met.

**Eligibility Requirements: <u>Exclusion Criteria</u> -** a response coded other than that prompted renders a participant ineligible for enrollment.

_____(N) 10. Participant has had prior treatment for HCC by any method. [see Section 5.1.12]

_____(N) 11. Surgical candidate. [see Appendix IX]

_____(N) 12. Hepatic or portal vein tumor invasion.

_____(N) 13. Extrahepatic tumor.

_____(N) 14. Active infection. [see Section 5.2.12]

_____(N) 15. History of cholendochoenteric anastomosis and or spincterotomy of duodenal papilla.

_____(N) 16. Absolute contraindication to intravenous iodinated contrast. [see Section 5.2.1.5]

**The following questions will be asked at Study Registration:**

_____ 1. Name of institutional person registering this case:_____

_____(Y) 2. Has the Eligibility Checklist (Inclusion/Exclusion Q1-16) been completed?

_____(Y) 3. Is the participant eligible for this study?

___/___/_____ 4. Date the study-specific Consent Form was signed (mm-dd-yyyy)
(must be prior to study entry)

_____ 5. Participant Initials (last, first): Numeric number may be coded other than the assigned case number, ####.

_____ 6. Verifying Physician (Site PI)

_____ 7. Participant's ID Number (optional: this is an institution's method of tracking participant to a case number; code 99999)

___/___/_____ 8. Date of Birth (mm-dd-yyyy)

_____ 9. Ethnic category
1 Hispanic or Latino
2 Not Hispanic or Latino
9 Unknown

_____ 10. Race (check all that apply☐ 1 = No, ☒2 = Yes)
- ❑ American Indian or Alaskan Native
- ❑ Asian
- ❑ Black or African American
- ❑ Native Hawaiian or other Pacific Islander
- ❑ White
- ❑ Unknown

_____ 11. Gender
1. Male
2. Female (Complete question 20, negative pregnancy test…)

_____ 12. Participant's country of residence (if country of residence is other, proceed to Question 13 for completion)
1 United States (Complete question 14, Zip code)
2 Canada
3 Other(Complete question 13, Other country, specify)
9 Unknown

_____ 13. Other Country, specify (completed if Q12 is coded **'Other'**)

_____ 14. Zip code (5 digit code, completed if Q12 is coded **'United States'**)

_____ 15. Participant's Insurance Status
0 Other
1 Private Insurance
2 Medicare
3 Medicare and Private Insurance
4 Medicaid
5 Medicaid and Medicare
6 Military or Veterans Administration
7 Self pay
8 No means of payment
9 Unknown/Decline to answer

_____ 16. Will any component of the participant's care be given at a military or VA facility?
1 No
2 Yes
9 Unknown

___/___/_____ 17. Initial RFA Treatment Date (mm/dd/yyyy)

___/___/_____ 18. Registration Date (mm/dd/yyyy)

19. MELD Score:

☐ Score > 25

☐ Score 15 – 25

☐ Score < 15

Note: Per DSMC review and recommendations on May 17, 2007, the decision has been made that the two groups with MELD scores >15 will be closed for accrual. The study will only enroll participants with MELD score <15. Therefore, the study design is not stratified anymore and the total sample size is 40.

_____ (Y/NA) 20. If female, negative pregnancy test within 24-hours of RFA treatment?

_____ (Y/N) 21. Does the participant have a pacemaker?

Completed by:_____Date form completed: ___/____/____
**(Principal Investigator or Investigator Designee)**

Signature of person entering data onto the Web _____

# APPENDIX III

## PARTICIPATING INSTITUTIONS

A minimum of ten (10) participating institutions, Site Principal Investigators will be identified upon review and approval of completed ACRIN Protocol Specific Application (PSA).

# APPENDIX IV

## ACRIN Protocol-Specific Application Information

## ACRIN 6673

## MULTICENTER FEASIBILITY STUDY OF PERCUTANEOUS RADIOFREQUENCY ABLATION OF HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS

**Application Process**

The approval process for ACRIN 6673 includes submitting an ACRIN Protocol Specific Application (PSA). The complete Protocol-Specific Application is on the ACRIN web site at www.acrin.org/6673_protocol.html. This application is in addition to the ACRIN General Qualifying Application, which can also be found on the ACRIN web site.

# APPENDIX V

## ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction *(Karnofsky 90-100)*.

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work *(Karnofsky 70-80)*.

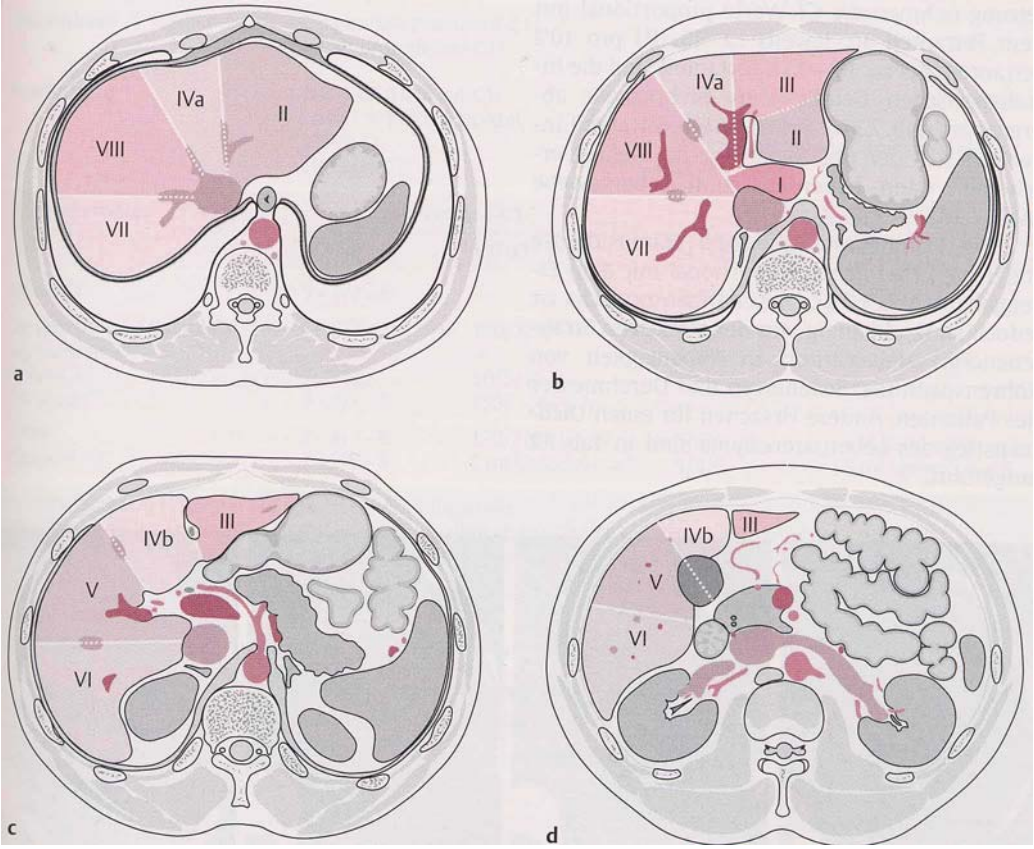
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (*Karnofsky 50-60)*.

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours *(Karnofsky 30-40)*.

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20)*.

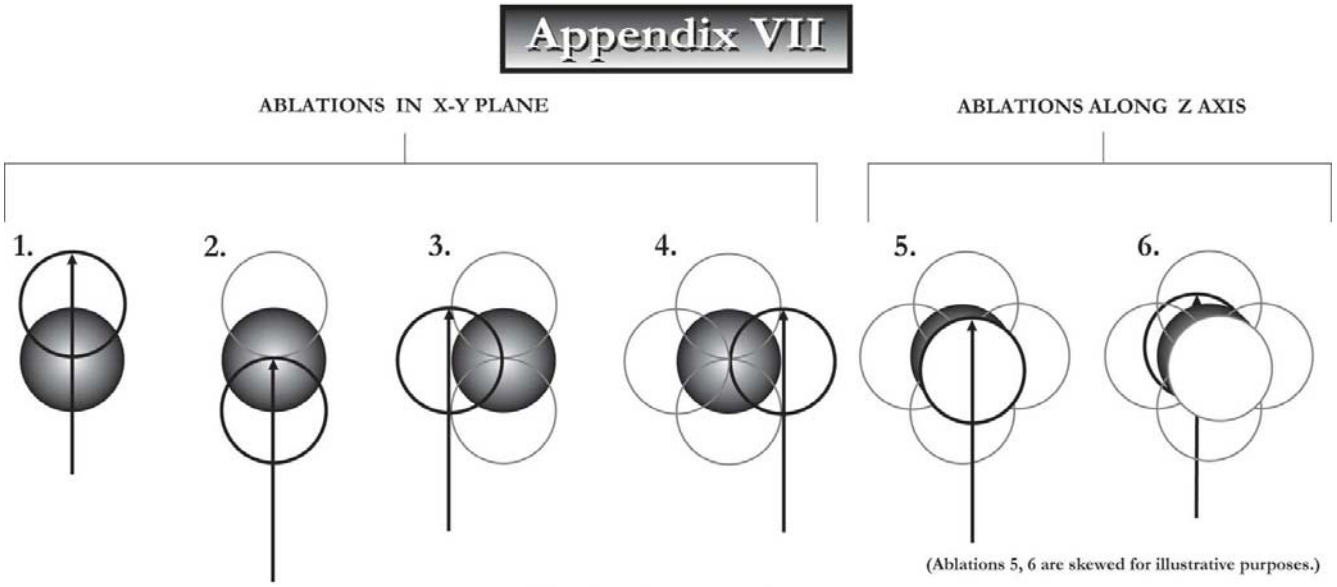
# APPENDIX VI

## DIAGRAM OF THE LIVER



## APPENDIX VII

### Ablation Strategy Diagram




Six (and Five)-ablation technique

-The needle tip is in the x-y plane in the first four figures. (1) The needle tip is advanced to the far side of the tumor, extending 1 cm distal to tumor margin. A single ablation is performed. (2) Then, the needle is withdrawn until the tip of the needle touches the proximal margin of the first ablation. A second ablation is performed. (3) The needle is then withdrawn and readvanced laterally to skirt the margin along the echogenic response of the first two ablations so that the active element of the needle straddles the length of the first two ablations. An ablation is performed. (4) The needle is again withdrawn and in a similar manner, readvanced to opposite lateral margin along the echogenic response of the first two ablations. An ablation is performed. (5&6) The needle is withdrawn and redirected. The first of the final two ablations is performed in one or the other direction in the z axis. The needle is advanced along the edge of the echogenic response made by the previous four ablations such that the active element straddles the first and second ablations along the y axis and is centered between the third and fourth ablations in the x axis.

-The ablation technique for five ablations is identical to the six ablation technique, except for the omission of the second ablation.

## Appendix VIII

## STUDY TERMINOLOGY AND DEFINITIONS

1. **MELD Score:** MELD stands for Model End Stage Liver Disease (ESLD), a disease severity scoring system applied to adult liver patients. MELD score is calculated using a relatively simple formula that relies on three readily available objective variables:

   - Serum creatinine (Scr; mg/dL)
   - Total bilirubin (Tbil; mg/dL)
   - INR (international normalized ratio)

   The following rules must be observed when using this formula:

   - 1 is the minimum acceptable value for any of the three variables.
   - The maximum acceptable value for serum creatinine is 4.
   - The maximum value for the MELD score is 40.

   MELD Score = 10 **{**0.957 Ln(Scr) + 0.378 Ln(Tbil) + 1.12 Ln(INR) + 0.643**}**

2. **Milan Criteria:** The criteria (> 3.0 cm but $\leq$ 5 cm if single tumor, $\leq$ 3 cm if 1 to 3 tumors, no invasion of blood vessels or lymph nodes) used by Mazzaferro et al in their report ("Milan criteria").
3. **Barcelona Criteria:**
   a. **Radiological criteria:** two coincidental imaging techniques (CT, MRI, US, angio) showing > 2cm arterial enhancing tumor nodule
   b. **Combined criteria:** single imaging technique (CT, MRI, US, angio) showing > 2cm arterial enhancing tumor nodule with AFP $\geq$ 400 ng/mL
4. **Tumor Growth Criteria:** A discrete hypervascular tumor that has been identified on two sequential imaging studies (CT or MRI) and grown >1cm in diameter.
5. **Ablation session:** a single intervention episode that consists of one or more ablations performed on one or more tumors.
6. **Ablation treatment:** Given that sessions may be repeated, a "**treatment"** consists of one or more "sessions"; and is used to define the completed effort to ablate one or more tumors
7. **Tumor size:** Greatest diameter in cm**.**
8. **Ablation zone:** The term "ablation zone" is used to describe the radiologic region or zone of induced treatment effect (i.e., the area of gross tumor destruction visualized by imaging). The term "lesion" is to be avoided given potential confusion as to the intended meaning as the term "lesion" has been used to refer to both the "ablation zone" as well as the underlying tumor to be ablated itself.
9. **Benign periablational enhancement**: This finding can be seen at both pathology and on contrast enhanced imaging and typically suggests a benign physiologic response to thermal injury (initially reactive hyperemia and subsequently fibrosis and giant cell reaction) [61]. Depending on the protocol used for contrast enhanced imaging (injection rate and scanning delay), this transient finding can be seen immediately following ablation and can last for up to 6 months post-ablation. This finding usually manifests as penumbra, or a thin rim peripheral to the

zone of ablation, that can typically measure up to 5 mm acutely, but most often measures 1 – 2 mm. It is a relatively concentric, symmetric, and uniform process with smooth inner margins that needs to be differentiated from "irregular peripheral enhancement". The finding is most readily appreciated on the arterial phase for CT, with persistent enhancement often seen on delayed images at MRI.

10. **Irregular peripheral enhancement**: represents residual tumor occurring at the treatment margin. In contrast to "benign peri-ablational enhancement", residual unablated tumor often grows in scattered, nodular, or eccentric pattern. This sign indicates incomplete local treatment (i.e., residual unablated tumor). As such, if not subject to further therapy these foci tend to continue to grow. Given the delayed enhancement characteristics of many hypovascular tumors, often this finding is best appreciated by comparing portal venous or delayed (3 or more minutes following contrast injection) images to baseline images.
11. **Local tumor progression**: Many have used the term "local recurrence" to describe the appearance over follow up of foci of untreated disease in tumors that were previously considered to be completely ablated as local recurrence. This is often a misnomer given the fact that the tumor in essence did not recur, but was never completely treated. Hence, the process often described is in actuality "residual unablated tumor". However, in many cases it is virtually impossible to determine whether there was incompletely treated viable tumor that continued to grow, or if a new tumor (or in the case of HCC, "daughter" or "satellite" tumors) grew at the original site. Given this reality, "**local tumor progression**" is the preferred terminology over "local recurrence".
12. **Primary and Secondary technique efficacy rates**: Given that multiple treatments of image-guided tumor ablation therapy are often given over the course of the disease, primary and secondary technique efficacy rates should be reported. The "**primary efficacy rate**" is defined as the percentage of tumors successfully eradicated following the initial procedure or a defined course of treatment. The "**secondary or assisted efficacy rate**" is defined as including tumors that have undergone successful repeat ablation following identification of local tumor progression. The term "**re-treatment**" should be reserved for describing ablation of locally progressive tumor, in cases where complete ablation was initially thought to have been achieved based upon imaging demonstrating "adequate" ablation of the tumor.
13. **Non-surgical candidate**: A patient who is determined to be inappropriate for a liver resection for reasons that include: tumor in an unresectable location, co-morbid disease, insufficient hepatic reserve.
14. **Non-Protocol Tumor-** Subtle hypervascular nodules $\leq$1cm, no more than 3 in number.
15. **Off-Study Criteria-** Participants will not be followed after the initial ablation session by serial CT scans (3 month visits) for 18 months if the participant undergoes treatment for HCC by any method other than RFA, and if there is evidence of extrahepatic tumor on the follow-up abdominal CT scan. In addition, Protocol re-ablation of tumors or ablation of new tumor(s) will not be allowed.

## Appendix IX

### Assessment of Tumor Resectability

**ACRIN Institution #:** _____
**ACRIN 6673**

**Patient's Name:**_____ **Patient's I.D. No:**_____

I have evaluated _____ and have found him not to be a liver resection candidate for the following reason(s):

☐ Tumor in unresectable location.

☐ Co-morbid disease making the patient a poor surgical candidate.

☐ Insufficient hepatic reserve.

Surgical Oncologist Signature: _____ Date: _____