Irreversible Electroporation Ablation for Colorectal Metastases to the Lung

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Surgery of limited pulmonary metastases from colorectal cancer appears to confer a survival benefit. However, many patients with metastatic disease may have multiple co-morbidities and limited lung function, restricting their ability to undergo therapeutic surgical procedures. Irreversible electroporation (IRE) offers a promising alternative to traditional surgical and thermal ablation procedures. Focal thermal ablation has been observed to be a safe and effective alternative. However the use of thermal ablation in the lung is restricted by biophysical properties of lung tissue that impact the reliability with which clinically relevant temperature change can be achieved and maintained in the target tissue, to ensure adequate tissue destruction. Therefore, an ablation technique that does not rely on increased tissue temperature changes for tumor destruction may provide an alternative therapeutic modality for care of patients who are non-surgical candidates.

IRE is a new form of tissue ablation that uses strong pulsed electric fields to create persisting pores in the cell membrane, leading to cell death. This modality for inducing cell death does not rely on sustained changes in tissue temperature and therefore, IRE may be considered a non-thermal ablative tool that can be potentially applied in locations where thermal ablation techniques have limited effectiveness. Target locations can include tumors adjacent to large blood vessels or airways that can dissipate heat and limiting temperature changes needed to ensure cell death. This protocol seeks to explore the application of IRE for local treatment of patients with metastatic colorectal cancer to the lung in a treat and resect trial, with safety of this technique as the primary end point.

The NanoKnife System, manufactured and marketed by Angiodynamics has received FDA clearance for the surgical ablation of soft tissue (510(k) Number: K080376). While it can be used in multiple locations in the body, it has not received clearance for the therapy or treatment of any specific disease or condition. The proposed safety study is not intended to support a future marketing application.

This clinical study is a safety study of open surgical IRE ablation of lung metastases from colorectal cancer. Approximately (and consistently) 50 colorectal cancer metastasectomies performed each year by the Thoracic Service. Our plan is to enroll 10 patients in an “ablate and resect” study to assess the safety of IRE ablation. Just prior to resection of their metastatic disease, the target lesions will be ablated using IRE. Safety data from this study will be assessed for any device related complications and will be used to support a future feasibility study of percutaneous IRE.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The purpose of this study is to determine whether IRE using the NanoKnife system is safe for use within the lung when treating colorectal cancer metastases, and to document the severity and incidence of any adverse effects (AE) or severe adverse effects (SAE) that may arise during or immediately following completion of treatment. As a relatively new clinical tool, there are limited data on the safety and best use practices for using IRE to treat lung metastases. We hypothesize that IRE can be a useful alternative to radiofrequency ablation (RFA) for ablation of colorectal metastases in the lung, and may provide benefit to patients whose tumor locations contraindicate the use of RFA for treatment.

The scientific aims of this study are to:

1. Assess complications experienced after using IRE for performing ablations in the lung using the NCI Common Terminology Criteria for Adverse Events (CTCAE).
2. Measure safety by the ability to maintain the integrity of critical structures within or immediately outside the ablation zone following treatment.
3. Evaluate resected tissue for assessment of the ablation zone and comparison with expected zone based on choice of treatment parameters.
4. Perform CT imaging to demonstrate the ability to ablate the tumor without causing major complications to surrounding critical structures. Specific imaging methods can be found in the Imaging section of this protocol.
5. Perform histopathologic assessments on the surgically resected tissue. Specific histopathologic assessments can be found in the histopathology section of this protocol.
6. Assess safety through a complete physical examination and standard safety laboratory tests for each patient per the Schedule of Events (Section 10).
   Evaluate Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effects (ADEs), Serious Adverse Device Effects (SADEs), and Unanticipated Adverse Device Effects (UADEs) and generate a safety profile.

3.0 BACKGROUND AND RATIONALE

IRE ablation using the Nanoknife system is cleared for ablation of soft tissue without specific indications and is currently clinically used at Memorial Sloan Kettering Cancer Center (MSKCC) and other hospitals around the world under the discretion of the attending physician. The current study is focused on a specific soft tissue ablation, that is colorectal lung metastases, and seeks to evaluate peri-procedural safety of this technique.

Surgical Metastatectomy for Colorectal Metastases in the Lung

Colorectal cancer is the third most common cause of cancer death for both men and women. (1) The lungs are the most common extra-abdominal site of metastases in patients affected by colorectal cancer, and approximately 10% of patients with colorectal cancer will develop lung metastases.(2) Since the first successful report of pulmonary metastatectomy for colorectal carcinoma in 1944, several studies, including the International Registry of Lung Metastases, have reported improved survival rates in selected patients undergoing lung resection for colorectal metastases (3-5) A recent meta-analysis reported for selected patients undergoing pulmonary metastatectomy for colorectal cancer an overall 5-year actuarial survival rate ranging between 38.3% and 63.7% (median 52.5%).(6) With this foundation of data, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommends ridding isolated lung metastases from colorectal cancer (7)`

Although surgical metastatectomy is the gold standard for treatment of these metastases in the lung, patients could benefit from a less invasive approach through faster recoveries and fewer complications. Percutaneous ablation offers a minimally invasive lung preserving technique suitable for patients with co-morbidities.

Image-Guided Lung Radiofrequency Ablation for Colorectal Metastases

A number of groups have reported on the safety and efficacy of lung radiofrequency ablation for colorectal metastases. These reports have demonstrated a preservation of lung function after the procedure with no significant change in pulmonary function tests.(8,9) Similarly they have shown no deleterious effect in quality of life. Efficacy of local tumor control, however, has been variable. A multicenter Japanese study reported an 11% local tumor progression

rate in patients with small (< 3 cm) tumors that rose to 50% progression with large tumors (3.1-6 cm).(10) However, in contrast, Hiraki et al (11) have reported only a 31% single session local control rate. In the multi-national Lancet Oncology study there were no procedure related deaths. There were 26% patients requiring chest tube placement. Minor complications were pneumothorax, pleural effusion, and self-limiting hemorrhage. This study also looked at quality of life using the Short Form (SF)-12) and the Functional Assessment in Cancer Therapy-–-Lung (FACT-L) questionnaires. These demonstrated no deterioration from the ablation.(12)

Limitations of Radiofrequency Ablation in the Lung

Some of the efficacy limitations of radiofrequency ablation in the lung described above concern its unpredictable zone of ablation. In our own work we have seen these limitations appear most strikingly for tumors greater than 3 cm in size. Ablations for lung cancers treated with RFA had a 65% local progression-free rate at 12 months if they were smaller than 3 cm, but had only a 12% local progression-free rate for tumors greater than 3 cm (unpublished). Some of the factors that weigh in on the ablation zone are physiological and others are electrical. The physiologic limitation of radiofrequency ablation in the lung concerns the “heat sink” effect in which flowing blood cools the area that is trying to be heated. This has been demonstrated in many studies.(13-15) Electrical conductivity is also an important issue in the ablation effectiveness. Computer modeling has demonstrated a strong correlation between tissue electrical conductivity and RF heating. Inferior heating and distribution of heating effects occurs with tissue like lung that has poor thermal conductivity(16-17)

Multi-tined applicators that increase the electrode surface area, ionic fluid infusion, and protocol optimization have been attempts to lower the electrical impedance in lung tissue to permit current flow. However, fluid infusion is unpredictable and may increase complications while multi-tined electrodes may increase the pneumothorax and pose additional injury through errant needles.18-19 Protocol optimization often leads to inadequate RF heating Finally, the thermal effects of radiofrequency ablation can affect the structural integrity of non-targeted critical structures such as nearby large airways and blood vessels. The intense heating used during RFA can coagulate the collagen in the extracellular matrix of these luminal structure, leading to tissue break down and complications such as bronchopleural fistula and abscess.20

Irreversible Electroporation Tumor Ablation: A Non-Thermal Technique

Irreversible electroporation (IRE) is an FDA approved, non-thermal ablative tool that creates pores in cell membranes through the application of pulsed direct current. While “reversible electroporation” that allow cell membrane pores to heal has been used in medicine for transmembrane drug delivery for many decades, the application of high voltages that create irreversible electroporation is relatively new. Its application to destroy cells has been demonstrated in small animal tumor models, and large animal tissues.(21-23) Most recently clinical applications have been reported. (24)At MSKCC nearly 100 IRE ablations have been performed clinically. (25) Retrospective reports on some of these patient studies have been published. In the Kingham et al. (25) study it was shown in 65 tumors that IRE was safe and feasible adjacent to vessels. In the Silk et al. (27) study it was similarly found safe for use adjacent to biliary structures.

IRE’s ablative effect has been shown not to rely on sustained increases in tissue temperature, and therefore is considered non-thermal.(26) This raises the possibility of an ablative tool that is not affected by the “heat sink” effect seen with thermal ablation. IRE appears to effect cells while sparing the scaffold of tissues such as collagen and fibrous

tissue. This has been demonstrated by preservation of vessels (28), rectal wall (29) and bile ducts (30) in animal models. Preservation of bronchi in the lung may avoid the thermal ablation complication of bronchopleural fistula (31). Treatment parameters and ensuing size and shape of the ablation zone can be roughly determined using numerical models of the distribution of electrical energy within the target tissue (32). This allows for a more predictable ablation zone based on the placement of the electrodes. This is not easily achieved using currently available thermal ablation devices

Therefore, this study is intended to assess the safety of surgical and eventually percutaneous ablation using the Nanoknife system for the ablation of lung metastases.

Animal Studies

We performed a non-GLP, academic study of IRE of the lung in 11 pigs and performed short-term observation of the animals (0, 1, 4 and 21 days) to assess safety, feasibility and morbidity following ablation (31). Ablations were deliberately performed close to critical structures (bronchovascular structures and <2cm from the heart). A total of 25 ablations were performed, and were followed up with contrast enhanced CT imaging and compared with histological analysis. Ablations were performed using a single set of treatment parameters (9 Trains of 10 70 µsecond pulses with applied voltage of 1700-2500V between the needle electrodes). The treatments were performed with ECG synchronization. Acute analysis (<4days) of ablation specimens indicated necrotic cell death of ablated tissue with necrosis of bronchial and vascular epithelium but the major bronchvascular architecture was maintained. Chronic ablations showed bronchiolitis obliterans and alveolar interstitial fibrosis. No significant cardiac arrhythmias were noted during or following the procedures. Additionally, any thermal injury to tissue was found restricted to a small region (<0.5mm) in proximity to the electrodes. Numerical modeling was used to plan ablations of size 2.0-2.5cm in length and 2.7-3.0cm in depth. CT measurement at immediate post treatment, at 8 hours and at one week indicated lesion of 2-4.5cm in length at the maximum dimension. The reversible zone typically appears as zone of concentric enhancement surrounding the ablated region, the size of this zone was variable and approximately 2-3mm in size. The same was observed in histology, as a region of hyperemia and edema but with absence of necrotic cell death.

The actual electric field developed in the tissue as an effect of the applied voltage can also be influenced by anatomical structures such as blood vessel, or the bronchus (33). For this clinical application, it is well known that lung tumors and metastatic tumors in the lung have electrical conductivity 2-3 times that of surrounding lung parenchyma (34-36). Numerical modeling and simulation is well researched for its use in determining optimal treatment parameters when applying DC current to biological tissue (37-38). Therefore we performed numerical modeling specific to IRE ablation of tumors in lung tissue using actual tissue impedance data found in literature (39). Based on our own results, we have found that an adequate electric field with sufficient homogeneity can be developed by surrounding the tumor with needle electrodes placed in the healthy tissue immediately adjacent to the tissue.

The lung has higher electrical impedance than other organs (for example, the liver) and also has poorer thermal conductivity (40-41). The electrical and thermal property of the lung has made it a difficult target to plan and deliver RF current driven thermal ablation. The primary ablation mechanism of IRE is different from clinically used thermal techniques. IRE does not rely on sustained changes in tissue temperature for ablation of the target region. While there exist transient temperature increase during application of IRE pulses, the kill mechanism is

largely independent of any rise in tissue temperature. Based on our large animal model studies, and results from numerical simulations, we assert that IRE ablation can be performed using pulse parameters currently approved and clinically used for soft tissue ablation. Adjustments to ablation probe geometry and placements, and minor changes to applied voltage will be sufficient to achieve complete ablation in our selected targets.

The parameters proposed for ablation in patients is also supported by a pre-clinical large animal model study reported by Goldberg et al(42). Goldberg et al. reports a comprehensive study of varying key IRE parameters (pulse width, number of pulses, distance between probes and applied voltage) with the size, and the quality of ablations created in swine liver. They report that ablation size plateaued beyond a pulse width of 50 microseconds, applied 50 times; increasing these parameter values did not show any significant change in ablation size. They also reported a direct correlation between applied voltage and ablation size, with the maximum applied voltage causing a large ablation of uniform quality. Additionally, they reported that 2.0 cm was the maximum effective spacing between the electrodes for creating large, complete ablations. Even with additional increase in applied voltage, further increase in electrode spacing caused hourglass shaped ablations.

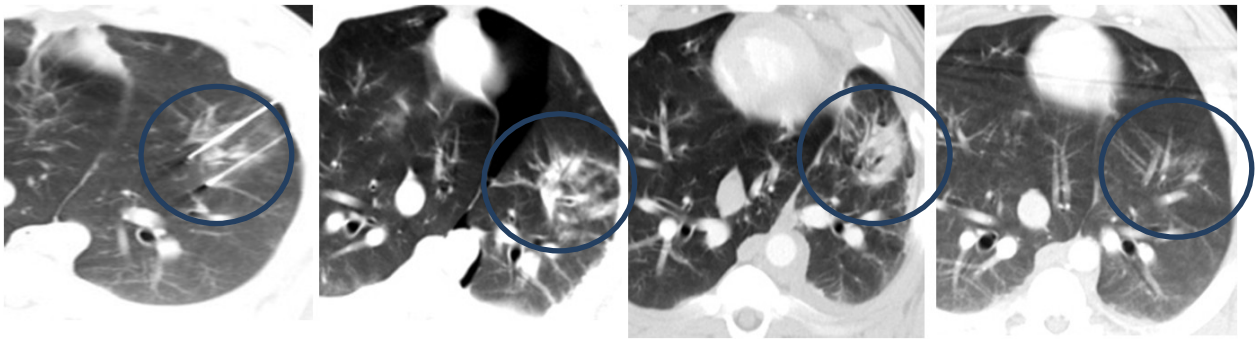


Figure 1: Our results from applying IRE ablations in swine lung. CT images show placement of electrodes, immediate, 1 week, and 3 weeks post-IRE. (left to right). Circle demonstrates ablation zone.

Based on the experimental data and clinical experience it is hoped that this would allow operators to comfortably treat tumors up to 3.0 cm diameter. Also, using our experience with prior animal studies, a protocol was developed to use EKG gated synchronized IRE ablations to minimize possibility of cardiac arrhythmia. (43) Electrical pulses from IRE have been known to cause muscle stimulation.

Complications following IRE will be assessed using the NCI Common Terminology Criteria for Adverse Events (CTCAE). In addition to the complications observed with other lung ablation procedures, such as bleeding, and infection, IRE-specific complications such as cardiac arrhythmias will be particularly note and graded with the CTCAE.

Alternative Practices or Procedures

Surgical resection of colon metastases to lung is the mainstay of treatment. However, resection can be costly in terms of recovery time and loss of lung function. Additionally, many patients have medical co-morbidities that make them unfit for surgery. Lastly, patients with lung metastases often develop additional lung metastases making repeated surgeries difficult. An alternative approach to treating lung metastases has been thermal ablation.

This, however, has had limitations due to thermal conductivity of lung and "heat sink" limitations of vessel and bronchus diffusion of heat. In effect, this reduces patients who can benefit from ablation therapy and also in some patients this also leads to incomplete ablation which results in local disease progression. If successful, IRE ablation would potentially benefit Medicare patients by offering them a less invasive and more lung preserving treatment for colorectal lung metastases.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The purpose of this safety study is to assess peri-procedural safety of IRE using a treat and resect trial.

"Ablate and Resect" Surgical Safety Study of IRE. Colorectal cancer patients with oligometastatic colorectal cancer in the lung who are eligible for lung resection surgery may be eligible for this prospective study. As advised by the FDA based on our preliminary submission, we will recruit and treat 10 patients with 6 month minimum follow-up and assess for potential adverse events such as unexpected thrombosis, and cardiac arrhythmias. Eligible lesions will be greater than 1.0 cm in size. Additional details regarding inclusion and exclusion criteria can be found in the Human Subject Protection section. We will use the EKG-gated (Accusync), IRE NanoKnife Ablation system (AngioDynamics, Queensbury, NY). Nanoknife is FDA cleared for clinical use to perform soft tissue ablations. Though Nanoknife has been clinically available for over 3 years, there are no publications detailing clinical trial experiences from prospective clinical trials.
Often, localization of metastases in the lung parenchyma to delineate adequate margins is done by palpation of the lung, which leads to the creation of a 5 or more centimeter incision between the ribs to allow the surgeons fingers to enter the pleural space. IRE ablation would be done through that same access incision. Patients who are unlikely to have such an incision created would not be enrolled on the trial. Choice of thoracoscopic resection versus open thoracostomy will be based on the surgeons' clinical decision and will not be influenced by the study.

4.2 Intervention

The IRE procedure will be performed in the operating room at the time of scheduled clinical resection of colorectal lung metastases by the surgeon with guidance from the Interventional Radiologist. The IRE study procedure will be performed under general anesthesia with a paralytic agent to prevent muscle excitation during the NanoKnife procedure. The patients will be sterilely prepared and draped according to the standard of care for a thoracotomy (pulmonary metastatectomy). The NanoKnife procedure will be performed in accordance with the FDA-cleared Instructions for Use (IFU). The IRE will be performed in an open fashion with palpitation and plastic guide to place the needles. Image guidance will not be used.
For the purposes of this study, a set target volume will be ablated using 2 probes spaced approximately 1.0 cm to 1.5 cm apart and at 2.0 cm electrode exposure. To study safety, this study will include only a 2 probe ablation. Commercially available Nanoknife spacers will be utilized to ensure proper probe placement. We are not limiting the upper limit of size.

The treatment parameters will be a minimum application of 1,600 V/cm between electrodes used for treatment delivery, using 90 microsecond pulse width, for a total of 90 pulses for

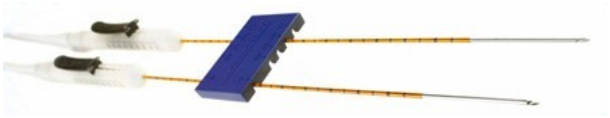
each pair of electrodes. The NanoKnife system will place each IRE pulse 70 milliseconds after the patient's R wave with this cardiac synchronization facilitated by ECG synchronization using the Accusync device. Conductivity and impedance measurements will be taken using the needle electrodes used to deliver treatment.

Ablation of the target volume will be followed by a resection of the tumor tissue and tumor margin as per standard surgical procedures for a pulmonary metastasectomy. Surgical resection and de-vascularization (i.e. cutting off the blood supply) of the tumor will be completed after a minimum of 15 minutes has elapsed following completion of the ablation procedure.

We will allow multiple lesions from the same patient to be treated. While each lesion will be analyzed separately we will keep the enrollment target at 10 patients and as a result the number of lesions treated on the study may exceed 10.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The NanoKnife device is used to perform Irreversible electroporation (IRE) and has received FDA clearance for ablation of soft tissue [510(k) Number: K080376]. The NanoKnife System is produced manufactured by AngioDynamics, Queensbury, New York. The NanoKnife® System transmits non-thermal energy from the NanoKnife Generator to electrodes placed in a target area. The electrodes work in a two-pole operating mode, and up to six electrodes can be placed at a fixed distance apart in soft tissue to create several two-pole electrode configurations. The NanoKnife System with six outputs is indicated for surgical ablation of soft tissue. IRE ablation is believed to work by putting small pores in the cell membrane. These pores are irreversibly patent and lead to loss of cell homeostasis. Cells die; however, the protein fibrous architecture of organs and tubular structures is believed to be preserved. Though Nanoknife has been clinically available for over 3 years, there are no prospective studies and publications detailing clinical trial experiences with colorectal metastases to the lung.



6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Diagnosed Colorectal cancer with oligometastatic colorectal cancer in the lung
- Lung lesion size is greater than 1 cm
- Patient will undergo surgical resection as per consultation with their thoracic surgeon and medical oncologist

- Patient is cleared to undergo paralytic anesthesia.
- Patients 18 years old and older

6.2 Subject Exclusion Criteria

- Patients with history of cardiac dysrhythmia
- Known heart failure (EF < 40%)
- Pacemaker/defibrillator
- Patient's with any metallic cardiac implant
- Patient on anti-coagulation therapy and are unable to stop therapy for the perioperative period
- Women who are pregnant and/or nursing
- Patients with metal implants less than 5 cm from the treatment zone

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, they will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

If a patient is lost to follow-up prior to six months, patient will be replaced.

8.0 PRETREATMENT EVALUATION

All patients referred for possible study entry will be screened to determine eligibility. The pretreatment evaluation will include the following routine standard of care procedures before IRE Ablation:

- Physical Exam
- CBC, Comprehensive Panel, PT& PTT
- Pregnancy test for females of child bearing age (11-50 yo) and potential to have children
- Baseline Chest CT
- Chest X-ray
- EKG

Pregnancy and Laboratory test will be administered as per standard of care for surgery.

Screen failures will be documented in a screening log.

9.0 TREATMENT/INTERVENTION PLAN

The study procedure will be performed according to the standard of care for thoracic surgical procedure under general anesthesia, which may include the use of epidural analgesia. A Paralytic agent, which is also standard of care, will serve to prevent muscle excitation during

the NanoKinfe procedure. The patients will be sterilely prepared and draped according to the standard of care for a thoracotomy (pulmonary metastasectomy). The NanoKnife procedure will be performed in accordance with the FDA-cleared Instructions for Use (IFU).

For the purposes of this study, a set target volume will be ablated using 2 probes spaced approximately 1.0 cm to 1.5 cm apart and at 2.0 cm exposure.

Commercially available Nanoknife spacers will be utilized to ensure proper probe placement as necessary.

The treatment parameters will be 1,600 V/cm and 90 microseconds per pulse, for a total of 90 pulses for the probe pairing. The NanoKnife system will place each IRE pulse 70 milliseconds after the patient's R wave with this cardiac synchronization facilitated by ECG synchronization. Conductivity and impedance measurements will be made from the electrodes.

Ablation of the target volume will be followed by a resection of the tumor tissue and tumor margin as per standard surgical procedures for a pulmonary metastasectomy. Surgical resection and de-vascularization (i.e. cutting off the blood supply) of the tumor will be completed after a minimum of 15 minutes has elapsed from the time of ablation.

Upon resection, the investigating surgeon will mark the electrode entry sites and orientation, as well as mark the approximate center of the ablation zone. The tissue specimen may be marked using either of the following methods:

- Using appropriate markers, e.g., 2 or 3 inch angio-catheter type IV introducers
- Using the electrodes from the study procedure as markers, i.e., the electrodes can be cut off and left placed in the tumor following the ablation and resection

Any other marking or inking of the tumor to facilitate routine pathology of the resected specimen may be performed as needed. The marked tumor will then be placed in an appropriate specimen container and sent for pathology examination.

Once the study procedure has been completed, the probes will be removed and discarded appropriately. Upon completion of the surgery patients will be observed in the PACU and then observed on the surgical floor.

Subjects will receive treatment on one lung at a time. If both lungs have suitable resectable metastases, the subject may return at a later date to have the other lung treated. The subject will not receive a new subject ID#, but will have all applicable data collected on additional case report forms.

Post Procedure (within 24-72 hours)

The following assessments must be performed within 24-72 hours after the procedure stop time:

- Physical assessment
- Vital signs
- Laboratory Tests:

- CBC, Comprehensive Panel, PT& PTT

- Review of medications
- Review of adverse events
- AP and Lateral Chest X-ray (performed according to standard radiological procedures)

1 month Follow-Up

The 1 month Follow-Up visit must take place within 30 days (+/- 14 days) after the procedure date.

The following assessments must be performed at this visit:

- Physical assessment
- Vital signs
- Laboratory Tests:
  - CBC, Comprehensive Panel, PT& PTT
- Review of medications
- Review of cancer therapies
- Review of adverse events
- Chest CT

6 month Follow-Up

The 6 month Follow-Up visit must take place within 6 months (+/- 30 days) after the procedure date.

The following assessments must be performed at this visit:

- Physical assessment
- Vital signs
- Laboratory Tests:
  - CBC, , Comprehensive Panel, PT& PTT
- Review of medications
- Review of cancer therapies
- Review of adverse events
- Chest CT

Histological assessment of resected tumor

Tissue samples of resected lung will undergo standard histopathologic evaluation. Gross pathologic assessment using Triphenyl tetrazolium chloride (TTC) assay will be used to

evaluate the zone of irreversible electroporation (IRE). Routine histology with hematoxylin and eosin (H&E) may be used to characterize acute tissue changes in the ablation and border regions. Mitochondrial stains for viability will also be applied. Mason Trichome (MT) stains will be applied to assess the morphological status of collagen within the treatment region. Pathological Analysis will be used to construct numerical models that will try to assimilate the distribution of electric fields during treatment delivery.

IRE creates large stable pores in cell membranes that result in the loss of cellular homeostasis and cell death. The process of morphological cellular changes that can definitively be called cell death typically takes 2 to 6 hours. Due to the timing and length of the study procedure, it is unlikely that the tissue specimens examined in this study will exhibit definitive necrosis in the target ablation volume. However, early morphologic cellular changes may be observed in the ablation zone.

Changes in the tissue specimen that may be expected to be observed following the study procedure may include, but are not limited to, the following:

- Edema (swelling)
- Capillary congestion with red blood cells
- Cellular shrinkage
- Pyknosis (nuclear shrinkage)
- Karyorrhexis (nuclear or chromatin fragmentation)
- Reduced hematoxylin intensity (if H&E staining is performed)

Any histologic observations of the ablation zone will include delineation of the zones where acute tissue changes are present and will be recorded.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	PreTreatment Evaluation		Ablation		Post Ablation (within 24-72 hours)		1 Month Follow Up (+/- 14 days) Post Ablation		6 Month Follow Up (+/- 30 days) Post Ablation
History, Physical Assesment, Vital signs, Review of medications, Review of cancer Therapies	X				X		X		X
Laboratory Test (• CBC, Comprehensive Panel, PT& PTT)	X				X		X		X
Review of Averse Events					X		X		X
Pregnancy Test	X								
EKG	X								
Chest CT	X						X		
IRE Ablation			X						
Chest X-ray (AP & Lateral)	X				X				*

**Pregnancy and Laboratory test will be administered as per standard of care for surgery.*

11.0 TOXICITIES/SIDE EFFECTS

Irreversible electroporation (IRE) uses needle electrodes to deliver a current that generates an electro-magnetic field across cell membranes causing formation of expanding pores resulting in localized necrosis - cell death – of the targeted tissue. Complications related to the device and surgical IRE procedure are rare. In 100 cases at MSKCC there are no reports of serious adverse events related to IRE. All Adverse Events, whether related to surgery or the IDE, will be recorded in the Toxicity Case Report Form in the Clinical Research Database. Most of the AEs will likely be related to surgery. AEs that are believed to be directly from the IRE will be noted. If there are 3 or more grade 3 or higher device related AEs, then we will stop the study.

Complications related to surgical resection (which is the standard of care for colorectal metastases to the lung) are well established. Potential device complications include:

Due to Electric Current

- Risk of cardiac arrhythmia. Synchronizing the pulse delivery with the EKG so that pulses are given during the refractory period of the cycle should minimize this risk.
- Involuntary muscle contraction at the time of the electric pulse, which stops at the end of the pulse. This is managed by giving a paralytic agent prior to the electrical pulse delivery.
- Neuropathic Pain

Due to Electrode Placement

- Risk of infection for the patient
- Risk of bleeding

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Safety will be measured by using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0).

The goal of this study is to establish safety.

If there are 3 or more grade 3 or higher device related AEs, then we will stop the study.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Participation in the study is strictly voluntary. Patients have the right to withdraw from the study at any time. If a patient chooses to withdraw, he or she must inform the investigator immediately. Results will be released on Clinicaltrials.gov within one year of the conclusion of the study interventions (after followup is completed of final patient accrued). If the study is stopped early, data will be posted within one year of termination.

14.0 BIOSTATISTICS

The study goal is to assess early evidence of safety before progressing to a percutaneous study. The number of patients chosen for this study is empirical and was performed at the behest of suggestions from FDA reviewers who reviewed a prior version of this protocol. The frequency of adverse events will be tabulated separately by type, severity and time of onset. Safety assessment performed during this study is largely expected to be qualitative in nature. The results will be presented using descriptive statistics.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

N/A

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Quarterly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

This proposal is for a prospective clinical trial investigating safety of a new lung ablation tool in patients with limited colorectal cancer metastases to the lung. Participant will be eligible if they have limited colorectal metastases in their lung. Requirements in general require adequate hematopoietic, cardiac and pulmonary function for lung ablation. Subjects will be recruited from the MSKCC Oncology Clinics and consented in the Interventional Radiology or Surgery clinics.

Criteria for removal of patients from research studies include: 1) patient wishes to withdraw; 2) new data indicate a better therapy is available; or 3) unacceptable toxicity. Patients removed from research studies will be offered the best available therapy or palliative care as appropriate. Compliance with privacy policies will be upheld.

There are no potential benefits to these patients already planning surgery.

The following tests/labs will be Research Non-Billable:

- Labs drawn at post-procedure, 1 month and 6 month follow-up
- Chest CT at 1 month follow-up

Potential risks will be related to needle based electroporation and include bleeding, infection, and cardiac arrhythmia. Alternatives include other forms of ablation, surgery, radiation, or no intervention.

Women and Minority Inclusion in Clinical Research

This clinical trial is in confirmation with the National Institutes of Health (NIH) Revitalization Act of 1993, PL 103-43, signed into law on June 10, 1993. The NIH Revitalization Act of 1993 directed the NIH to establish guidelines for inclusion of women and minorities in clinical research. The statute states that:

In conducting or supporting clinical research for the purposes of this title, the Director of NIH shall ensure that:
(a) women are included as subjects in each project of such research; and
(b) members of minority groups are included in such research. 492B(a)(1)

Patients will not be billed for the IRE.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported. All events will be recorded and reviewed by the Principle Investigator to determine if the SAE is associated with the surgery or the IRE. The PI will determine SAEs for each case and only SAEs possibly, probably, or definitely related to the IRE ablation will be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)

- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND

17.2.1

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1 Cancer Facts & Figures 2010, American Cancer Society 2010.

2 Turk PS, Wanebo HJ. Results of surgical treatment of non-hepatic recurrence of colorectal carcinoma. Cancer 1993; 71:4267-4277.

3 Blalock A. Recent advances in surgery. N Engl J Med 1944; 231:261-267.

4 Mountain CF, McMurtrey MJ, Hermes KE. Surgery for pulmonary metastases: A 20 year experience. Ann Thorac Surg 1984; 38:323-330.

5 Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastatectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. J Thorac Cardiovase Surg 1997; 113:37-49.

6 Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg 2007; 84:324-338.

7 Version 2010 NCCN Clinical Practice Guidelines in Oncology: Colon Cancer.

8 Brunelli A and Salati M. Preoperative evaluation of lung cancer: predicting the impact of surgery on physiology and quality of life. Curr Opin Pulm Med 2008; 14:275-281.

9 Kim AW, Faber P, Warren WH, et al. Repeat pulmonary resection for metachronous colorectal carcinoma is beneficial. Surgery 2008; 144:712-718.

10 Yamakado K, Hase S, Matsuoka T, et al. Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: a multicenter study in Japan. JVIR 2007; 18:393-398.

11 Hiraki T, Gobara H, Iishi T et al. Percutaneous radiofrequency ablation for pulmonary metastases from colorectal cancer: midterm results in 27 patients. JVIR 2008; 18:1264-1269.

12 Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). Lancet Oncology 2008; 9:621- 628.

13 Solazzo SA, Liu Z, Lobo SM, et al. Radiofrequency ablation: importance of background tissue electrical conductivity-an agar phantom and computer modeling study. Radiology 2005; 236:495-502.

14 Lobo SM, Liu Z-J, Yu NC, et al. RF tumour ablation: computer simulation and mathematical modeling of the effects of electrical and thermal conductivity. Int J Hyperthermia 2005; 21:199-213.

15 Liu Z, Lobo SM, Humphries S, et al. Radiofrequency tumor ablation: insight into improved efficacy using computer modeling. AJR 2005; 184:1347-1352.

16 Schramm W, Yang D, Haemmerich D. Contribution of direct heating, thermal conduction and perfusion during radiofrequency and microwave ablation. Conf Proc IEEE Eng Med Biol Soc 2006; 1:5013-5016.

17 Lu DS, Raman SS, Vodopich DJ, Wang M, Sayre J, Lassman C. Effect of vessel size on creation of hepatic radiofrequency lesions in pigs: assessment of the “heat sink” effect. AJR 2002: 178:47-51.

18 Pereira PL, Trubenbach J, Schenk M, et al. Radiofrequency ablation: in vivo comparison of four commercially available devices in pig livers. Radiology 2004; 232:482-490.

19 Kim TS, Lim HK, Kim H. Excessive hyperthermic necrosis of a pulmonary lobe after hypertonic saline enhanced monopolar radiofrequency ablation. Cardiovasc Interv Radiol 2006; 29:160-163.

20 Brace CL, Hinshaw JL, Laeseke PF, Sampson LA, Lee Jr FT. Pulmonary thermal ablation: comparison of radiofrequency and microwave devices by using gross pathologic and ct findings in a swine model. Radiology 2009; 251:705-711.

21 Miller L, Leof J, Rubinsky B. Cancer cells ablation with irreversible electroporation. Technol Cancer Research Treatment 2005; 4:699-706.

22 Edd JF, Horowitz L, Davalos RF, Mir LM, Rubinsky B. In-vivo results of a new focal tissue ablation technique: irreversible electroporation. IEEE Trans Biomed Eng 2006; 53:1409-14-15.

23 Lee EW, Chen C, Prieto VE, Dry SM, Loh CT, Kee ST. Advanced hepatic ablation technique for creating complete cell death: irreversible electroporation. Radiology 2010; 255:426-433.

24 Ball C, Thomson KR, Kavnoudias H. Irreversible electroporation: a new challenge in “out of operating theater” anesthesia. Anesth Analg 2010; 110:1305-1309.

25. Kingham TP, Karkar AM, D'Angelica MI, Allen PJ, Dematteo RP, Getrajdman GI, Sofocleous CT, Solomon SB, Jarnagin WR, Fong Y. Ablation of perivascular hepatic malignant tumors with irreversible electroporation. J Am Coll Surg. 2012 Sep;215(3):379-87. doi: 10.1016/j.jamcollsurg.2012.04.029. Epub 2012 Jun 16.

26 Davlos RV and Rubinsky B. Temperature considerations during irreversible electroporation. Int J Heat Mass Transfer 2008; 51: 5617-5622.

27. Silk MT, Wimmer T, Lee KS, Srimathveeravalli G, Brown KT, Kingham PT, Fong Y, Durack JC, Sofocleous CT, Solomon SB. Percutaneous Ablation of Peribiliary Tumors with Irreversible Electroporation. J Vasc Interv Radiol. 2013 Nov 18. pii: S1051-0443(13)01503-0. doi: 10.1016/j.jvir.2013.10.012.
28. Maor E, Ivorra A, Mitchell JJ, Rubinsky B. Vascular smooth muscle cells ablation with endovascular nonthermal irreversible electroporation. J Vasc Interv Radiol. 2010 Nov;21(11):1708-15.

29. Srimathveeravalli G, Wimmer T, Monette S, Gutta NB, Ezell PC, Maybody M, Weiser MR, Solomon SB. Evaluation of an endorectal electrode for performing focused irreversible electroporation ablations in the Swine rectum. J Vasc Interv Radiol. 2013 Aug;24(8):1249-56. doi: 10.1016/j.jvir.2013.04.025. Epub 2013 Jun 21.
30. Wimmer T, Srimathveeravalli G, Gutta N, Ezell PC, Monette S, Kingham TP, Maybody M, Durack JC, Fong Y, Solomon SB. Comparison of simulation-based treatment planning with imaging and pathology outcomes for percutaneous CT-guided irreversible electroporation of the porcine pancreas: a pilot study. J Vasc Interv Radiol. 2013 Nov;24(11):1709-18.
31. Deodhar A, Monette S, Single GW Jr, Hamilton WC Jr, Thornton RH, Sofocleous CT, Maybody M, Solomon SB. Percutaneous irreversible electroporation lung ablation: preliminary results in a porcine model. Cardiovasc Intervent Radiol. 2011 Dec;34(6):1278-87. doi: 10.1007/s00270-011-0143-9. Epub 2011 Mar 31.
32. Neal RE 2nd, Garcia PA, Robertson JL, Davalos RV. Experimental characterization and numerical modeling of tissue electrical conductivity during pulsed electric fields for irreversible electroporation treatment planning. IEEE Trans Biomed Eng. 2012 Apr;59(4):1076-85. doi: 10.1109/TBME.2012.2182994. Epub 2012 Jan 6.
33. Ben-David E, Ahmed M, Faroja M, Moussa M, Wandel A, Sosna J, Appelbaum L, Nissenbaum I, Goldberg SN. Irreversible electroporation: treatment effect is susceptible to local environment and tissue properties. Radiology. 2013 Dec;269(3):738-47. doi: 10.1148/radiol.13122590. Epub 2013 Oct 28.
34. Joines WT, Zhang Y, Li C, Jirtle RL. The measured electrical properties of normal and malignant human tissues from 50 to 900 MHz. Med Phys. 1994 Apr;21(4):547-50.
35. Sanchez B, Vandersteen G, Martin I, Castillo D, Torrego A, Riu PJ, Schoukens J, Bragos R. In vivo electrical bioimpedance characterization of human lung tissue during the bronchoscopy procedure. A feasibility study. Med Eng Phys. 2013 Jul;35(7):949-57.
36. Morimoto T, Kimura S, Konishi Y, Komaki K, Uyama T, Monden Y, Kinouchi Y, Iritani T. A study of the electrical bio-impedance of tumors. J Invest Surg. 1993 Jan-Feb;6(1):25-32.
37. Daniels C, Rubinsky B. Electrical field and temperature model of nonthermal irreversible electroporation in heterogeneous tissues. J Biomech Eng. 2009 Jul;131(7):071006. doi: 10.1115/1.3156808.
38. Brace CL. Radiofrequency and microwave ablation of the liver, lung, kidney and bone: What are the differences. Curr Probl Diagn Radiol. 2009 May-Jun;38(3):135-43.
39. Srimathveeravalli G and Solomon SB. Treatment Planning Considerations for IRE in the Lung: Placement of Needle Electrodes is Critical. Talk presented at the SIR Annual Symposium, 2013.
40. Ahmed M, Liu Z, Humphries S, Goldberg SN. Computer modeling of the combined effects of perfusion, electrical conductivity, and thermal conductivity on tissue heating patterns in radiofrequency tumor ablation. Int J Hyperthermia. 2008 Nov;24(7):577-88. doi: 10.1080/02656730802192661
41. Dielectric properties of body tissues in the frequency range of 10Hz – 100 GHz. http://niremf.ifac.cnr.it/tissprop/
42. Ben-David E, Appelbaum L, Sosna J, Nissenbaum I, Goldberg SN. Characterization of irreversible electroporation ablation in in vivo porcine liver. AJR Am J Roentgenol. 2012 Jan;198(1):W62-8.
43. Deodhar A, Dickfeld T, Single GW, Hamilton WC Jr, Thornton RH, Sofocleous CT, Maybody M, Gónen M, Rubinsky B, Solomon SB. Irreversible electroporation near the heart:

ventricular arrhythmias can be prevented with ECG synchronization. AJR Am J Roentgenol. 2011 Mar;196(3):W330-5.

20.0 APPENDICES