MSK PROTOCOL COVER SHEET

Trial of IRE in Cholangiocarcinoma (TOn/C): Phase II

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Rationale: The majority of patients with perihilar cholangiocarcinoma (PHC) have locally advanced disease {LAD} upon presentation or exploratory laparotomy; for this reason, they are not suitable candidates for curative resection[1]. Additionally some of the patients develop locally advanced recurrence during their course of disease. Therefore, in most patients with this type of biliary tract cancer, only palliative concepts can be offered. ERCP guided and/or percutaneous transhepatic biliary drainage offer the best survival, because in combination with sufficient drainage, reduction of tumor masses in the lumen of the bile duct was shown to prolong patient survival[2]. Effectiveness of photodynamic therapy (PDT) was investigated in two randomized controlled and a few controlled studies[3-8]. But these studies failed to prove efficacy with clear impact on clinical outcomes. Moreover, PDT has not become part of normal clinical practice because it causes skin phototoxicity lasting for 3-4 weeks and requires technology not available at most centers. Other thermal ablative methods, such as radiofrequency ablation, are affected by a heat-sink effect when tumors are located close to vascular structures, such as the liver hilum, which can limit effectiveness, and there are concerns with injuries to biliary and vascular structures in treating these areas. These limitations may be overcome by irreversible electroporation {IRE}, which is a non-thermal tissue ablation method that has been used to treat liver tumors in over 60 patients at MSK. By exposing cancer cells to a sufficient electric field by IRE, cell plasma membranes are disrupted and cells undergo apoptotic or necrotic cell death[9, 10]. Therefore, IRE is considered as non-thermal ablation technique and is currently applied to treat liver tumors where thermal ablation techniques are contraindicated.

Objective: This study will investigate the outcomes of IRE for the treatment of unresectable, locally advanced PHC..

Study design: A single center phase II study.

Study population: 20 patients with locally advanced PHC deemed unresectable due to preoperatively determined primary tumor characteristics and/or distant lymph node metastases (N2} or due to discovery of unresectability on exploratory laparotomy.

Main study endpoints:

The primary outcome is patency of biliary drainage. In patients with plastic percutaneous drains this is defined as ability to remove plastic biliary drains within 1.5 months of the IRE procedure without need for reinsertion of a drain or stent. For patients with metal stents in place the definition of patent biliary drainage is 4-months without cholangitis post IRE procedure.

Secondary outcomes are the success rate of completing IRE (defined as percentage of planned pulses completed}, complications, duration of hospital stay, quality of life, impact of IRE on post-procedural CT imaging and blood biomarker response, time between IRE and start of palliative chemotherapy, metal stent patency, progression-free and overall survival. Prolonged hospital stay is defined as hospital stay for more than 10 days. The average length of stay for major liver procedures is 8 days. Patients with hilar cholangiocarcinomas often have biliary drains and stents so require extra care as inpatients after any procedure. Complications will be defined as patients experiencing a clinically relevant IRE-related complication within 30 days post-IRE, defined as CTCAE (version 5.0} grade

3 or higher complications requiring re-intervention, prolonged hospital stay, intensive care admission, re-admission or leading to mortality.

Follow up: 30 days after intervention for the primary endpoint. For survivalendpoints, there is a 2-year followup.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

The primary objective of this study is to assess patency of biliary drainage. In patients with plastic percutaneous drains this is defined as ability to remove plastic biliary drains within 1.5 months of the IRE procedure without need for reinsertion of a drain or stent. For patients with metal stents in place the definition of patent biliary drainage is 4-months without cholangitis post IRE procedure.

Secondary objective:

The secondary outcomes of interest are

- Duration of hospital stay
- Complications
- Quality of life
- Tumor response on CT imaging and blood biomarker response
- Time between IRE and start of palliative chemotherapy
- Duration of palliative chemotherapy
- Progression-free and overall survival
- Success rate of completing IRE (defined as percentage of planned pulses completed)

3.0 BACKGROUND AND RATIONALE

Perihilar cholangiocarcinoma (PHC),also known as Klatskin tumor, is the most commontype of bile duct cancer, with an annual incidence of 1to 2 per 100,000 in Western countries. It arises at or near the confluence of the right and left main bile duct. Patients typically present with obstructive jaundice and are staged with cross-sectional imaging of the abdomen and chest. In the absence of metastatic disease, patients are eligible for resection with curative intent, which is the only treatment that confers a chance of long-term survival[11]. Five-year overall survival (OS) after resection varies from 13% to 40% across series with more than 100 patients[12]. The poor 5-year OS reflects a high recurrence rate of 49 to 76% after curative intent resection of PHC [13]. Only 50% of the patients were suitable candidates for surgery due to unresectability at presentation and another 40% are found to have locally advanced or metastatic disease during exploratory laparotomy. In patients with disease ultimately deemed unresectable, approximately half of tumors are considered locally advanced because of

unreconstructable vascular involvement or extensive biliary involvement. Liver transplantation in these cases is only performed in a few experienced centers worldwide with strict selection criteria and extensive preoperative work-up including neoadjuvant treatment. Unfortunately, high dropout rates up to 30% prior to transplantation are reported. Systemic chemotherapy is the mainstay of treatment for patients who are not candidates for curative resection or neoadjuvant therapy followed by liver transplantation. Traditionally, the preferred regimen has been the combination of gemcitabine and cisplatin and offers a median progression-free survival of 8 months and overall survival of 12 months[14]. The recently released results fran the BILCAP randomized trial of adjuvant capecitabine compared to best supportive care showed an apparent lack of benefit in the hilar cholangiocarcinoma patients (HR 1.09; 95% CI 0.68, 1.71; ASCO 2018 abstract). Trials in patients with more advanced disease suffer from a lack of accrual of patients with locally advanced hilar cholangiocarcinoma, so we have to extrapolate from trials like BILCAP.

The goals of palliative biliary drainage are to relieve jaundice, prevent cholangitis and liver failure, and improve quality of life [15]. Biliary stents are not without risk and have been associated with occlusion, migration, cholecystitis, and tumor ingrowth and seeding[16]. Successful biliary drainage has obvious palliative advantages to leaving patients undrained due to the morbidity of untreated cholangitis. In addition, in one randomized trial of plastic vs. metal stents, there was a survival advantage with metal stents compared to plastic stents (due to longer patency rates) [17]. "'1etal stents are a more durable and cost-effective option as they have a patency superior to that of plastic stents, with patients requiring less frequent procedures (Table 1) [18]. IVorbidity related to stents can occur even within 30 days of placement (39% plastic stents and 12% metal stents) [19]. Although the overall prognosis of unresectable PHC is poor, patients with locally advanced PHC or lymph node metastases

Table 1. Time of patency (months)

	Plastic stents	"'1etal stents	P value
Sanachan et al r171	1.0	3.0	<0.0001
Raiu et al r181	1.9	5.6	<0.0001

beyond the hepatoduodenal ligament have significant longer survival (14 to 16 months) compared to patients with organ metastases (3 to 5 months)[20]. 12% of these patients even survive for more than 36 months[20]. This particular subgroup of PHC patients with primary locally advanced disease may therefore benefit from ablative therapies that counteract tuma growth and potentially improve biliary stent patency and survival. In the past decade, several different ablative techniques like stereotactic body radiation therapy, photodynamic therapy (PDT), (intraductal) radiofrequency ablation {RFA), brachytherapy and microwave ablation have been investigated. Local tumor reduction by PDT in combination with stent therapy is effective for reducing cholestasis. For patients with unresectable hilar cholangiocarcinoma, two randomized studies and several controlled studies have shown an advantage in survival over stenting alone, given improved stent patency[21]. Furthermore, some trials demonstrated a gain in QoI or in performance status[4-7]. But PDT has major limitations such as skin phototoxicity for 3-4 weeks due to the use of slowly degradable photosensitizers in PDT[22]. In addition, thermal ablative modalities {i.e. RFA) are limited by the disadvantages of surrounding tissue heating causing strictures to bile ducts and thromboses to portal vein and

hepatic artery branches and the heat-sink effect. This effect is caused by blood flow in surrounding vessels creating an area where optimal temperatures are not reached, leaving viable cancertissue in situ [23]. This is particularly challenging in PHC because of the typical bcation in the liver hilum near the portal vein and hepatic artery. Considering these limitatbns, there is a need to investigate new non-thermal ablative techniques in the treatment of bcally advanced PHC.

IRE is FDA approved for soft tissue ablation. Bile duct cancers are considered soft tissue.The most extensively studied organ for use of IRE has been the liver and the liver hilum, where delicate structures in the hepatoduodenal ligament preclude intervention using thermal ablation techniques. Demonstration of lack of significant acute injury to hepatic vessels and bile ducts by the early work of Lee et al [24] has now been corroborated by several authors with confirmed safety with up to 8 weeks of follow-up[25, 26].An overall complication rate of 16% has been recently described in a meta-analysis[27]. /Is a comparison, in a review on hepatic RF ablation in 3,670 patients, the overall complication rate was 9%,with rates of 7%, 10%, 10%, and 32% for percutaneous, laparoscopic, simple open, and combined open RF ablation[28].

Ih one study using serial computed tomography (CT) scanning, IRE lesions created around large hepatic veins showed minimal early narrowing, but with complete recovery over time and no evidence of late thrombosis or occlusion[26]. IRE around hilar bile ducts similarly showed overall resistance to significant injury, with some ducts exhibiting, at worst, clinically insignificant late strictures [29].Three major studies have been published by our group at MSK in the past about irreversible electroporation in perivascular or peribiliary hepatic malignant tumors [30-32]. Silk et al [32] evaluated biliary complications after IRE of 19 liver metastases in nine patients within 1 cm of the common, left, or right hepatic duct. One patient showed subsegmental bile duct prominence without increased bilirubin; this still existed after 11 months, without progressive dilation or segmental atrophy. Retrospective review of computed tomography images showed that one needle was placed in direct contact with the bile duct. Two other patients showed bile duct dilation with increased bilirubin, for which one required stent placement; both conditions appeared to be secondary to tumor progression. Kingham et al [30] treated 28 patients with 65 tumors, of which most were located < 1 cm from a major hepatic vein or portal pedicle, similar to patients with PHC. The overall morbidity was 3%. Complications included 1 intraoperative arrhythmia and 1 postoperative portal vein thrombosis. There were no treatment-associated mortalities. At. median follow-up of 6 months, there was 1 tumor with persistent disease (1.9%) and 3 tumors recurred bcally (5.7%)[30]. Ih the Netherlands, a phase VII feasibility study of IRE in patients with advanced PHC (ALPACA-trial) was initiated this year[33]. A series of 26 patients with unresectable hilar cholangiocarcinoma was also recently published {IV'artin et al, Safety and efficacy of irreversible electroporation in the treatment of obstructive jaundice in advanced hilar cholangiocarcinoma. HPB, 2018 in press). This retrospective review compared these patients to 137 patients with unresectable hilar cholangiocarcinoma who did not undergo IRE. The median catheter free time in the IRE patients was 305 days (range 92-458 days). Of the 137 control patients, 80 (59%) had an admission for biliary drain infection, occlusion, or other catheter related problem. This bolsters

our hypothesis that IRE in patients with unresectable perihilar cholangiocarcinoma can prolong the stent patency and therefore prevent septic complications. In addition, only 2 of 26 patients had a grade 3 or higher complication,.

The demonstration of tissue structure sparing in the many organs (especially in the liver) supports the relative safety of IRE, and bodes well for this technology's potential. However, several investigators have pointed out the lack of complete understanding of how best to optimize IRE treatments in a variety of tissues, healthy, and neoplastic. Altering the treatment parameters of the energy transmitted to the tissue may produce zones of IRE as well as zones that may be subjected to additional effects including thermal damage, especially in tissue immediately surrounding an electrode. As demonstrated by the work of Faroja et al, tissue temperatures exceeding protein denaturation can be achieved by manipulation of certain dosing parameters. Recent work also showed differences in imaging and histopathology effects as a function of distance from the IRE electrode, with an immediate perielectrode zone that appeared to have more coagulative changes in contrast to the expected non-coagulative IRE zone marked by congestion. Choi et al. showed potential damage to the bile duct mural architecture when the IRE electrodes were immediately adjacent to the ducts. As a safety precaution, placement of electrodes < 3 mm to central bile ducts should be avoided.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a prospective, single-center phase II study to look at the outcomes of\ IRE with the use of NanoKnife® system (AngioDynamics, Queensbury, NY) in patients with preoperatively diagnosed locally advanced, unresectable PHC due to vascular or lymph node involvement, or those with potentially resectable tumors (those that are expected to be fully resectable before surgery) that appear intraoperatively to be locally advanced or metastasized to N2 lymph nodes at exploratory laparotomy.

4.3 Intervention

The study will evaluate the outcomes of using IRE in patients with intraoperatively determined advanced unresectable PHC. The study will include data from 20 patients that have this IRE procedure performed as standard of care by hepatopancreatobiliary surgeons with experience using IRE.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The NanoKnife (AngioDynamics, Queensbury, NY) IRE device will be used in all patients. The device is cleared by the US Food and Drug Administration for use in ablating soft tissue. The

IRE device comprises a generator, a foot pedal, and 15- or 25-cm-long electrodes. The electrodes used to treat these patients have a tip length ranging from 5 to 40 mm. This distance represents the active tip of the electrode and the remainder of the needle is insulated. The IRE device generates 1,500 to 3,000 V. Voltage is determined by a standard algorithm (AngioDynamics) that uses factors such as the intended size of the ablation zone, the number of probes, the distance between probes, and the length of the active electrode tip.[15] The size or shape of the tumor determines the number of electrodes used.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

The study population consists of 20 adult patients who are diagnosed with locally advanced, unresectable PHC. Unresectability will be established either preoperatively, based on imaging and other preoperative testing, or intraoperatively in patients undergoing planned exploratory laparotomy. Patients will be recruited at the outpatient clinic. In cases of a planned exploratory laparotomy, patients will be asked to participate in the study in case disease is deemed unresectable during surgery. These patients will undergo IRE during the same operative session. Patients with unresectable tumors based on imaging at initial visit or preoperative workup, will be asked to participate in the study and receive IRE via laparotomy. Prior to surgery, biopsies will be taken to verify perihilar cholangiocarcinoma. Patients with resectable PHC, PHC eligible for liver transplantation or organ metastasized PHC at surgical exploration will be excluded. The subject exlusion criteria outlined below is evaluated per standard of care for the IRE procedure and as such is listed in this protocol.

6.2 Subject Inclusion Criteria

In order to participate in this study, a patient must meet all of the following criteria:

- e 18 years or older
- Capable of providing written and oral informed consent in English

Meets criteria for unresectable disease:

- Locally advanced disease based on preoperative work-up demonstrating that the tumor is unresectable due to portal vein, hepatic artery, and/or bile duct involvement, insufficient hypertrophy response of the future liver remnant after portal vein embolization, or patients not able to tolerate major liver surgery

- Found to be unresectable intraoperatively based on vascular, biliary, or lymph node (N2) involvement upon exploratory laparotomy

- Patients will be assessed for chemotherapy prior to treatment with IRE, but given the common problem of recurrent cholangitis, some patients will not be candidates for chemotherapy until after IRE is performed.

6.3 Subject Exclusion Criteria

- Locally advanced PHC eligible and accepted for liver transplantation evaluation
- PHC with > 5 cm extension abng the common hepatic duct or common bile duct on preoperative imaging or intraoperative ultrasound
- Metastases to peritoneum, liver or other organs confirmed by percutaneous biopsy, staging laparoscopy or intraoperative frozen section
- Lymph node metastases beyond N2 stations, confirmed by intraoperative frozen sections or radiographic diagnosis
- History of cardiac disease:
    - Congestive heart failure (NYHA class >2)
    - .Active Coronary Artery Disease (defined as myocardial infarction within 6 months prior to screening)
    - Cardiac arrhythmias requiring anti-arrhythmic therapy or pacemaker (beta blockers are permitted)
- Ally implanted stimulation device (defined as implantable cardiac device and a pacemaker)
- Uncontrolled hypertension (blood pressure must be 160/95 mmHg at the time of screening on a stable antihypertensive regimen)
- Uncontrolled infections (> grade 2 NCI-CTC, version 30)
- Epilepsy
- Both narrowing (sclerosis) of the main portal vein and a reduced diameter of either the common hepatic artery, celiac trunk or superior mesenteric artery of >50%

7.0 RECRUITMENT PLAN

All patients will be recruited in outpatient clinic by one of our hepatopancreatobiliary (HPB) attendings (PK, WJ, JD, VB, MD, AW, KS). Full study information will be provided by the study physician or one of the investigators during the outpatient clinic appointment.

8.0 PRETREATMENT EVALUATION

Due to the nature of disease, patients with PHC undergo extensive pre-operative work-up (e.g., laboratory testing, CT or MR imaging, biliary drainage, liver function tests) prior to surgical exploration and potential portal vein embolization. In the present study, patients that will undergo open RE during exploratory laparotomy will have undergone these preoperative work-up procedures as standard of care. Additionally Quality of life will be assessed during the pre-treatment visit using the Functional Assessment of Cancer Therapy-Hepatobiliary instrument (FACT-Hep). FACT-Hep is a 45-item self-report instrument designed to measure QoL in patients with hepatobiliary cancers. It comprises the FACT-General (FACT-G) and the hepatobiliary subscale (Hep). The FACT-G consists of 27 items that measure 4 domains of well being in cancer patients: physical well being (PWB), social/family well being (SWB),

functional well being (FWB), and emotional well being (EWB).The instrument employs a Likert-type format (0 "not at all" to 4 "very much"). Lower total scores reflect lower QoI. The FACT-G score is a total of the subscale scores. The FACT-G has demonstrated internal consistency, score stability, relability, and validity [34-39]. The Hep is a reliable and validated disease-specific subscale consisting of questions relating to pruritus, jaundice, and drainage catheters[40,41).Patients will not be replaced if they do not complete these questionnaires.

9.0 TREATMENT/INTERVENTION PLAN

Preoperative biliary drainage

Biliary drainage for malignant hilar strictures or masses is a complex procedure requiring considerable skill and experience. Candidates for IRE who initially present with potentially resectable PHC undergo preoperative biliary drainage as part of the standard preoperative work-up. In the present study, the exact approach of biliary drainage (i.e. endoscopically or percutaneously, specified liver segments, unilateral or bilateral) prior to surgery is decided by surgeon. A metal biliary stent is not considered a contraindication for IRE as long as a no-touch technique is pursued (i.e. IRE electrodes are not in contact with the metal stent).

Antibiotic prophylaxis

Antibiotic prophylaxis will be administered according to the MSKCC's protocol prior to biliary drainage and IRE.Patients will receive one 2g dose of Cefotetan IV, 30-60min prior to surgery. The same antibiotic will be used for the treatment of cholangitis (2g Cefotetan IV every 12 hours). In case of a patient allergy to Cefotetan, patients will receive Clindamycin/Gentamicin as alternative antibiotic treatment.

Intraoperative IRE procedure

Antibiotic prophylaxis is administered prior to the operation. During exploratory laparotomy, resectability of the tumor is assessed by the attending surgeon. When the tumor appears resectable, a resection will be performed. In case of non-nodal (extra)hepatic dissemination of the tumor, no procedure will be performed. In both cases the patients will be excluded frcrn this study. Only when the tumor appears non-resectable, but non-metastasized, an IRE procedure will be performed.The IRE procedure will be performed under ultrasound guidance by the attending surgeon.

NanoKnife® device settings

The NanoKnife® IRE device (AngioDynamics, Queensbury, NY) will be used in this study in normal clinical fashion. This means the machine will be configured to deliver 90 pulses lasting one microsecond each, high-voltage (1500-3000 V) direct current (25-45 A) electrical pulses. Before administering the 90 one-microsecond therapeutic pulses, a test pulse at 270 V is delvered. Typically, 90 pulses will be delivered in 9 sets of 10 pulses between paired unipolar electrodes, with an exposed tip of 1.5-2.0 cm. The voltage setting for each electroporation will

be determined by the distance between each pair of electrodes and will be aimed at 1500 V/cm, with the intent to generate at least 1000 V between electrodes. The electrodes will be placed in and around the tumor under ultrasound guidance according to the manufacturer's guidelines, aiming at a macroscopically complete ablation with a 5 mm margin, with the inter-electrode distances 10-24 mm and a maximum angulation between electrodes of 15°. The predicted treatment zone will be automatically calculated using the NanoKnife generator software according to a system-based protocol that takes into account the exact position of all electrodes. The number of probes used for ablation is dependent on tumor size. If the lesion is larger or has a different shape than the area that one set of probes can cover (according to manufacturer's guidelines), multiple ablations will be performed, until the whole tumor area is ablated. Number of probes, number of probe replacements (per probe) due to unsatisfactory placement, number of pulses (for each pair of electrodes), probe length, space between probes, pulse voltage (amplitude, Volt), pulse length (µsec), pulse interval (ms) will be carefully noted. All complications (cardiac and non-cardiac) will be carefully registered and monitored).

Specific attention will be paid to the placement of electrodes close to bile ducts as previous research demonstrated that biliary strictures may occur when needles are placed within 3 mm of the bie ducts[29,42].

Post IRE treatrrent

Patients will be monitored on the recovery and surgical wards daily, according to current medical practice. Patients with endoscopic or percutaneous plastic drains will be evaluated for definitive metal stents (fully-, partially- or uncovered self-expanding metal stents) or removal of drains if obstruction appears to be treated by IRE in all patients through an endoscopic or percutaneous approach at least 7 days after the IRE procedure. This 7-day window is built in to avoid manipulation of the biliary tree immediately after IRE. Bile ducts to atrophic liver lobes will not be drained. Following exploratory laparotomy and open IRE, patients will undergo treatment in an enhanced recovery program. Patients will be monitored on the recovery and the surgical ward daily and discharged when fully recovered from the laparotomy, according to current medical practice.

General treatment

Patients with advanced PHC generally receive optimal palliative chemotherapy and adequate biliary drainage with metal stenting. In the current study, patients undergo local ablative therapy of the tumor. As it may be difficult to distinguish local IRE-related effects on computed tomography scans or MRI from residual tumor tissue or tumor progression, it was decided that all patients in the current study will be proposed to receive palliative chemotherapy.

Palliative chemotherapy

All patients will be seen by the medical oncologist at I\IISKCC prior to intraoperative IRE is performed, and palliative chemotherapy will be discussed. Patients will be offered optimal palliative chemotherapy according to medical oncology preferences. Palliative chemotherapy is not mandatory to participate in the trial, as some patients will not be eligible due to ongoing

cholangitis. Palliative chemotherapy post procedure is preferably started within 6 weeks after IRE when the patient has recovered from definitive metal biliary stent placement. The start of chemotherapy may be postponed inthe event of IRE-or biliary drainage-related complications. Hbwever, delay of start to chemotherapy is not expected. Ih fact, we suspect that patients will be likely have a better chance of being treated with chemotherapy and for a longer duration of time,due to stent patency.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Data collection prior and during hospital admission

Prior to the procedure we will collect:

Baseline parameters: Demographics, tumor characteristics and serum markers that will be routinely collected are: age, sex, comorbidity,body mass index (BMI), tumor size,tumor growth pattern, arterial or venous vascular involvement, nodal status, cancer antigen (CA) 19.9, lgG4, albumin, C-reactive protein (CRP), leukocytes. If lgG4 level is normal at baseline further measurements are not necessary and will therefore not been included in the follow up.

During the hospital stay,we will collect data on serum liver enzymes and inflammatory parameters (WBC, CRP).

Follow up

During follow up,after discharge, patients will be seen in the outpatient clinic, as is routine practice for post-operative/post-procedural patients, for clinical evaluation and laboratory testing of liver enzymes, inflammatory parameters (WBC, CRP), Albumin and tumor markers (CA 19.9).

Ih this study, patients will also be seen in the outpatient clinic at 2 weeks, 4 weeks, and approximately 6, 12, and 24 months, as is routinely performed for clinical follow-up currently. Laboratory tests obtained at visits after the first post-procedure visit will be determined by the surgeon.

The date of disease progression is defined as the date of CT scan on which the first suspected lesion is defined.

Quality of life will be assessed at the initial clinic visit, initial post-operative visit (2 weeks fran surgery), and at subsequent post-operative visits .±. 1 month from 3,6,9,12, and 24 months following the IRE procedure. The Functional Assessment of Cancer Therapy-Hepatobiliary instrument {FACT-Hep) will be used. If patients are unable to complete the questionnaires at the desginated visits for any reason,they will be offered the option of returning the QOL via mail.

Imaging

CT and rvRI scans used for routine clinical care will be used for this protocol. If patients are receiving chemotherapy, a pre-chemotherapy scanwill be obtained 4-6 weeks post procedure, as per standard clinicalpractice. If no chemotherapy is planned a scan at 4-6 weeks will be clinically appropriate to assess disease progression,treatment response, and stent patency. Scans every 4-6 months will be used in patients on and off chemotherapy to evaluate for disease progression, which is consistent with current practices for routine management of patients with PHC. Tumor response is defined as a loss of enhancement for hypervascular tumors and as alack of persistent tumor rim enhancement for hypovascular tumors on contrast imaging studies. Persistent disease is defined as residual tumor enhancement on the posttreatment imaging studies, and local recurrence is defined as an enhancing tumor within 1cm of an ablation zone.

In order to diagnose complications such as biliary leakage, intra-abdominal abscesses or bleeding, ultrasound and CT are used. When disease progression is expected, a CT is performed to confirm (or refute) the clinical suspicion. This procedure is consistent with normal clinicalstandards.

Follow up of subjects withdrawn from treatment

Patients withdrawn from treatment will not have undergone the IRE procedure and are therefore considered not to have participated in this study. These subjects will receive normal follow-up outside this study.

11.1 TOXICITIES/SIDE EFFECTS

In the postoperative period we will observe for known IRE-specific toxicities. These include (expected frequency in parenthases):

- Hemorrhage, requiring blood transfusion,radiological, or surgicalintervention (3%)
- Hepatic abscess requiring surgery, drainage, or antibiotic therapy alone (5%)
- Biliary stenosis requiring stent placement, bile leakage requiring radiological or surgicalintervention (4%)
- Portalhypertension, portobiliary fistula, hemobilia, thrombosis of hepatic artery or portal vein (3%)
- Hepatic infarction (3%)
- Large biloma (above 5cm) (3%)
- Liver failure (1%)
- Cardiac arrest, heart attack, cardiac arrhythmia during IRE (1%)
- Diaphragmatic paresis (lesion in liver segment VIII) {1%)

Expected adverse events associated with the delivery of strong electric pulses are cardiac arrhythmias and severe muscle contractions. To prevent these events, pulses are generally delivered in the refractory period of the heart and with deep muscle paralysis [43]. Despite electrocardiographic synchronization, passage of high-voltage pulses into the body can still cause conduction disturbances in the heart. In a recent published meta-analysis by Scheffer et al., cardiac arrhythmias occurred in 4 of 194 patients (2%), but they were all atrial arrhythmias that resolved spontaneously or within 24 hours after therapy[27]. With the administration of muscle relaxants, no uncontrolled muscle contractions were reported[30, 32, 44-48]. Only Thomson et al. reported a transient increase in systolic blood pressure in all patients directly after IRE (20-30 mm Hg), which normalized spontaneously[46].

Retrospective comparison showed that numerous liver capsule punctures during IRE did not cause subcapsular hemorrhage and pain after hepatic IRE and RF ablation showed similcr moderate pain intensity with comparable amounts of self-administered pain medication[49].

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOMEASSESSMENT

The primary endpoint is biliary drainage patency. This will be measured as a marker of therapeutic response. Biliary drainage patency in patients with metal stents is defined as the period between IRE treatment and stent occlusion or patient death. Occlusion of the stent is a clinical event. This is defined as recurrent jaundice with cholestasis, cholangitis (fever, increase in serum bilirubin, leukocytosis), stent failure that leads to replacement of a stent, or need to insert a new drain or stent within 4 months. Biliary drainage patency failure in patients that with plastic drains is defined as patients that cannot have plastic drain removed within 1.5 months of the IRE.

The patients and caregivers are told about the symptoms of cholangitis and are asked to contact our hospital immediately in case of signs of obstruction. If stent obstruction is suspected, ERC will be performed and stents are changed if necessary.

Tumor response will not be evaluated in this trial by imaging via RECIST criteria as Klatskin tumors are difficult to measure as they are growing along the biliary tract.

Subjective evaluation of the ablation zone to determine the appearance of an IRE associated ablation zone in the hilar area will be performed on postoperative scans.

Persistent disease is defined as residual tumor enhancement on the first post-treatment imaging study, and local recurrence is defined as an enhancing tumor within 1 cm of an ablation zone.

Ni a secondary endpoint we are measuring overall survival. If there is a response to our treatment, we would expect there may be a longer overall survival.

Response on blood biomarker is defined as decrease of blood marker by >20% from the pre-treatment value.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Patients who withdraw before 120 days due to complications will be counted as failures for the patency objective. Patients who withdraw before 30 days will be counted as having experienced a complication for the purposes of the secondary objective.

14.1 BIOSTATISTICS

The primary objective of this study is to assess biliary drainage patency after IRE treatment of hilar cholangiocarcinoma. In patients with plastic percutaneous drains this is defined as ability to remove plastic biliary drains within 1.5 months of the IRE procedure without need for reinsertion of a drain or stent. For patients with metal stents in place the definition of patent biliary drainage is 4-months without cholangitis post IRE procedure.

We will enroll 20 patients. f\fean patency is approximately 1.5 months for plastic stents and **4** months for metal stents. Assuming an exponential distribution time to failure, we extrapolate that the patency rate at 1.5 months for plastic stents and at 4 months for metal stents will approximately be 37% and we will use this number as our historical control rate. If 10 or more of the 20 patients we plan to enroll display patency (at 1.5 months for plastic and 4 months for metal stents) then we will recommend IRE for further study. This decision rule has 8% Type I error and 12% Type II error for distinguishing between patency rates of 37% and 65%.

The secondary outcomes of interest are:

- Safety will be assessed by determining the proportion of patients experiencing a clinically relevant complication within 30 days post-IRE, defined as CTCAE (version 5.0) grade 3 or higher complications requiring re-intervention, prolonged hospital stay, intensive care admission, re-admission or leading to mortality. After accruing the first 8 patients, we will do an interim analysis of safety. If 4 or more of these 8 patients experience a grade 3 complication within 30 days post-IRE (as defined above) then the study will stop for lack of safety. A 30 day observation window will follow after the eigth patient is enrolled. If one patient in the first 8 patients has a grade 4 or 5 complication the study will be halted. If none of these conditions are met then the we will accrue another 12 patients. If 6 or fewer of the total group of 20 patients have a grade 3 complication we will conclude that the safety endpoint has been met. This safety monitoring rule has an 81% chance of stopping the study early for safety concerns if the true probability of complications is 35%. If there is a death during the 30-day post-procedure period the study will be halted to examine the relationship of death to the procedure. We will examine the cause of death for all 30-day deaths and determine if it could be related to the procedure. If the death can possibly be related to the

procedure then the protocolwill be stopped. To continue with the protocol after a death, we will submit to IRB all the documentation related to the ascertainment of cause of death and describe how it cannot be related to the IRE procedure.

- Duration of hospital staywill summarized with median, range and quarti es.
- Quality of life will be summarized by average subscale scores at each visit and change from previous visit will also be reported by the same summary statistics.
- Tumor response on CT imaging and blood biomarker response will be reported as a binomial proportion with a 95% confidence interval. RECIST criteria cannot be applied to Klatskin tumors as they are radiographically difficult to assess. This instead will be a subjective evaluation of the ablation zone to determine the appearance of an IRE associated ablation zone in the hilar area. This is currently unknown.
- Time between IRE and start of palliative chemotherapy will summarized with median, range and quartiles
- Duration of palliative chemotherapy will summarized using Kaplan-fv1eier statistics
- Progression-free and overall survival will summarized using Kaplan-I'v'leier statistcs
- Success rate of completing IRE reported as a binomial proportion with a 95% confidence interval

Expected accrual rate, accrual duration, and study duration

Our anticipated accrualrate is approximately 1 patient per month. This accrualrate is based on analyzis of potentially eligible patients seen at our Outpatient Clinic in the last 2 years (2016 and 2017). Thus, it should take approximately 1.5 years to accrue the 20 patients needed for the trial. Allowing for 2 months of follow-up to obtain the primary endpoint on the last patient enrolled and 4 months to assemble, analyze and interpret the data the total study duration is projected to be at most 2 years. Patients who consent to the procedure but do not have it will be considered a screen failure. They will be replaced by another patient and their questionnaire data will be removed from the study.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 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.

The indMdual signing the Eligibility Checklist will confirm whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 {Protocol Participant Registration).

All participants must be registered through the Clinical Trial Management System (CTMS).The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded into CTMS.

15.2 Randomization

Not applicable

16.1 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, patient registration, eligibility confirmation, data collection, abstraction and entry, data reporting, sample de-identification, 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 REDCap database on a secure server.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of consent and 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. The principal investigator will maintain final responsibility for data during the study and during the final analysis of data. Breaches of protocol, problems with informed consent, or discrepancies in data accuracy will be reported to the IRB as required.

16.3 Data and Safety Monitoring

The Data and Safety M>nitoring (DSM) Plans at I\Ilemorial 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 M>nitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines .The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety M>nitoring Plans can be found on the MSKCC Intranet at: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20M>nitoring%20Plans.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.

16.3 Regulatory Documentation

Prior to implementing this protocolat I'v1SK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB}. There will be one protocol document an each participating site will utilize that document.

17.1 PROTECTION OF HUMMI SUBJECTS

The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments). The study will seek in every way to protect the rights of human subjects. The potential risks will be dscussed in detail with the patients. Potential side effects as outlined above will be discussed with the patients. No patient will be required to participate in the study and participation or lack of participation will not affect the patient's subsequent care or treatment. The cost of getting the IRE procedure is not paid by the study sponsor. so the patient or their insurance company will have to pay for this. Participation will be purely voluntary and subjects will not be reimbursed for participation in the study. Throughout the study, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular patient in the study. All adverse events (AEs} will be fully disclosed to the IRB in a timely fashion as required.

17.2 Privacy

MSK'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}.

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in "1NY 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 signficant 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 participant 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 starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant 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

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

17.2.1

Any additional SAE reporting information required by the sponsor or drug supplier should be included in this section.

18.1 INFORMEDCONSENTPROCEDURES

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 IRS/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.

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20 APPENDICES

Appendix *A:.* FACT-Hep