Clinical Experience with NanoKnife® System Featured at Society of Interventional Radiology Conference (SIR 2012, five oral presentations) and at Society of Surgical Oncology Conference (SSO 2012, 1 oral presentation)

SIR 2012

A prospective, multicenter phase II clinical trial using irreversible electroporation for the treatment of early stage HCC

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Purpose: Radiofrequency ablation (RFA) is the standard treatment for nonsurgical patients with early-stage hepatocellular carcinoma (HCC). However, its ability to achieve complete tumor eradication is dependent on tumor size and location. Irreversible electroporation (IRE) is a novel, non-thermal ablation technique that uses high-voltage DC current to induce irreversible disruption of cell membrane integrity. We conducted a phase II prospective, multicenter clinical study to evaluate the efficacy and safety of IRE as first-line nonsurgical treatment for early-stage HCC. This trial is registered with ClinicalTrials.gov, number NCT01078415.

Materials: Patients were eligible if they had Child class A cirrhosis; ECOG performance status of 0; ASA score ≤ 3; prothrombin time ratio > 50%; platelet count > 50,000 / ml; and 1-3 HCC tumors 3 cm or less in longest diameter. Exclusion criteria included eligibility for surgical resection or transplantation; presence of vascular invasion or extrhepatic metastases; Child class B or C; and cardiac insufficiency, ongoing coronary artery disease, or arrhythmia. Eligible patients were scheduled to receive IRE as the sole anticancer therapy. The primary study endpoint was tumor response according to mRECIST — as assessed by independent, central, blinded review. Secondary endpoints were safety, overall survival, and local tumor recurrence.

Results: Twenty-six patients with 29 tumors were included in the study. All patients had biopsy-proven HCC. One-month overall patient response as assessed by central readers was CR in 20/26 (77%), PR in 4/26 (15%), SD in 1/26 (4%), and PD in 1/26 (4%). On a lesion-by-lesion basis, 23 of 29 tumors (79%) were scored as having undergone CR. No 30-day mortality occurred. Major complications included hemothorax due to needle puncture of an intercostal artery and requiring drainage (n =1) and transient hepatic decompensation undergoing spontaneous resolution (n =1).

Conclusions: Early efficacy and safety data collected in the first prospective multicenter study on the use of IRE in cancer treatment are promising and suggest that IRE can be a valuable new option for unresectable HCC.

SIR 2012

Percutaneous Irreversible Electroporation (IRE) of Surgically Unresectable Pancreatic Carcinoma: Single Center Safety Experience

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Purpose: Pancreatic carcinoma is surgically unresectable and without distant metastatic disease in 30% of newly diagnosed cases. We present our initial safety experience with percutaneous IRE in unresectable pancreatic carcinoma.

Materials: Four consecutive patients (3 male, 1 female), age 49-78, with surgically unresectable pancreatic carcinoma (stage III) were treated under general anesthesia. Average Eastern Cooperative Oncology Group (ECOG) grade was 1.5 (range 0-3). American Society of Anesthesiology (ASA) class was 3 in all patients. Seven percutaneous ablations were performed of five primary pancreatic tumors. Clinical evaluation, laboratory and imaging was performed at baseline, 24 hours, 1 month and 3 months.
Results: Seven technically successful ablations were performed in the four patients. No mortalities occurred at 30 days. No episodes of intraoperative arrhythmia occurred. Intraoperative transient hypertension occurred with all treatments (7/7). No patients had prolonged hypertension after completion of electroporation. There were no incidents of hemorrhage, infection, pancreatic fistula, or bowel injury. One treatment (1/7) was complicated by partial splenic infarction, which required no treatment. Average length of stay was 1.3 days. No patients required analgesics on discharge.

Conclusions: Percutaneous pancreatic IRE appears to be a safe method for pancreatic tumor ablation. Further studies will be needed to evaluate efficacy.

SIR 2012

Percutaneous irreversible electroporation (IRE) in the treatment of hepatocellular carcinoma (HCC) and metastatic colorectal cancer (mCRC) to the liver

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Purpose: Radiation ablation (RFA), transarterial chemo- or radioembolization are commonly used in the treatment of HCC and mCRC to the liver. IRE using the Nanoknife™ is a non thermal ablative modality, that can treat tumors abutting vascular structures without compromise of the vessels or concern for the heat sink effect of nearby blood flow.

Materials: We examined the records of patients (pts) referred for IRE for HCC and mCRC. The procedures were all done percutaneously under general anesthesia using a standard protocol. The primary endpoint was progression-free survival (PFS). Responses were assessed using the modified RECIST criteria.

Results: Between 1/2010 and 8/2011, 49 pts underwent percutaneous ablation of unresectable HCC and mCRC liver tumors using IRE – 33 with HCC and 16 with mCRC. A total of 76 lesions were treated in 62 sessions; the median number of lesions treated per patient was 1 (range 1-4) and the median tumor size treated was 2.1cm (range 0.8-6). After IRE, 20 pts (41%) had a complete response (CR), 19 (39%) had a partial response and 10 (20%) had stable disease as their best response. Two of the HCC patients were transplanted. The Kaplan-Meier estimated median PFS was 11.3 months (95% CI 9.6-12.9) for all pts, 11.6 months (95% CI 10.2-12.9) for HCC pts, and 10.4 months (95% CI 5.4-15.4) for mCRC patients. The one-year PFS was significantly higher for pts achieving a CR compared to those who did not achieve a CR (75% versus 59%, log rank p = 0.05). The number of liver lesions at baseline and size of the treated lesions were not associated with any differences in survival. The IRE was complicated in 6 pts (12%) by pneumothorax (2), pleural effusion (2), and atrial flutter/fibrillation during anesthesia (2). All pts recovered fully from these complications. One pt died within 1 month of the IRE due to disease progression.

Conclusions: IRE of liver tumors is safe. The PFS rates for pretreated mCRC and unresectable HCC are promising. A complete lack of enhancement of the treated lesion on the post-IRE CT scan appears to be associated with longer survival.

SIR 2012

Vessel patency post Irreversible Electro poration (IRE) ablation – A 15 month follow up

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Purpose: The purpose of this retrospective study was to assess the effect of the Nanoknife procedure on patency of vessels in close proximity to treated lesions. “Close proximity”, was defined as vessels within 1 cm of the treatment zone.

Materials: One of the major limitations of percutaneous ablation techniques is the inability to treat lesions close to vasculature due to the “heat sink” effect. IRE using the Nanoknife™ is hypothesized to preserve vessel
patency due to the protection offered by the collagenous skeleton of vessels, with minimal damage to the endothelium and the smooth muscle cells which undergo rapid repopulation and repair. Percutaneous IRE using the Nanoknife was performed in primary and metastatic tumors in different organs between January 2010 to June 2011. All procedures were performed under general anesthesia under CAT scan (CT) guidance. Immediate and/or 24 hour post procedure contrast CT and follow up images were evaluated for caliber of vessels, patency, and defects in flow.

**Results:** Seventy-nine IRE procedures, were performed on 56 patients (pts), to treat 72 lesions. 21 pts were male and 35 were female. Lesions were adjacent to pulmonary artery(1), hepatic arteries- right(14),left(3), common(2), external iliac artery(1), right renal artery(1), splenic artery(1), superior mesenteric artery(1 ), celiac axis (3)and aorta(1), right portal vein(RPV)(17), left portal vein(LPV) (8), main portal vein(3), hepatic veins-right(7), middle(6), left(4), SVC(1), IVC(7), external iliac vein(1) and right renal vein(2). One month follow up was available on all patients. Follow up range was 1-15months. 61 vessels were < 5mm, and 23 vessels were within 5-10mm from treatment zone. RPV showed mild narrowing in 2 pts and LPV showed a non occlusive thrombus in 1 pt after the procedure. All other vessels were found to be patent in the post procedure scans in the follow up period up to 15 months. Overall, narrowing or thrombosis occurred in 3 out of 84 vessels (3.6%; 95% CI 0.7 – 10.1%) in close proximity to the treatment zone.

**Conclusions:** IRE with nanoknife is safe in treating lesions adjacent to vessels, offering a distinct advantage over thermal ablative techniques.

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**SIR 2012**

**Downstaging locally advanced pancreatic adenocarcinoma (LAPC) with vascular encasement using percutaneous irreversible electroporation (IRE).**

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**Purpose:** To evaluate safety and resection rate in LAPC using IRE.

**Materials and Methods:** Persistent vascular encasement after neoadjuvant therapy for LAPC usually contraindicates resection. Neoadjuvant chemoradiation therapy can convert some patients (pts) with borderline or unresectable LAPC to resectability. Intraoperative RFA and Microwave have been used in the past, with limited success and a high complication rate. Percutaneous IRE using the Nanoknife™ is more versatile than other ablative modalities due to the lack of heat sink effect and morbidity associated with open surgery.We reviewed records of 8 pts with LAPC referred for IRE. The procedures were all done percutaneously under general anesthesia using a standard protocol. The primary endpoint was safety. Secondary endpoints included survival and resection rate after procedure.

**Results:** Between 12/2010 and 9/2011, 8 pts with biopsy-proven PC underwent percutaneous ablation of pancreatic tumors using IRE. Median age was 53 years (range 51-72), median time from diagnosis to IRE was 8.8 months (range 2.4-29.2) and the median tumor size was 2.8cm (range 2.5-6.8). All pts had prior chemo and 7 had prior radiation, with a median of 2 lines of prior therapies (range 1-4). Immediate and 24 hour post procedure CT with contrast demonstrated patent vasculature in the treatment zone in all pts. Two pts (25%) underwent surgery after IRE after 4 and 5 months respectively. Both had margin-negative (R0) resections and one had a pathologic complete response. Both remain disease-free at 2 and 6 months after resection respectively. Among the 6 remaining pts, 2 were lost to follow-up; one had progressive disease after 3 months. One pt had a negative follow-up PET scan and surgery is planned. Two remaining pts are under follow-up to determine resectability. Complications included spontaneous pneumothorax during anesthesia (n=1) and pancreatitis (n=1). Both recovered completely.

**Conclusion:** Percutaneous IRE of LAPC is feasible and safe. In our initial experience, 2 out of 8 pts with unresectable LAPC, achieved a margin-negative resection after IRE. One had a pathological complete response. A prospective neoadjuvant trial in LAPC incorporating IRE is planned.
Image Guided Irreversible Electroporation in Locally Advanced Pancreatic Cancer: Improved Overall Survival

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Background: Locally advanced unresectable pancreatic adenocarcinoma (LAC) is characterized by poor survival despite chemotherapy and conventional radiation therapy. We have recently reported on the safety of the use of irreversible electroporation (IRE) in the management of LAC. The aim of this study was to evaluate the overall survival in patients with LAC treated with IRE.

Methods: A prospective multi-institutional evaluation of 44 patients undergoing IRE for unresectable pancreatic cancer 12/2009 to 10/2010 were evaluated for overall survival and compared to 85 matched stage III patients treated with standard therapy defined as chemotherapy and radiation therapy alone.

Results: A total of 44 LAC pts have successfully undergone IRE, with 21 women, 21 men, median age of 61 (45 – 80 years). Twenty-nine patients had pancreatic head primary and 15 with body tumors, with 12 pts undergoing margin accentuation with IRE and 32 undergoing in-situ IRE. 40(90%) had pre-IRE chemotherapy alone or chemo-radiation therapy for a median duration 5 months. 32(73%) pts underwent post-IRE chemotherapy or chemoradiation. The 90 day mortality in the IRE patients was 1(2%). In a comparison of IRE patients to standard therapy we have seen a significant improvement in Local progression free survival (14 vs 6 months, P=0.01), Distant progression free survival (15 vs 9 months, p=0.02), and overall survival (20 vs 13 months, p=0.03).

Conclusion: IRE ablation of locally advanced pancreatic tumors remains safe and in the appropriate patient who has undergone standard neo-adjuvant therapy for a minimum of 4 months can achieve greater local palliation and improved overall survival when compared to standard chemoradiation- chemotherapy treatments. Validation of these early results will need to be validated in the current multi-institutional Phase 2 IDE study (G110102).