Ελληνική Εταιρεία
Ήπατος Παγκρέατος Χοληφόρων

IRE (NanoKnife) in HBP cancer

ES Felekouras

First Department of Surgery, Faculty of Medicine, National and Kapodistrian University of Athens , Laiko General Hospital, Dir. Prof. T. Liakakos

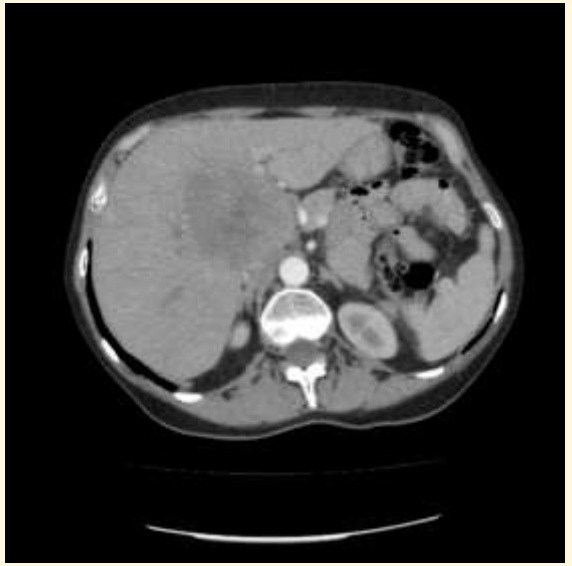
…searching for other ways to treat…

(in First Department of Surgery, Faculty of Medicine, National and Kapodistrian University of Athens , Laiko General Hospital)

- Liver Surgery in 1995
- Bloodless Liver Surgery in 2000
- RFA assisted Hepatectomy in 2002
- Hepatic Parenchymal Preservation Surgery in mcrc 2003
- Combine (sync) Liver and Colon resection in 2004
- MWA application in 2005
- PVE/PVL(O) and two stage Hepatectomy in 2007……
- ……..
- Pancreatic IRE in 2015
- ALPPS for mcrc in 2015 (Associating liver partition and portal vein ligation for staged hepatectomy) (Alex. Papalambros, John Griniatsos, Athanasios Petrou)
- …….
- Liver IRE
- ……..

The Issue

- Tumors located in close proximity critical structures such as vessels and / or nerves
- Unresectable
- Unablatable using a Thermal Approach
- Poor response or low QoL with Chemo/Radio Therapies
- Poor Patient QoL



The Need

A treatment modality that can cause cellular death

regardless

of tumor location without damaging critical structures

IRE

Irreversible electroporation

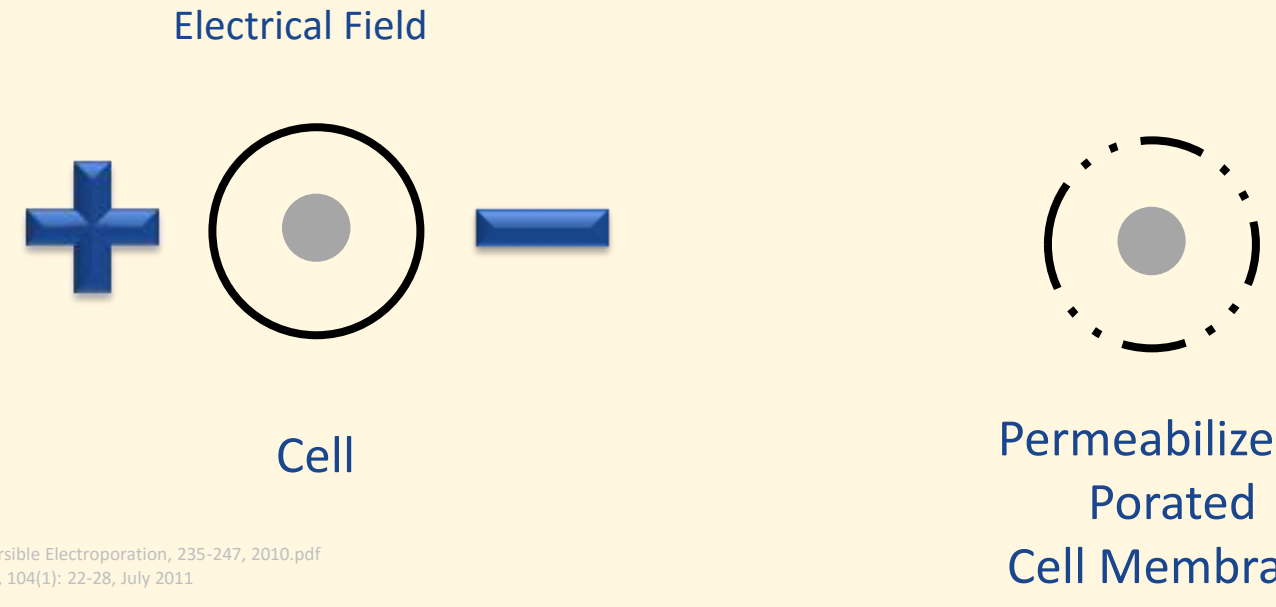
(IRE or NTIRE for non-thermal irreversible electroporation)

History

- First observations of IRE effects go back to 1898.
- However its use for modern medicine and using IRE for tumor ablation purposes was derived from electrochemotherapy and electroporation.
- In these treatment modalities IRE was an unwanted side effect to reversible electroporation (RE).
- The first study of a potential use of IRE was described by
  - Davalos et al. Ann Biomed Eng. 2005 Feb;33(2):223-31..

Electroporation

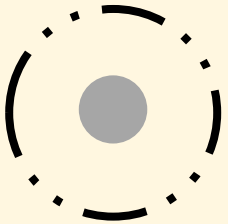
Electroporation:
The process of creating pores (holes) in the cell membrane using an electrical field (Utilizing ultra short pulsed but very strong electrical fields)



1. Li et al., PLoS ONE, 6(4): e18831, April 2011
2. Onik et al., Series in Biomedical Engineering Irreversible Electroporation, 235-247, 2010.pdf
3. Images adapted from: Bower et al., J. Surg. Oncol., 104(1): 22-28, July 2011

Electroporation

RE
Reversible Electroporation



Cell membrane is temporarily "porated" allowing for possible applications in:

EGT
Electro-genetherapy[2]

ECT
Electro-chemotherapy[2]

Electrical Field

Cell

Two kinds of damage can occur

IRE
Irreversible Electroporation

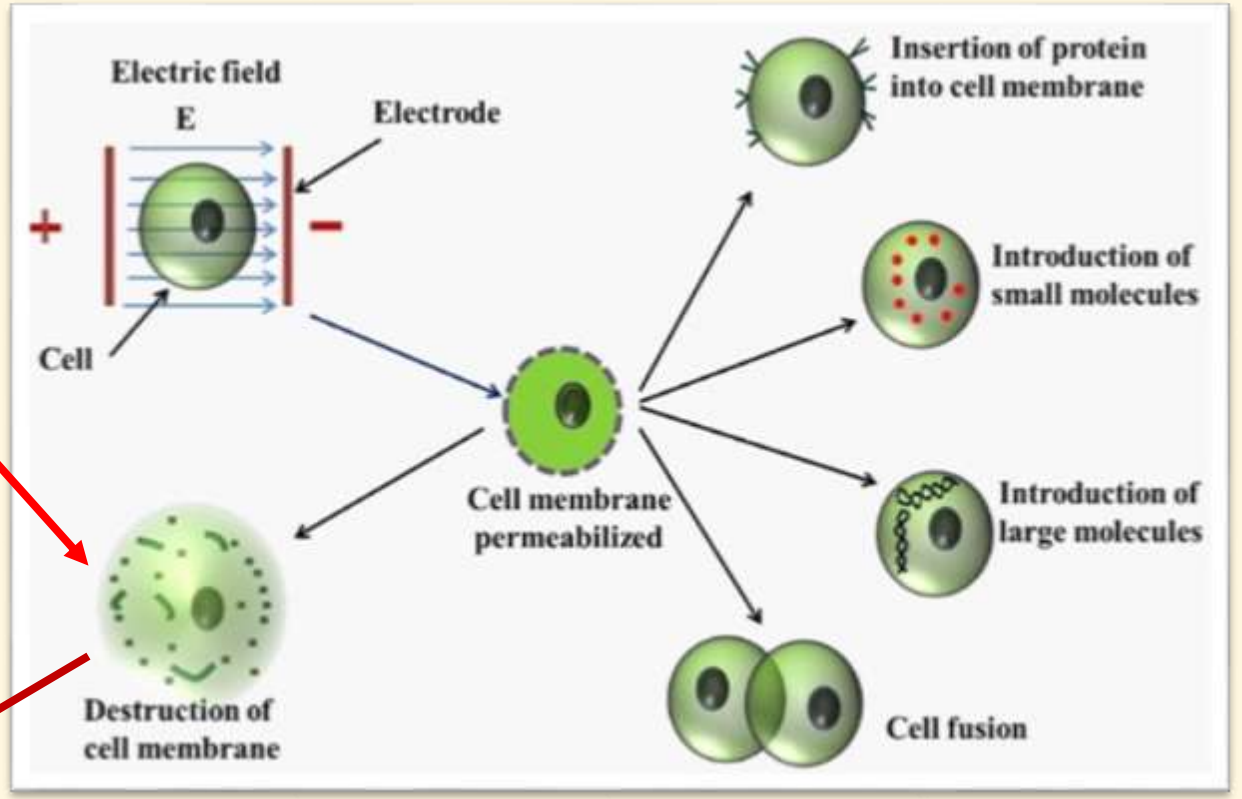
complete tissue death by means of apoptosis or "apoptosis-mimetic" necrosis[1].
(unique to the method: not necrosis as in thermal ablation or radiation)

NanoKnife™
Irreversible Electroporation

1. Li et al., PLoS ONE, 6(4): e18831, April 2011
2. Onik et al., Series in Biomedical Engineering Irreversible Electroporation, 235-247, 2010.pdf
3. Images adapted from: Bower et al., J. Surg. Oncol., 104(1): 22-28, July 2011

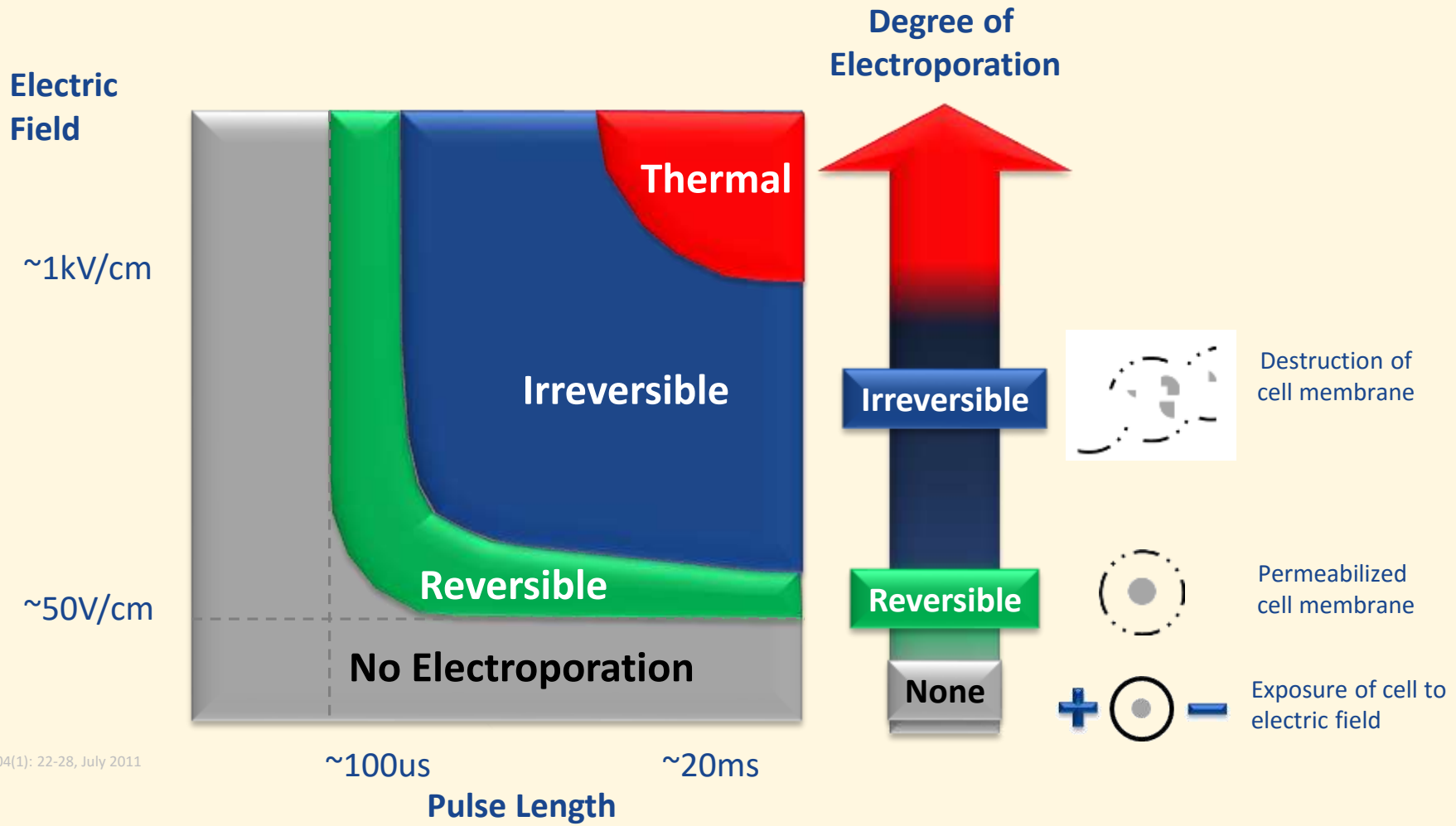
Electroporation

Electric field = Energy



IRE = High Voltage /Low energy

Electroporation



1. Adapted from: Bower et al., J. Surg. Oncol., 104(1): 22-28, July 2011

Apoptotic Induced Cell Death[1]

- Cell death occurs by apoptosis[2]
  - This immune mediated cell death allows[1]
    - Cellular clearance of debris[1]
  - Creates minimal tissue distortion[1]

Electrical Field

IRE
Irreversible Electroporation

Potential Immune system response[3]
Macrophages aid in clearing cell debris - Phagocytosis

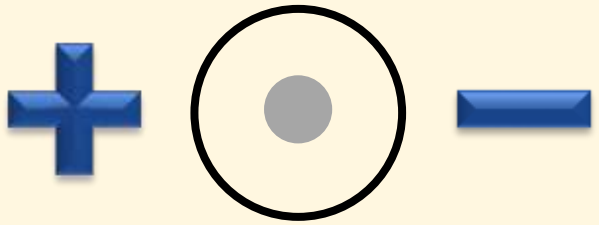
Cell

Apoptosis[2]

1. Meler, JD, Renal Applications of IRE, November 12th 2011, Presentation at Synergy 2011, Miami Florida, USA.
2. Li et al., PLoS ONE, 6(4): e18831, April 2011
3. Lee et al., Technology in Cancer Research and Treatment, 6(4): 287-293, August 2007

Potential immune system response in lesion resolution[1]

Electrical Field

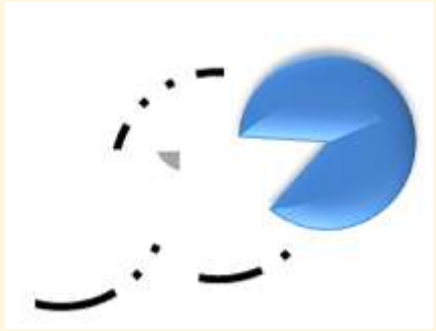


Cell

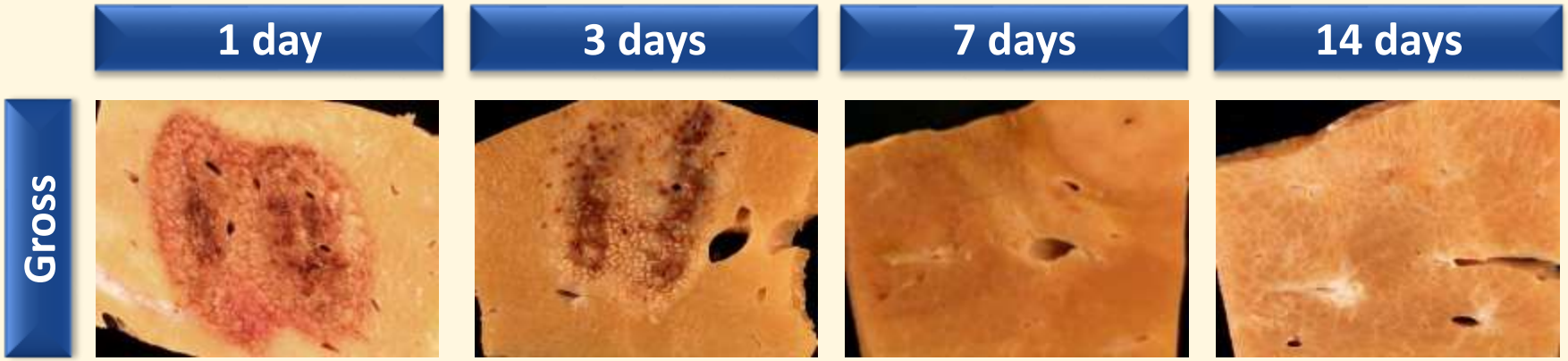
IRE
Irreversible Electroporation

Apoptosis[2,3]

Potential Immune system response[1]



Macrophages aid in clearing cell debris - Phagocytosis

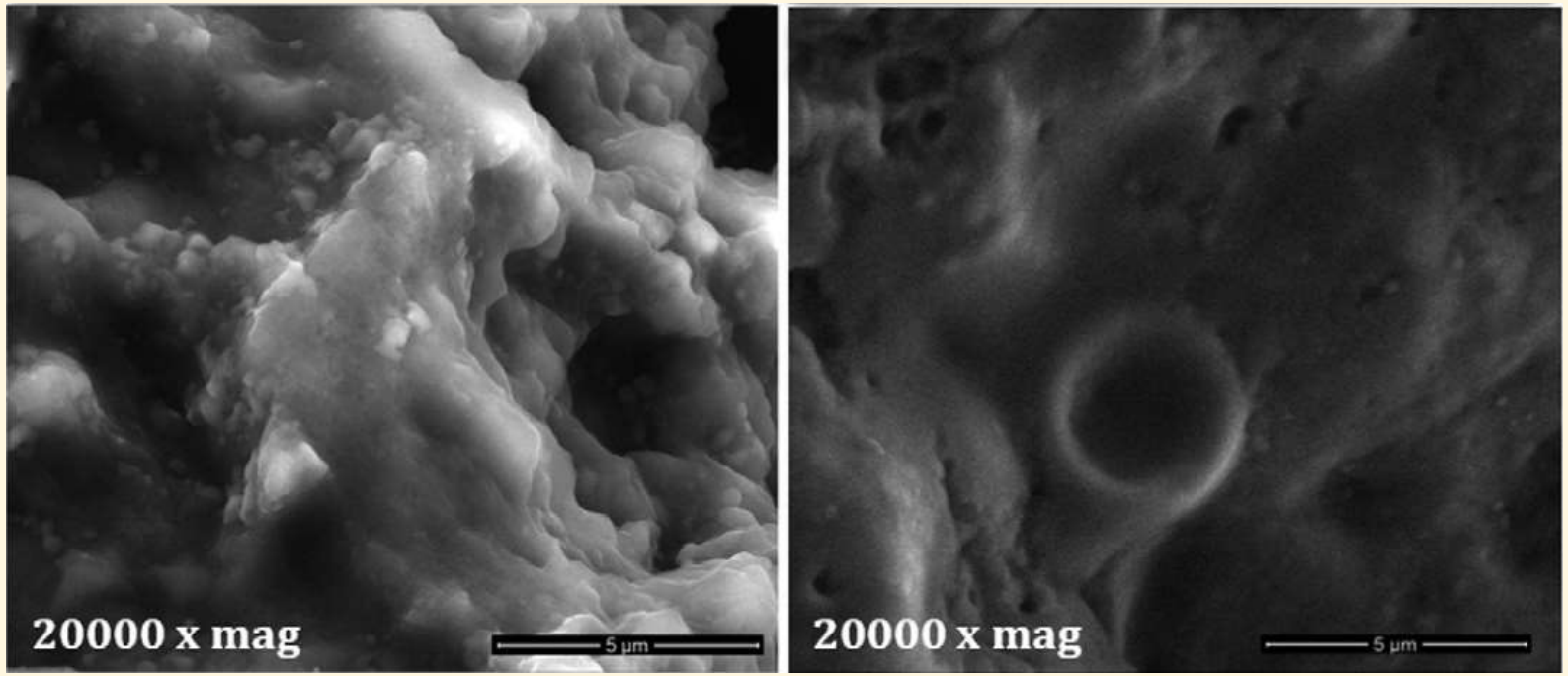


Images from AngioDynamics – Porcine Liver Animal Model

1. Lee et al., Technology in Cancer Research and Treatment, 6(4): 287-293, August 2007
2. Lee et al., Gut and Liver, 4 (Suppl. 1) 99- 104, Sep. 2010
3. Li et al., PLoS ONE, 6(4): e18831, April 2011

Electron Microscope Visualization of IRE Pores

- SEM image of normal rabbit hepatocytes without any detectable nanopores (Normal Liver) compared with IRE-ablated rabbit hepatocytes with numerous nanopores

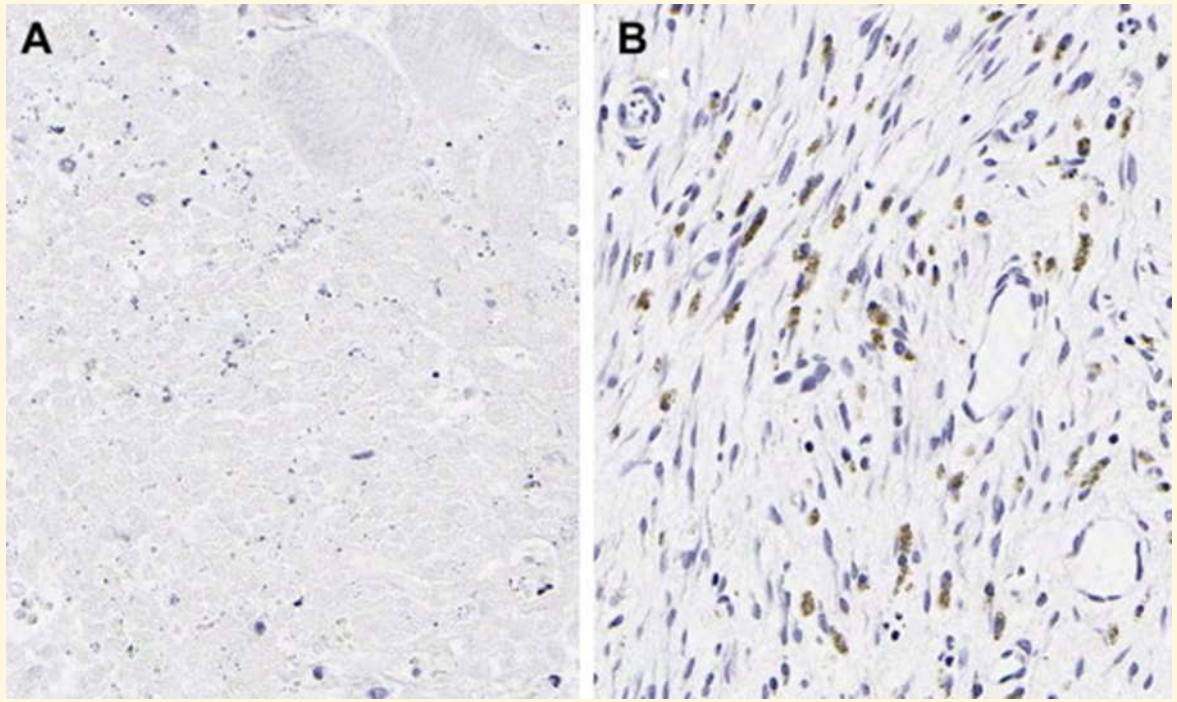


Normal Liver

IRE with Nanopores

1. Lee et al., JVIR, January 2012

Cell death by necrosis versus apoptosis



(A) Liver **necrosis** caused by radiofrequency ablation (RFA). (B) **Apoptotic cell death** caused by IRE dark brown stains are positive for TUNEL assay. TUNEL, terminal deoxynucleotidy...

Natanel Jourabchi, et al. **Irreversible electroporation (NanoKnife) in cancer treatment.** Gastrointestinal Intervention, Volume 3, Issue 1, 2014, 8–18

Pros and Cons

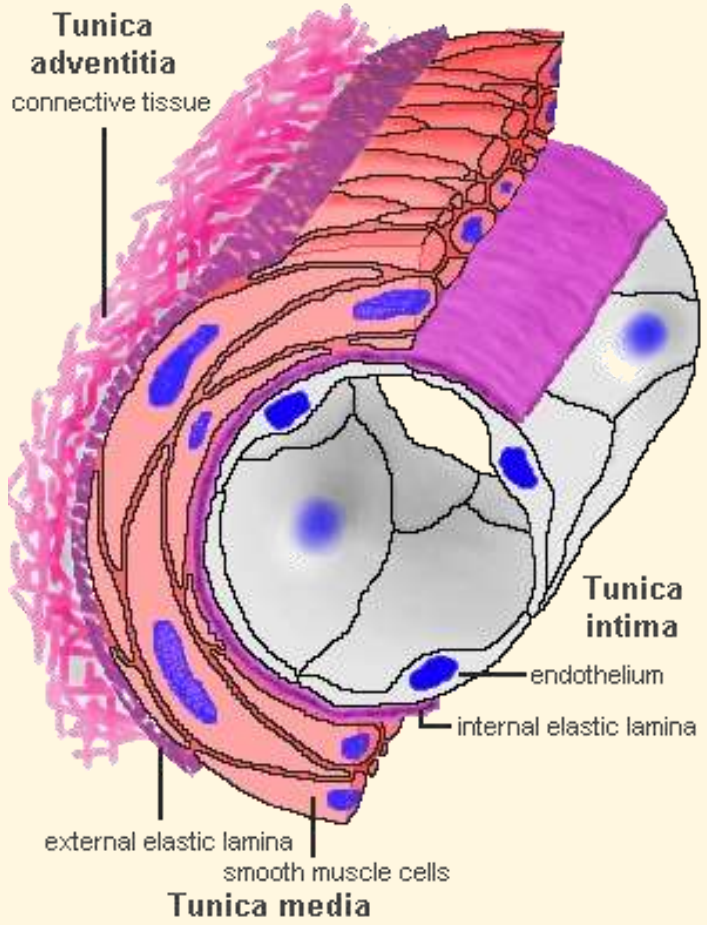
1. Tissue selectivity
    1. critical structures, such as the arteries, veins, and intrahepatic bile ducts were all preserved. Structures mainly consisting of proteins like vascular elastic and collagenous structures, as well as peri-cellular matrix proteins are not effected by the currents.
    2. The electrically insulating myelin layer, surrounding nerve fibers, protects nerve bundles from the IRE effects to a certain degree. Up to what point nerves stay unaffected or can regenerate is not completely understood.
2. Sharp margins between complete ablation and non-effected area
    1. The transition zone between reversible electroporated area and irreversible electroporated area is accepted to be only a few cell layers. Transitional areas as in radiation or thermal based ablation techniques are non-existent.
3. No heat sink effect
    1. which is a cause of many problems and treatment failures, is advantageous and increases the predictability of the treatment field. Geometrically, rather complex treatment fields are enabled by the multi-electrode concept.
4. Absence of thermally induces necrosis
    1. The short pulse lengths relative to the time between the pulses prevents joule heating of the tissue. Hence, by design, no necrotic cell damage is to be expected (except possibly in very close proximity to the needle). Therefore, IRE has none of the typical short and long term side-effects associated with necrosis.
5. Real time monitoring
    1. The treatment volume can be visualized, both during and after the treatment. Possible visualization methods are ultrasound, MRI, and CT.
6. Short treatment time
    1. A typical treatment takes less than 5 minutes. This does not include the possibly complicated electrode placement.

Current technical limitations of IRE are:

1. Strong muscle contractions due to direct stimulation of the neuromuscular junction.
2. Planning and performing IRE treatments in inhomogeneous tissue (like the lung) due to jumps of the relative permittivity in the treatment area.

Cellular vs. Non-Cellular

- All cells in ablation zone are affected by electrical field.
- Fibrous and Collagen Structures are not affected.
- Intact adventitia & laminae visible at 2 days with no smooth muscle cells present.
- Endothelium largely repopulates at 2 days.
- Smooth muscle repopulated at 2 weeks.

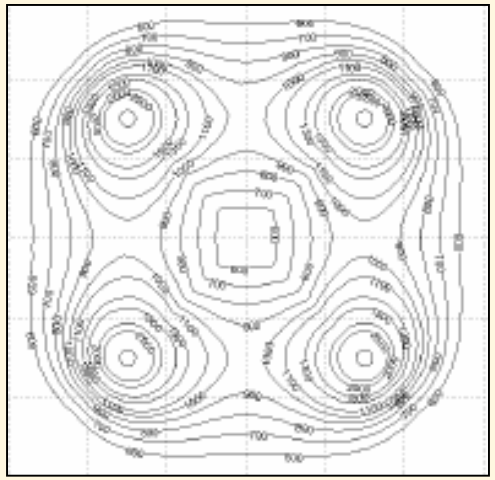


1. 1. ARC 991-1 Safety of Irreversible Electroporation of the Pancreas in a Porcine Model
2. Image @ Blue Histology, School of Anat. and Human Biology - The U. of W. Australia
3. http://www.lab.anhb.uwa.edu.au/mb140/Core\Pages/Vascular/Vascular.htm#ARTER

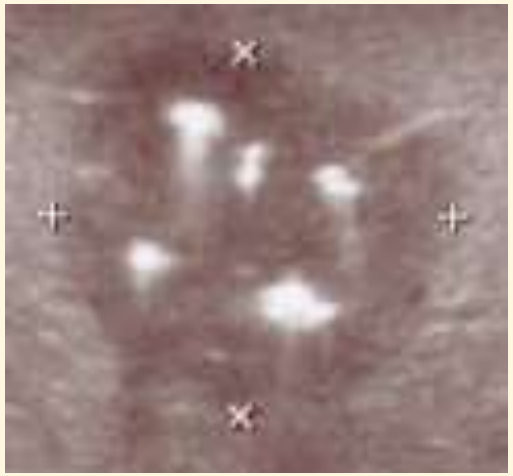
Predictable Ablations[1,2]

- NanoKnife Software calculates the programmed ablation zone (based upon mathematical model[1]), which
- correlates to the hypo echoic image immediately post-ablation[2], and to
- gross pathology[2].

Images from: Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007



Mathematical model of ablation zone



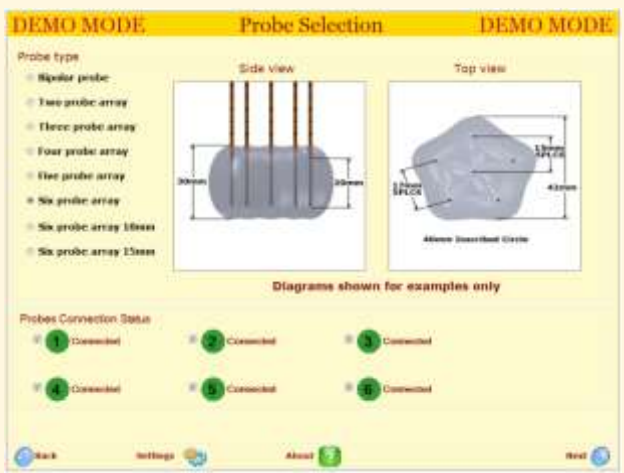
Ultrasound post-ablation

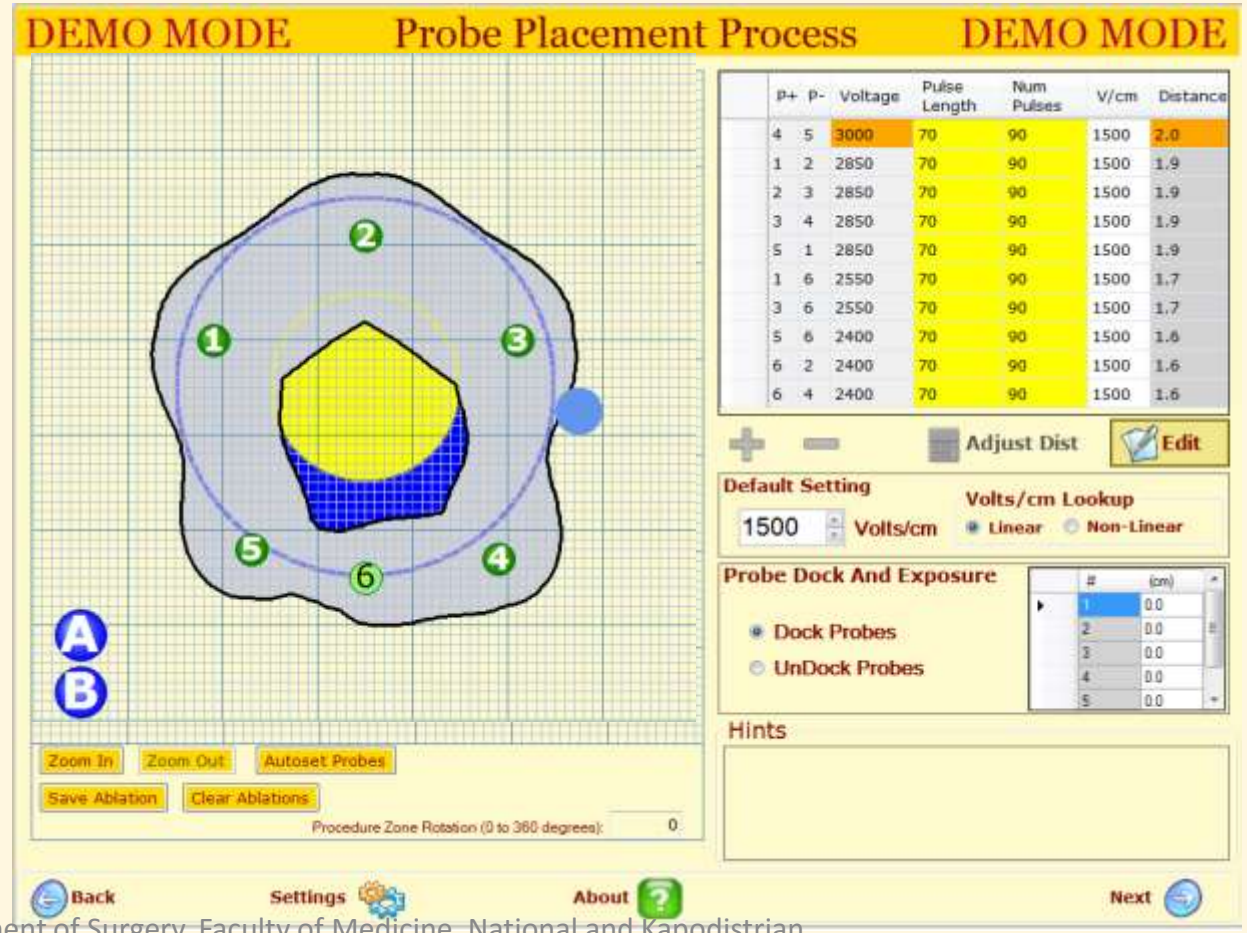
Gross pathology of ablation

1. Edd et al., Technology in Cancer Research and Treatment, 6(4); 275-286, August 2007
2. Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007

Predictable Ablations[1,2]

The NanoKnife® Treatment Planning Software v2.2.0.



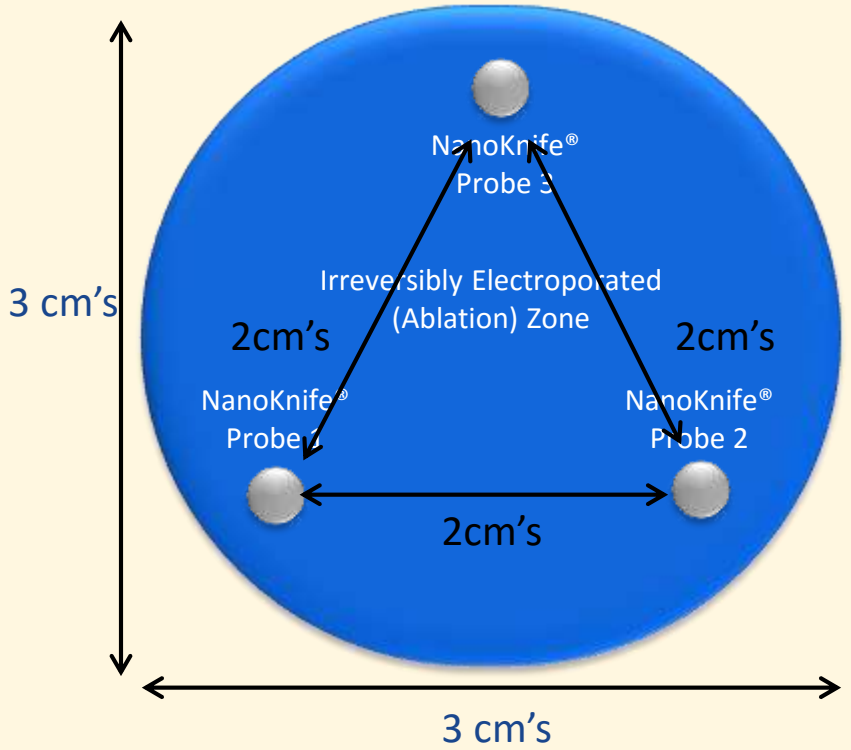


1. Edd et al., Technology in Cancer Research and Treatment, 6(6), 2007
2. Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007

Non-Thermal IRE Ablation[1]

Adapted from: Deodhar et al., AJR, Published Online, 196:W330-W335, March 2011

- IRE is a non-thermal ablative technique[1]
- the electric field created by IRE is devoid of any joule heating
- Application of short pulse, high voltage DC current.
- Rapid series of short electrical pulses
- Cell death occurs in the ablation zone
- Electrodes placed under CT or Ultrasound Guidance[2]

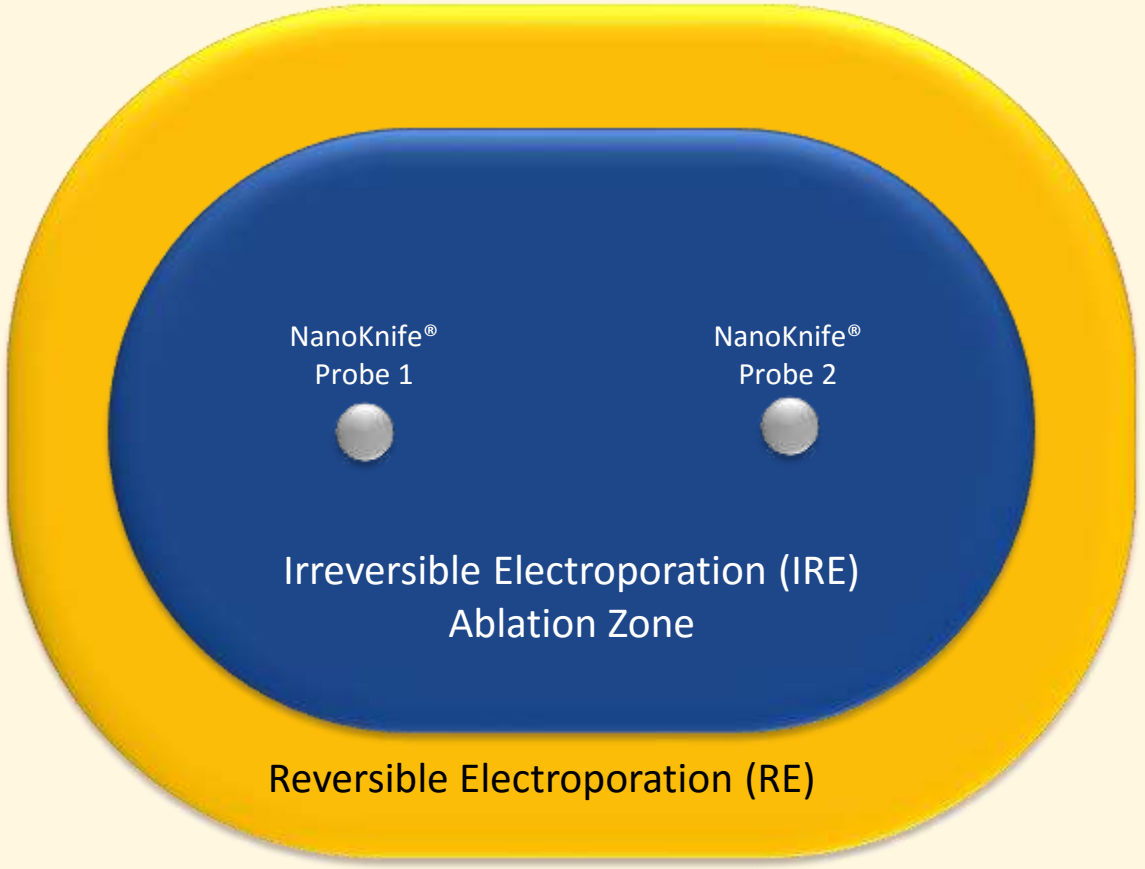


1. Li et al., PLoS ONE, 6(4): e18831, April 2011
2. Ball et al., Anesthesia & Analgesia, 110(5): 1305-9, May 2010

Electroporation

- Surrounding the ablation zone of Irreversible Electroporation (IRE) there will be an area of reversible electroporation[1].

Adapted from: Deodhar et al., AJR, Published Online, 196:W330-W335, March 2011



1. Deodhar et al., AJR, Published Online, 196:W330-W335, March 2011

Well Demarcated Post Ablation Zone

- Very precise ablation area on a cellular level – **Abrupt transition zone**.
- IRE produces a well defined region of tissue ablation as a result of loss of integrity of the cell membrane, **without** areas in which the extent of damage changes gradually, as during thermal ablation.[1]

1. Thomson et al., J Vasc Interv Radiol, 22(5):611-21 , May 2011

No Heat Sink Effect[1,2]

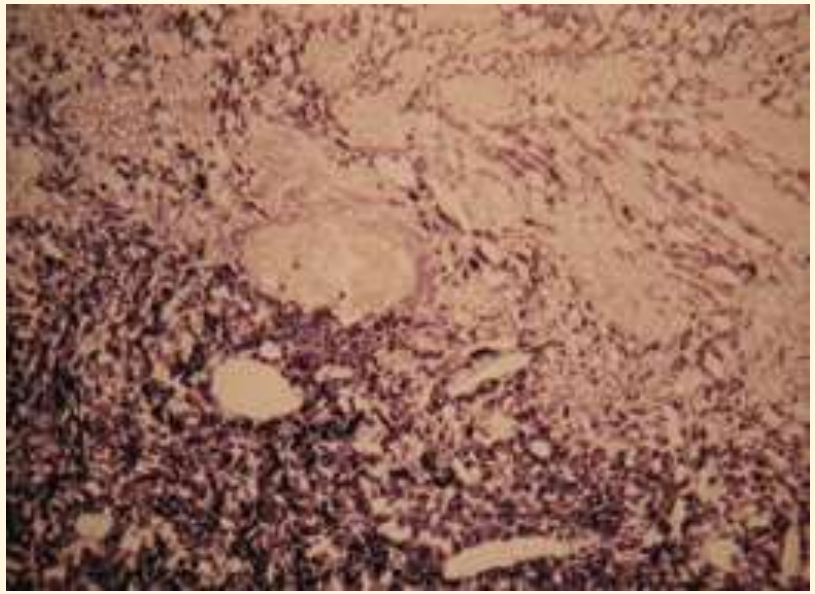
- IRE is a non-thermal technology; hence incomplete treatment secondary to the “heat sink” effect and heat injuries, appear not to be applicable to IRE. [1]
- No heat sink effect was evident adjacent to vessels with complete necrosis adjacent and often surrounding patent vasculature.[2]

Image from AngioDynamics® - Porcine Model

1. Deodhar et al., Urology, 77(3): 754-760, 2011
2. Onik et al., Technology in Cancer Research and Treatment, 6(4): 1-6, August 2007

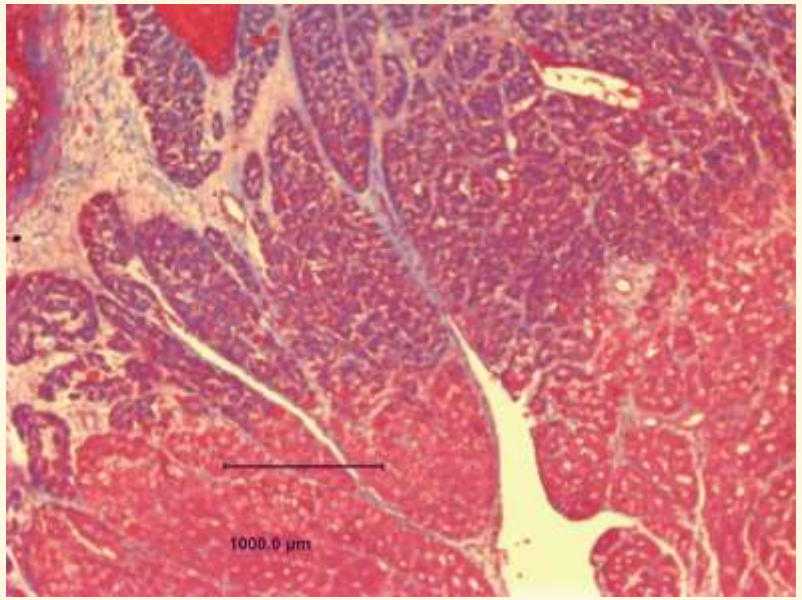
Ablation Precision On A Cellular level[1]

1. Image from: Tracy et al., BJU International, 107(12): 1982-1987, June 2011



1. NADH-stained porcine renal tissue at 1-h after IRE showing complete cellular death (upper portion of photograph), with a sharp delineation from the untreated tissue (lower portion of photograph).

2. Image from: Lavee et al., The Heart Surgery Forum, 2006-1202, 10(2), 2007



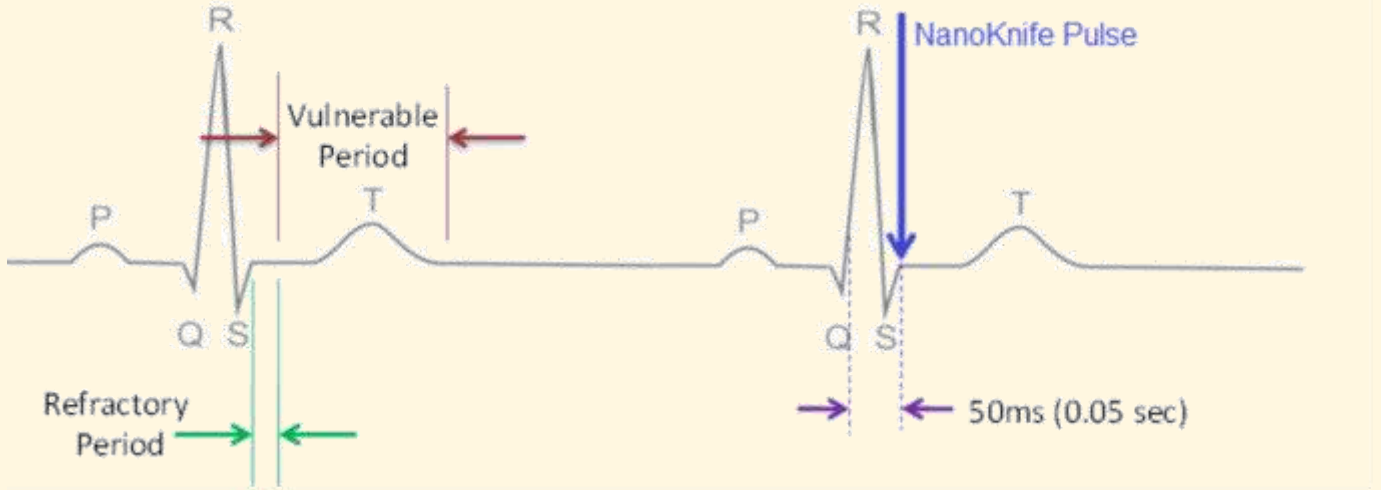
2. Higher magnification of an ablated area demonstrates a sharp demarcation line between the injured necrotic myocardial tissue (in purple) and the surrounding normal atrial myocardium (original magnification ×10).

1. Thomson et al., J Vasc Interv Radiol, 22(5):611-21 , May 2011

NanoKnife System

The AccuSync® Synchronization Device

- AccuSync® Synchronization Device:
  - External synchronization device.
  - The ECG Trigger Monitor automatically detects the R Wave.
  - Provided with each generator.



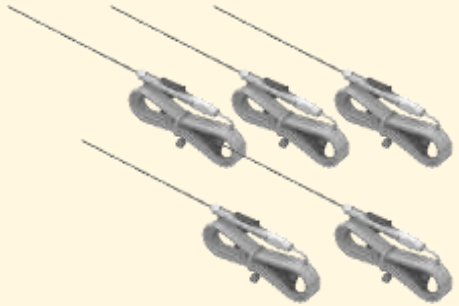
NanoKnife® System Consists Of

- NanoKnife® Generator
- Up to 6 Monopolar electrodes:
  - One Activator RFID Monopolar Electrode
  - Up to five RFID Monopolar Electrodes
- AccuSync® Synchronization Device

The NanoKnife® Generator

Activator RFID Monopolar Electrode

RFID Monopolar Electrode (up to 5)



The AccuSync® Synchronization Device

NanoKnife® Generator

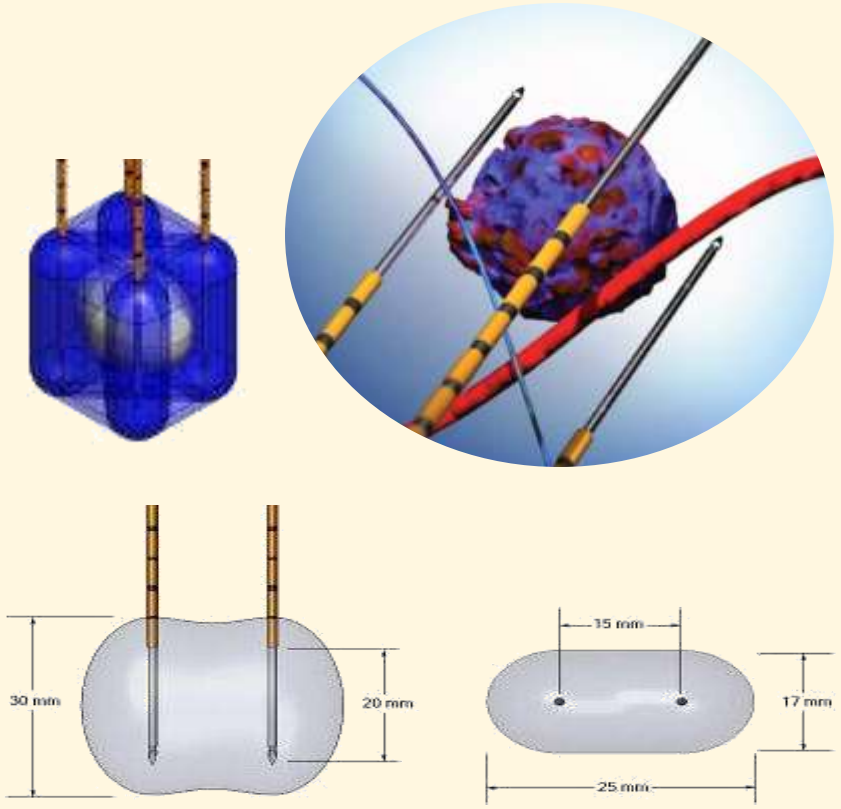
- Treatment Planning Software for procedure planning
- USB port to export patient data
- Up to 6 outputs with automatic ‘switching’
- Touchscreen or keyboard input
- Footswitch

The NanoKnife® Generator

Footswitch

NanoKnife® Probes

- 19 Gauge Needle
- 15 & 25cm lengths
- Max. distance between two needles is 2 cm's
  - Minimum of two electrodes
  - Field generates pores

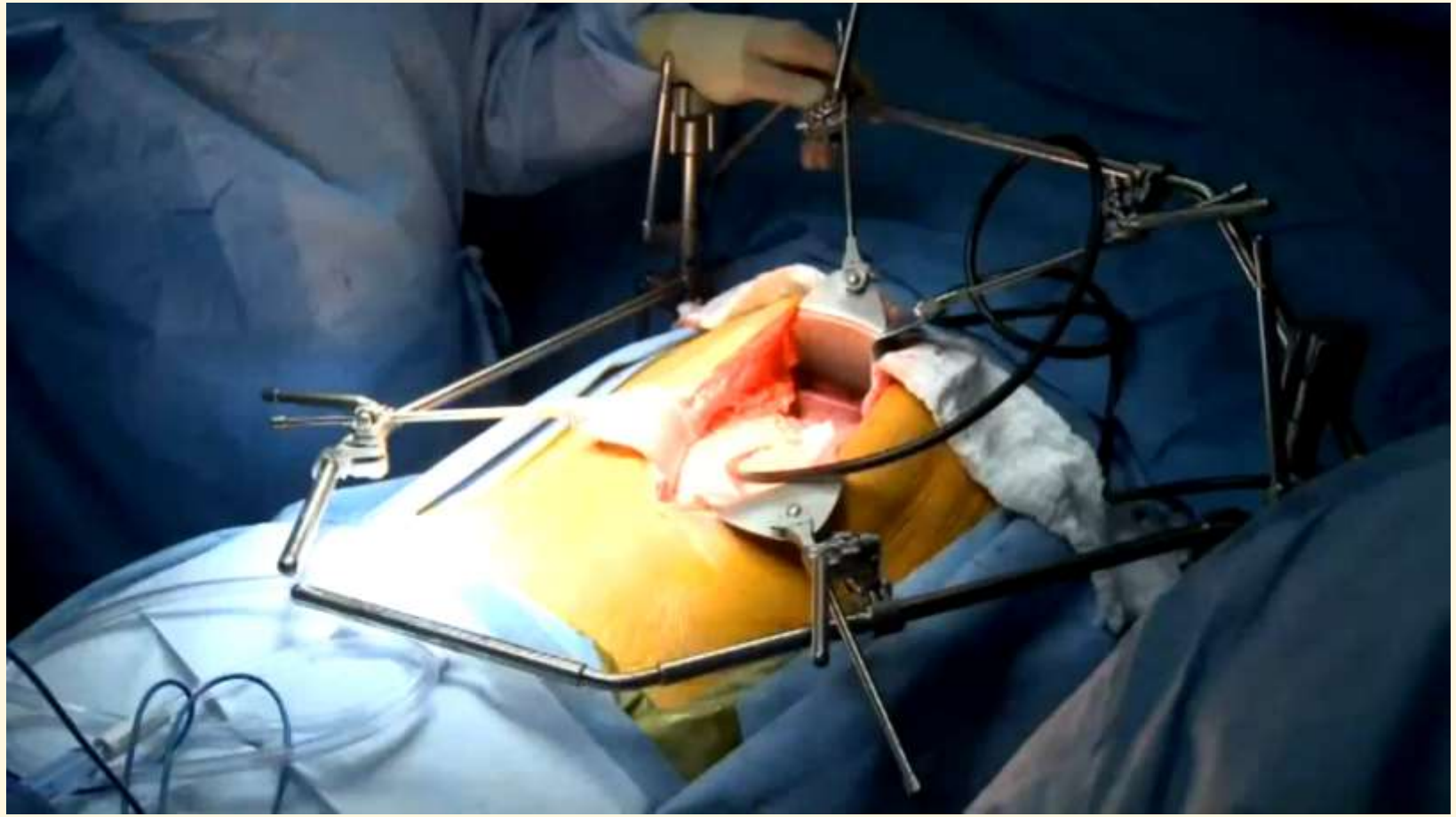


1. Martin et al., J Am Coll Surg, 10.1016, June 2012

The NanoKnife® Procedure

IRE for LAC

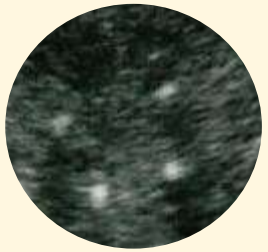
IO application: Martin RC



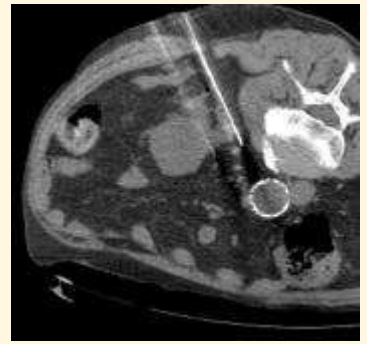
Imaging

- CT and or Ultrasound can be used with NanoKnife[1]:
  - Pre-procedure,
  - During ablation, and
  - Post-procedure
- MR Imaging:
  - May be used pre & post procedure
  - NanoKnife® electrodes are **not** MRI Compatible

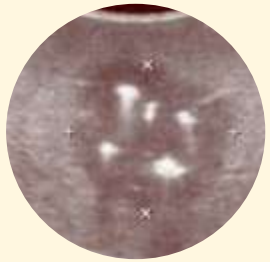
Ultrasound Showing Needle Placement[2]



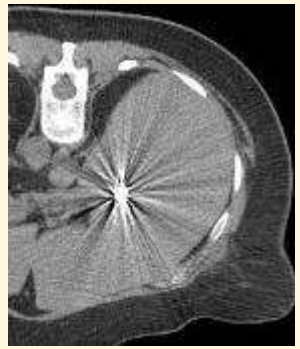
CT Showing Needle Placement[3]



Ultrasound During Ablation[2]



CT During Ablation[3]



1. Thomson et al., J Vasc Interv Radiol, 22(5):611-21 , May 2011
2. Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007
3. 2010-04-21 Renal – Valley Baptist – Fuentes – Final Needle Placement

Scope of application

- Prostate
- Liver, pancreas
- Sarcomas
- Kidney and Breast
- Other organs
  - Successful ablations in animal tumor models have been conducted for lung, brain, heart, skin, bone, head and neck cancer, and blood vessels

Anesthesia Considerations[1]

- Ablation with the NanoKnife System requires general anesthesia and muscle blockade
- Anesthetic with propofol induction, maintenance with oxygen/air/sevoflurane, and variable opioid regimes usually involving fentanyl or remifentanil.
- Nondepolarizing muscle relaxants used.
- Monitoring with oximetry, noninvasive arterial blood pressure, 5-lead electrocardiograph (ECG), temperature probe, bispectral index, and capnography.
- The majority of the patients had lower-body hot-air blankets.
- If using CT imaging during procedure - attention must be given to patient arm position: neuropraxia
- Defibrillator in-room
- Before procedure → Twitch test of 0 on the Train of Four Test

1. Ball et al., Anesthesia & Analgesia, 110(5): 1305-9, May 2010

1. Ball et al., Anesthesia & Analgesia, 110(5): 1305-9, May 2010

Pain Management[1]

- Postoperative pain managed with small doses of opioids or simple analgesics in most patients[1]
  - 53.6% of patients had no pain at all, despite only receiving fentanyl or remifentanil during the procedure.
  - Postoperative pain was experienced by 46.4%;
  - Also dependent on whether a patient is suffering from chronic pain before the procedure.

1. Ball et al., Anesthesia & Analgesia, 110(5): 1305-9, May 2010

Contraindications & Warnings

CONTRAINDICATIONS:

- Procedures based on high voltage pulses are not recommended in the following cases:
  - Ablation of lesions in the thoracic area in the presence of implanted cardiac pacemakers or defibrillators.
  - Ablation of lesions in the vicinity of implanted electronic devices or implanted devices with metal parts.
  - Ablation of lesions of the eyes, including the eyelids.
  - Patient history of Epilepsy or Cardiac Arrhythmia.
  - Recent history of myocardial infarction.

WARNINGS:

- **Arrhythmia Risk**
- Patients with Q-T intervals greater than 550 ms are at an increased risk for inappropriate energy delivery and arrhythmia. Verification of proper function of a synchronization device before initiating energy delivery is essential in these patients.
- Asynchronous energy delivery (240 PPM or 90 PPM modes) might trigger atrial or ventricular fibrillation, especially in patients with established arrhythmias or structural heart disease. Ensure that interventions (defibrillator, etc.) and appropriately trained personnel for dealing with cardiac arrhythmias are readily available.
- Using QRS synchronization devices whose output is not compatible with the specifications listed in this manual may result in ventricular fibrillation.
- Patients with established arrhythmias (i.e. Atrial Fibrillation, PVC's) should be carefully monitored for proper synchronization during energy delivery.
- Adequate precautions should be taken for patients with implantable electrical devices.

Advantages of IRE

- IRE is non-thermal
  - Little to no scar tissue formation
  - Structural Protein Sparing
    - Nerves and bile ducts in the area of ablation have the potential to heal after treatment
  - No heat sink effect
    - Compared to thermal techniques where blood flow dissipates heat. Electric pulses are not effected by blow flow.

Systematic Review of Clinical Safety and Efficacy in Liver and Pancreas[1]

- "Irreversible Electroporation for Non thermal Tumor Ablation in the Clinical Setting: A Systematic Review of Safety and Efficacy"

1. Scheffer et al., JVIR, epub, May 2014.pdf

Systematic Review of Clinical Safety and Efficacy in Liver and Pancreas[1]

- All articles regarding human use of IRE in Pancreas and Liver published between August 2010 and November 2013.
- PRISMA guidelines for reporting systematic reviews.

1. Scheffer et al., JVIR, epub, May 2014.pdf

Systematic Review of Clinical Safety and Efficacy in Liver and Pancreas[1]

Results: Efficacy of Hepatic IRE

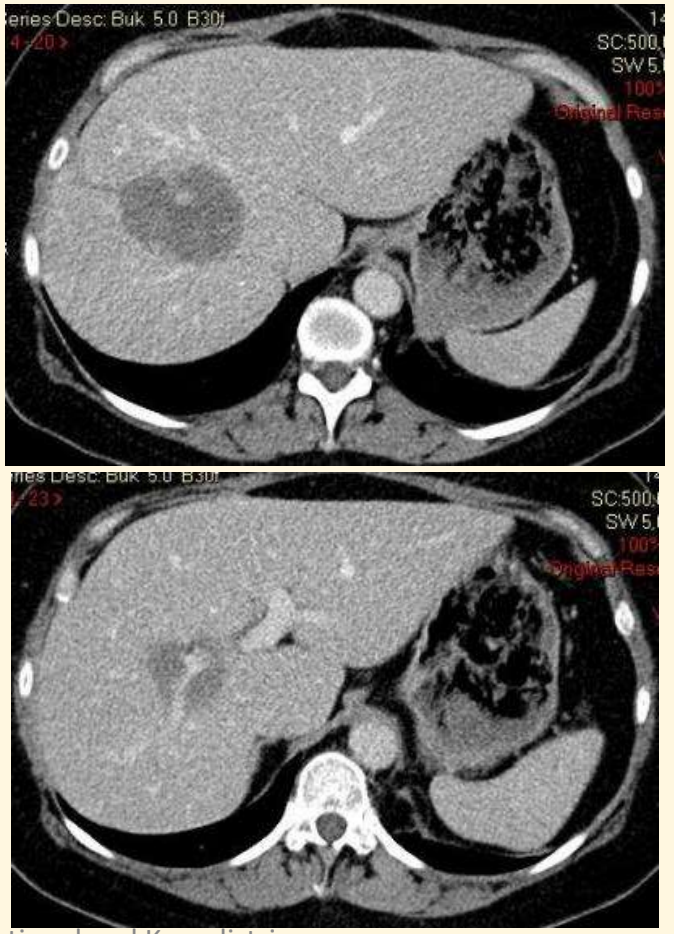
Author	No. patients	No. lesions	Size (cm, median, range)	Approach	Tumor type, per patient	Primary technique effectiveness (%)	Secondary technique effectiveness	
							Follow-up (months)	%
Cannon et al.(28)	44	48	2.5 (1.1-5.0)	Open (14) Perc (28) Lap (2)	HCC (14) CRLM (20) Other (10)	97	6 12	95 60
Cheung et al.(24)	11	18	1.9 (1-6.1)	Perc	HCC (11)	67	18	72*
Kasivisvanathan et al.(29)	1	1	2.8	Perc	CRLM	100	-	-
Kingham et al.(25)	28	54‡	1.0 (0.5-5.0)	Open (22) Perc (6)	HCC (2) CRLM (21) Other (5)	96	6	93
Silk et al.(26)	9	19	3.0 (1.0-4.7)	Perc	CRLM (8) Other (1)	ns	9	55
Thomson et al.(23)	13	45	2.8 (1.0-8.8)	Perc	CRLM (6) Other (7)	67	-	-
Total	106	185		**Open (36)** **Perc (68)** **Lap (2)**	**HCC (27)** **CRLM (56)** **Other (23)**			

1. Scheffer et al., JVIR, epub, May 2014.pdf

- Increased efficacy for tumors <3cm:
  - 93% <3cm and 100% <2cm (Cheung et al.)
  - 98% <3cm (Cannon et al.)
- No increased recurrence for tumors located <0.5cm from major portal vein (Kingham et al.)

Liver IRE – Swedish Uppsala Experience[1]

- Hemangioenditelioma : 5 x 5 x 4 cm
- University Uppsala Sweden
- Tumor is around right portal branch up to main portal vein.



1. Case courtesy of Dr. Anders Nissen, Uppsala University Hospital, Sweden

Liver IRE – Swedish Uppsala Experience[1]

- 4 needles
- Placed 2 cm apart
- 2 cm active exposure
- 2 retractions of 2 cm each
  - Ablation depth of 6 cm
- Needles replaced twice
  - 3 cylinders
- Total of 9 ablation cycles

Contrast enhanced ultrasound
24 hours Post-ablation

1. Case courtesy of Dr. Anders Nissen, Uppsala University Hospital, Sweden

Liver IRE – Swedish Uppsala Experience[1]

- Ablation size 7 x 5.5 x 5 cm.
- No Enhancement
- No complications
- Portal vein open
- No bile duct dilatation
- Patient discharged after 3 days

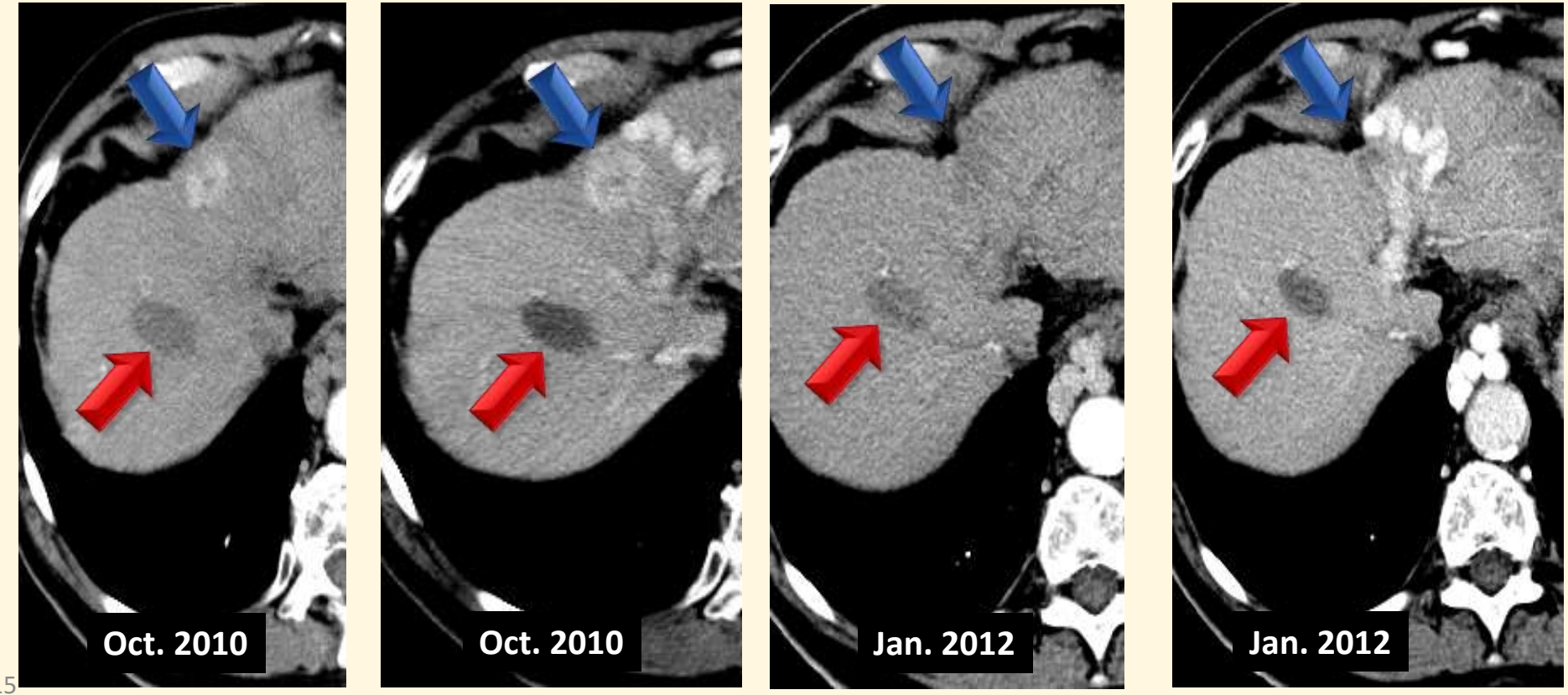
1. Case courtesy of Dr. Anders Nissen, Uppsala University Hospital, Sweden

Lesion Resolution[1]

Images courtesy of Dr. Narayanan

1. Images courtesy of Dr. G. Narayanan, University of Miami – Miller School of Medicine

- Hypodense lesion in all 4 images is an area of HCC treated with RFA (red arrows)
- Enhancing lesion anterior to it in the first 2 images was treated with IRE.



Ongoing Clinical Studies - Pancreas

- Leiden, pancreas, 15 patients (Leiden, NL)
- IREENA-S, liver-kidney-pancreas-mesenteric root, 25 pigs (Heidelberg)
- PANFIRE (Pancreas) and COLDFIRE (Liver) from the VUMC, Amsterdam
- IMPALA (Pancreas), AMC Amsterdam
- LAIKO (Liver Pancreas), Athens, Greece

Completed Studies
(finalizing data and publication)

- ONC-205, liver, 26 patients (Magdeburg, Paris, Pisa, Barcelona, Naples)
- ONC-208, pancreas, 10 patients (Verona)

The Issue

- Pancreas:
  - Average 6-9 month life expectancy post diagnosis
  - 80% - 85% of Locally Advanced Pancreatic Cancer (LAPC) Tumors are unresectable

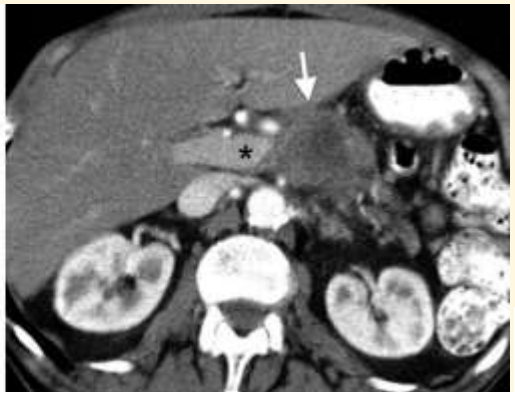
Pancreas IRE

- No reported pancreatitis[1]
- Open and percutaneous approaches
- Tumors infiltrating the SMA can be treated
- Could potentially assist Chemotherapy treatment

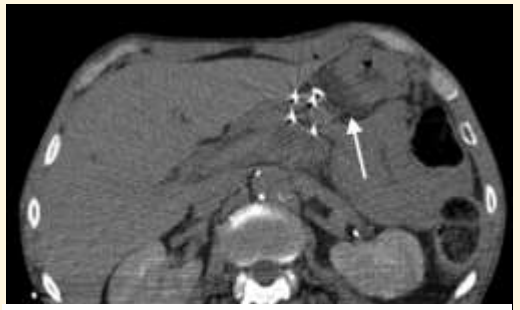
1. Bower et al., J. Surg. Oncol., 104(1): 22-28, July 2011

Pancreas Case Report[1]

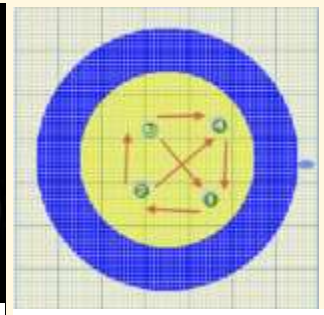
Occlusion of splenic artery.



Involvement of portal vein and superior mesenteric artery SMA.



Anterior needle placement. 22-g needle between the pancreas and stomach for hydrodissection (arrow).



Software shows 6 vectors of pulses.

No residual enhancement of tumor, with maintained patency and appearance of the splenic artery (arrow).

At the level of the superior mesenteric artery is also absence of enhancement

1. Bagla et al., JVIR, 23:142–145, January 2012

Pancreas Efficacy[1]

- “Irreversible Electroporation in Locally Advanced Pancreatic Cancer: Potential Improved Overall Survival”

Martin et al., Annals of Surgical Oncology, November 6 2012

1. Martin et al., Annals of Surgical Oncology, Online, Nov 6 2012

Pancreas Efficacy[1]

- A total of 54 Locally advanced unresectable pancreatic adenocarcinoma (LAC) patients underwent IRE successfully
- 35 patients had pancreatic head primary and 19 had body tumors
- 19 patients underwent margin accentuation with IRE and 35 underwent in situ IRE.
- 49 (90 %) patients had pre-IRE chemotherapy alone or chemoradiation therapy for a median duration 5 months.
- 40 (73%) patients underwent post-IRE chemotherapy or chemoradiation.

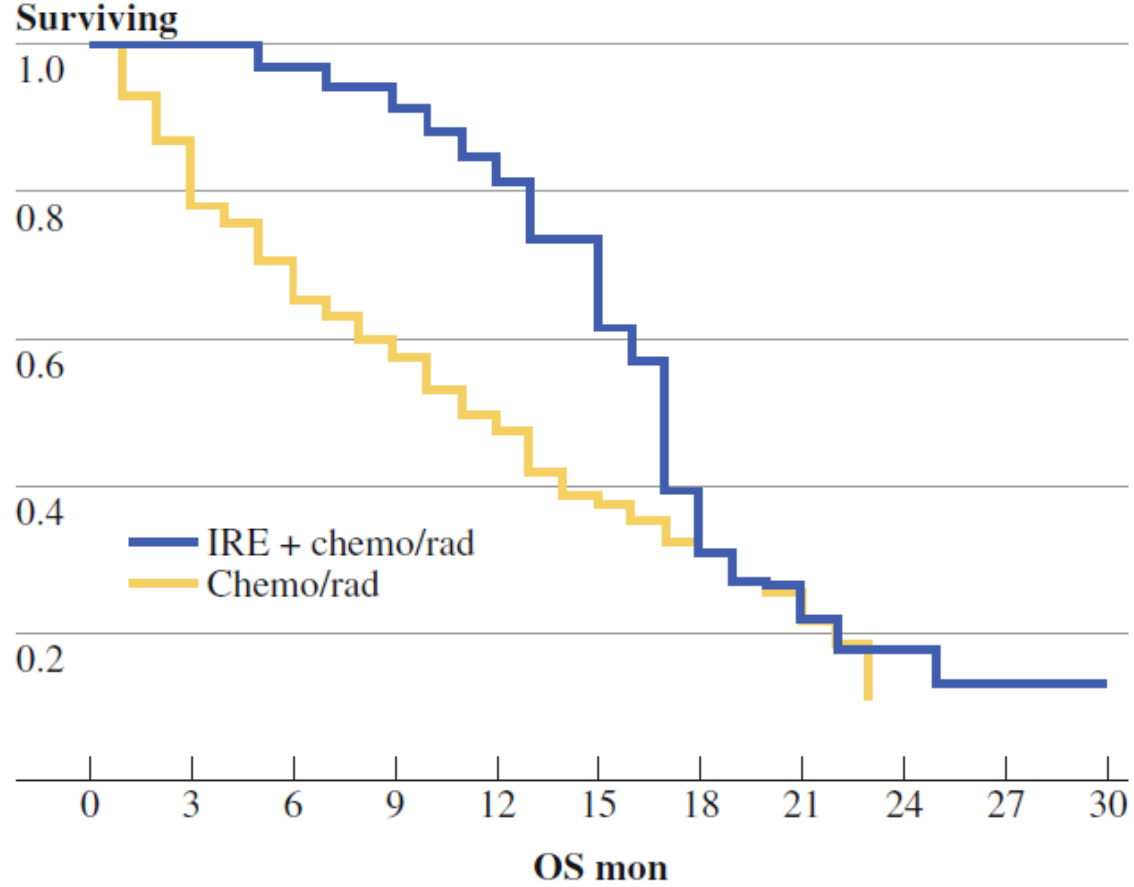
1. Martin et al., Annals of Surgical Oncology, Online, Nov 6 2012

Pancreas Efficacy[1]

- In a comparison of IRE patients to standard therapy, 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).

1. Martin et al., Annals of Surgical Oncology, Online, Nov 6 2012

Pancreas Efficacy[1]



Overall survival of the 54 patient with LAP treated with IRE and standard chemotherapy and/or radiation therapy versus the 85 patients treated with just chemotherapy and/or radiation therapy alone

1. Martin et al., Annals of Surgical Oncology, Online, Nov 6 2012

Pancreas Efficacy[1]

- IRE ablation of locally advanced pancreatic tumors remains safe and
- in the appropriate patient who has undergone standard induction therapy for a **minimum of 4 months** can achieve greater local palliation and potential improved overall survival compared with standard chemoradiation–chemotherapy treatments.

1. Martin et al., Annals of Surgical Oncology, Online, Nov 6 2012

Pancreas Safety[1]

- “Irreversible Electroporation Therapy in the Management of Locally Advanced Pancreatic Adenocarcinoma”

1. Martin et al., J Am Coll Surg. **2012** Sep;215(3):361-9. doi: 10.1016/j.jamcollsurg.**2012**.05.021. Epub **2012** Jun 21.
2. Martin RC 2nd et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. Ann Surg. 2015 Sep;262(3):486-94;

Pancreas Safety[1]

- 27 Patients underwent IRE
- 8 patients underwent margin accentuation with IRE in combination with left-sided resection (n=4) or pancreatic head resection (n=4).
- 19 patients had in-situ IRE.

1. Martin et al., J Am Coll Surg, 10.1016, June 2012

Pancreas Safety[1]

- All patients underwent successful IRE
- All 27 patients demonstrated non-clinically relevant elevation of their amylase and lipase, which peaked at 48 hours and returned to normal at 72 hour post-procedure.
- There was one 90-day mortality.

1. Martin et al., J Am Coll Surg, 10.1016, June 2012

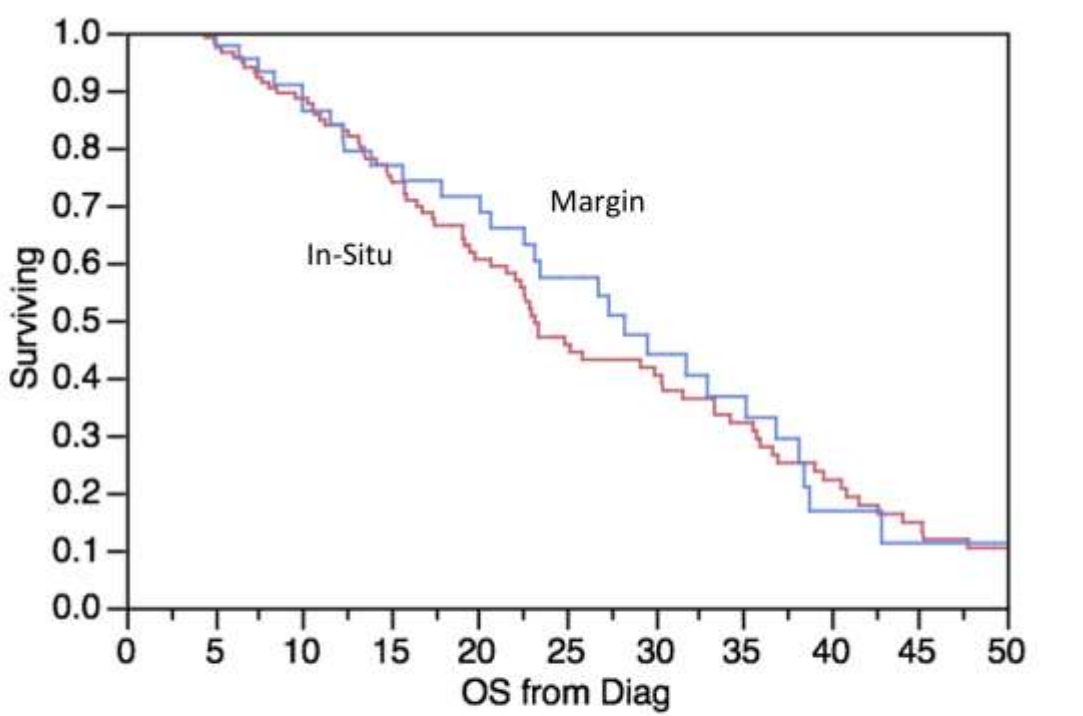
Pancreas Safety[1]

- No patient showed evidence of clinical pancreatitis or fistula formation.
- All patients completed 90-day follow-up

1. Martin et al., J Am Coll Surg, 10.1016, June 2012

Results

Characteristics	LAPC Resection & IRE (Margin) (N=50)	LAPC with IRE (Insitu) (N=150)
Location		
Head	13 (25%)	95 (63%)
Body/Neck	37 (75%)	55 (37%)
Lesion Size		
Axial	2.5 (1.8 x 5.5)	3 (1.0-6cm)
Anterior – Posterior	2.7 (1.4 x 6.7)	2.7 (1.6-7)
Caudal to Cranial	2.6 (1.6 x 5)	2.9 (1.5-5.5)
Vessel Invasion At Diagnosis		
Celiac Only	60%	7%
SMA Only	30%	3%
Celiac and SMA	5%	3%
PV-SMV Occlusion Only	0%	17%
Celiac/SMA w/ Vein Occlusion	5%	12%
Prior Chemotherapy	100%	100%
Gemzar Based	43%	60%
FOLFIRINOX	38%	29%
Prior Radiation Therapy	52%	47%
Type Pancreatic Resection		
Subtotal Left Panc with en-bloc Celiac Resection	25	Not Applicable
Subtotal Left Panc with Portal vein resection and celiac	12	
Whipple with Portal vein	13	
Post IRE Adjuvant Chemo	60%	69%
Post IRE Adjuvant XRT	11%	13%



Median Overall Survival: Margin 28.3 (range 9.2 to 85 months)
In-Situ 23.2 months (range 7.3 to 76.1 months)

Martin RC 2nd et al. Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. Ann Surg. 2015 Sep;262(3):486-94;

Pancreas Safety[1]

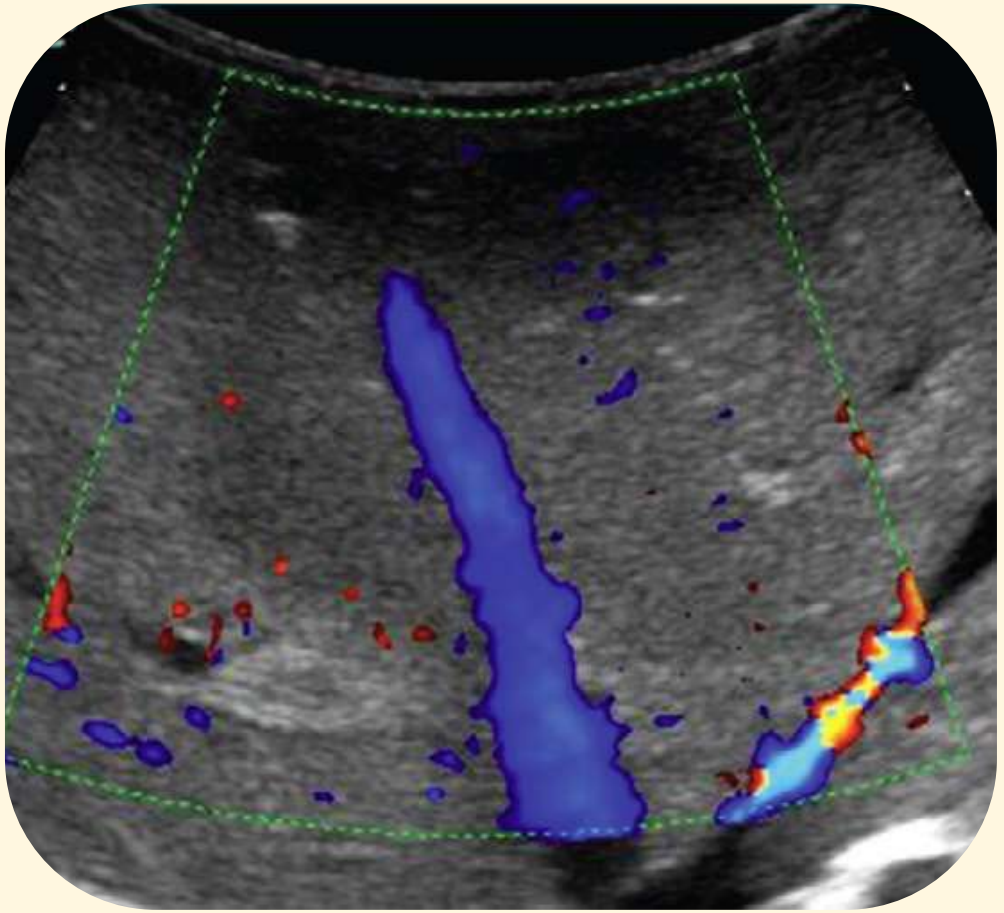
- Conclusions:
  - IRE ablation of locally advanced pancreatic cancer tumors is a safe and feasible primary local treatment in unresectable, locally advanced disease.

1. Martin et al., J Am Coll Surg, 10.1016, June 2012

Ultrasound (US)

- Axial color Doppler US scan shows a patent vessel coursing through treatment region.

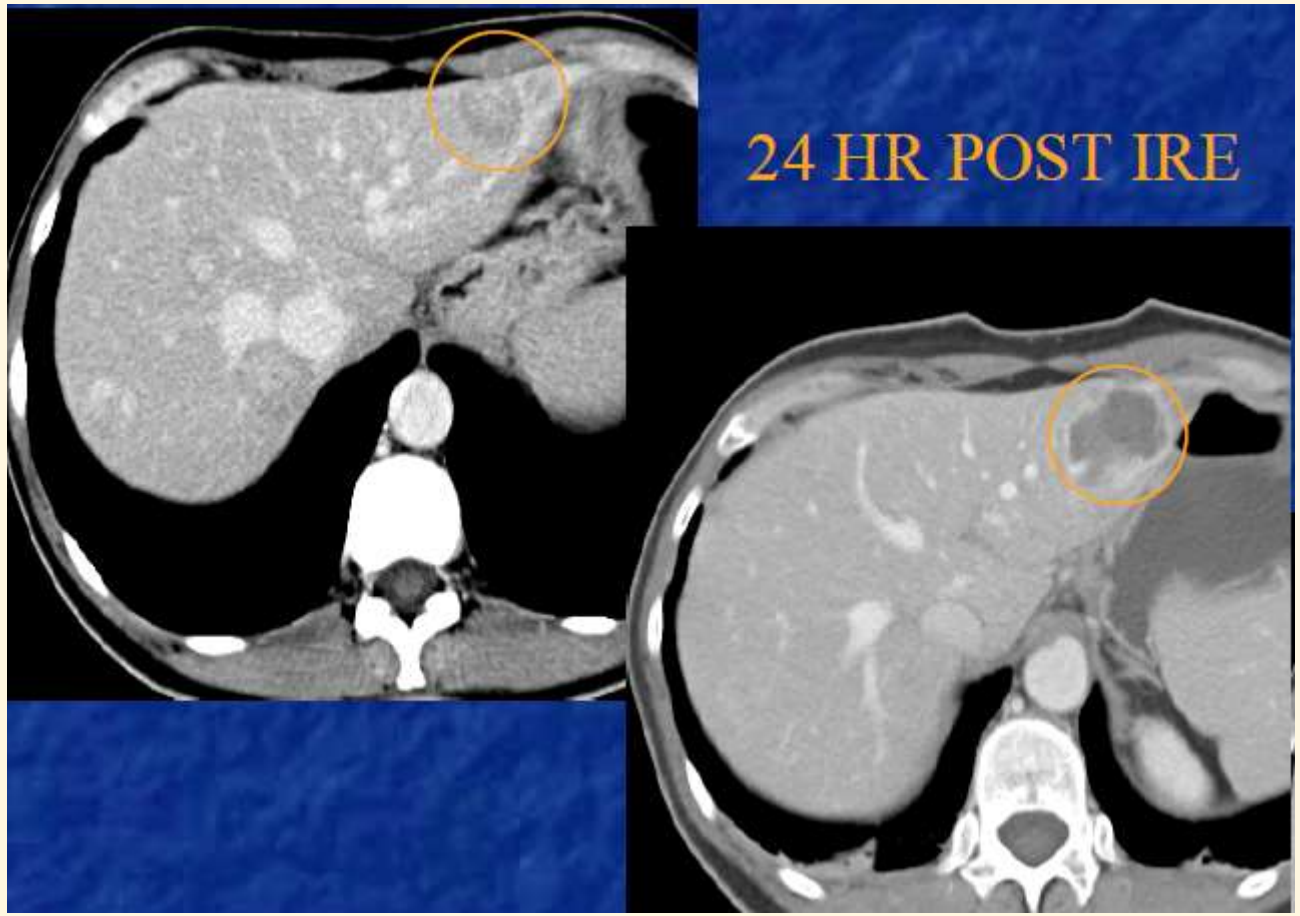
15 minutes Post-IRE



1. Appelbaum et al., Radiololgy, V262 N1, Jan 2012

Computerized Tomography (CT)

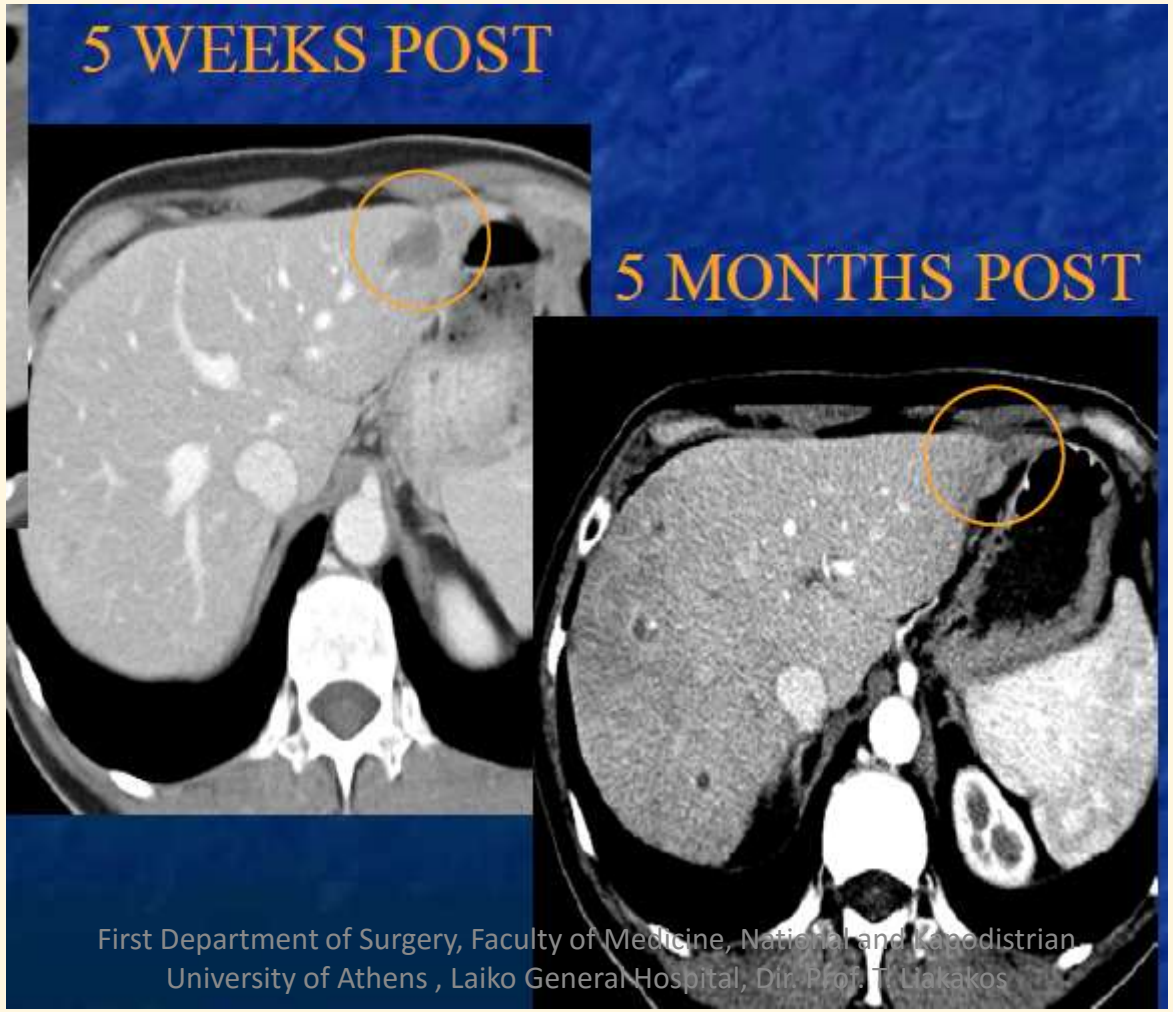
HCC IRE Treatment



1. G. Narayanan : Presentation at CIRSE 2013, Barcelona , Spain

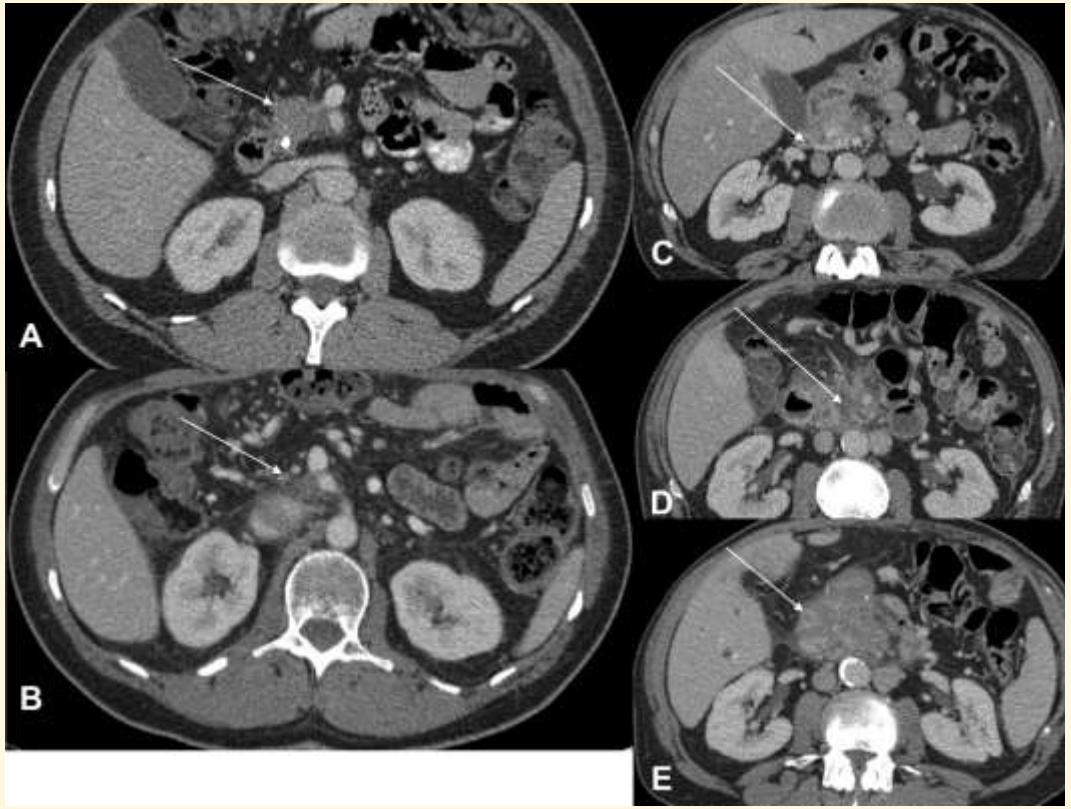
Computerized Tomography (CT)

HCC Post-IRE Treatment



1. G. Narayanan : Presentation at CIRSE 2013, Barcelona , Spain

Computerized Tomography (CT)



- (A) Preoperative CT image: patient 1, pancreatic adenocarcinoma is demonstrated (white arrow) with encasement of the superior mesenteric artery.
- (B) Postoperative CT image (6 months after irreversible electroporation): patient 1, an “amorphous” non-mass-like soft tissue density (arrow) is noted in place of the mass. This density persists for greater than 12 months.
- (C) First image (preoperative): patient 2, demonstrates a pancreatic mass (arrow) encasing the superior mesenteric vein.
- (D) Second image (2 weeks after irreversible electroporation): patient 2, the “amorphous” density (arrow) replacing the mass is somewhat heterogeneous compared with the previous example.
- (E) Third image (3 months after irreversible electroporation): patient 2, development of a new bulky mass (arrow) consistent with recurrence.

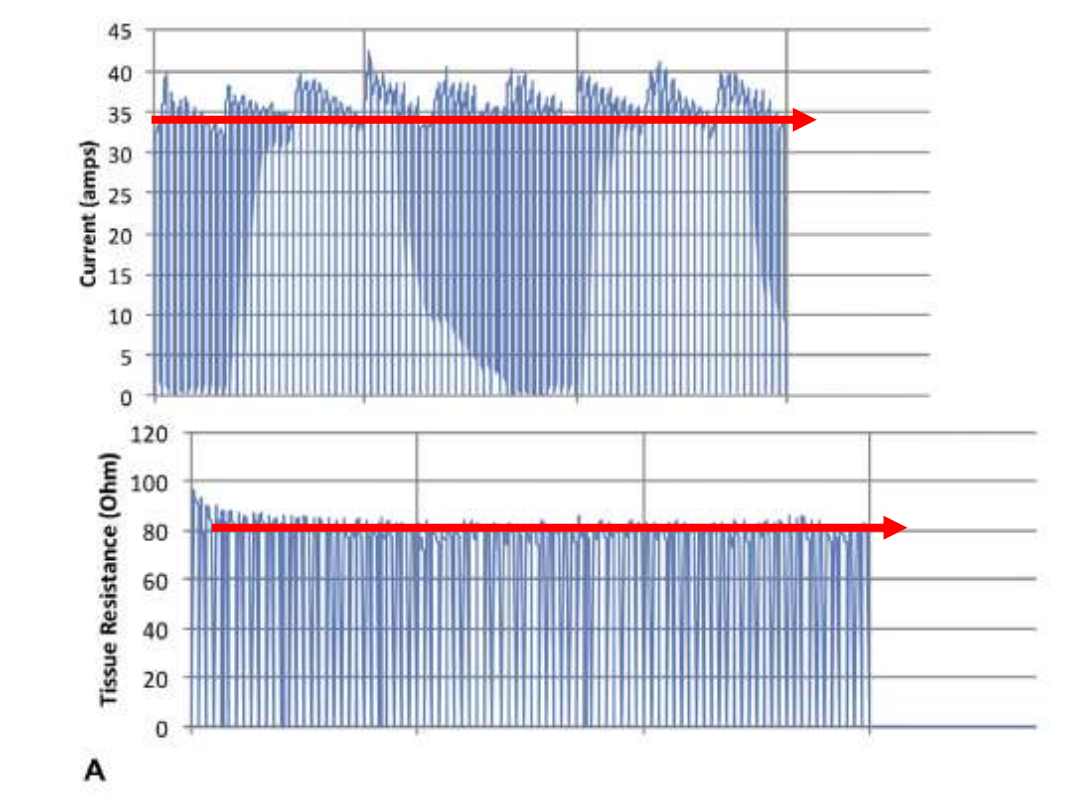
Martin et al. J Am Coll Surg 2014;218:179e187

Computerized Tomography (CT)

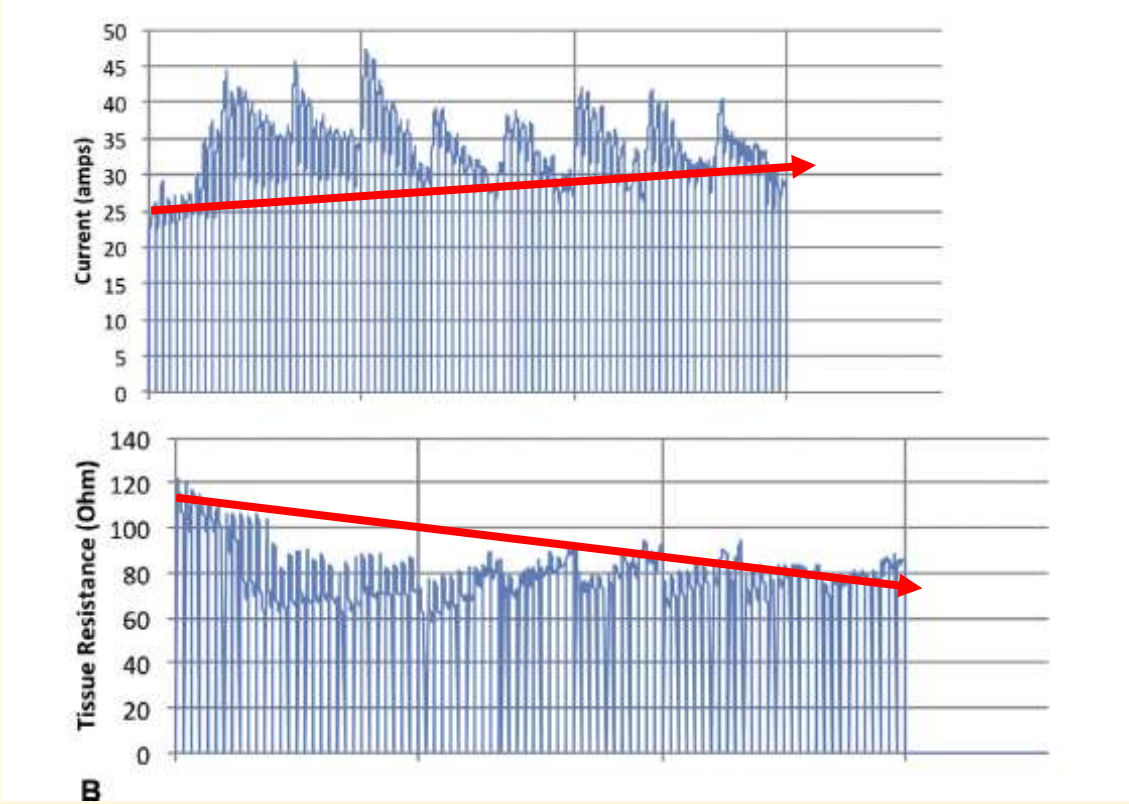
- Lack of enhancement
- Exaggerated zone of hypodensity with peripheral hypermia in post procedure imaging
- Decrease in size of this zone in the 1 month follow up imaging
- Preservation of vasculature in treatment zone

1. G. Narayanan : Presentation at CIRSE 2013, Barcelona , Spain

How to know that successfully deliver energy? Changing in resistance (drop)

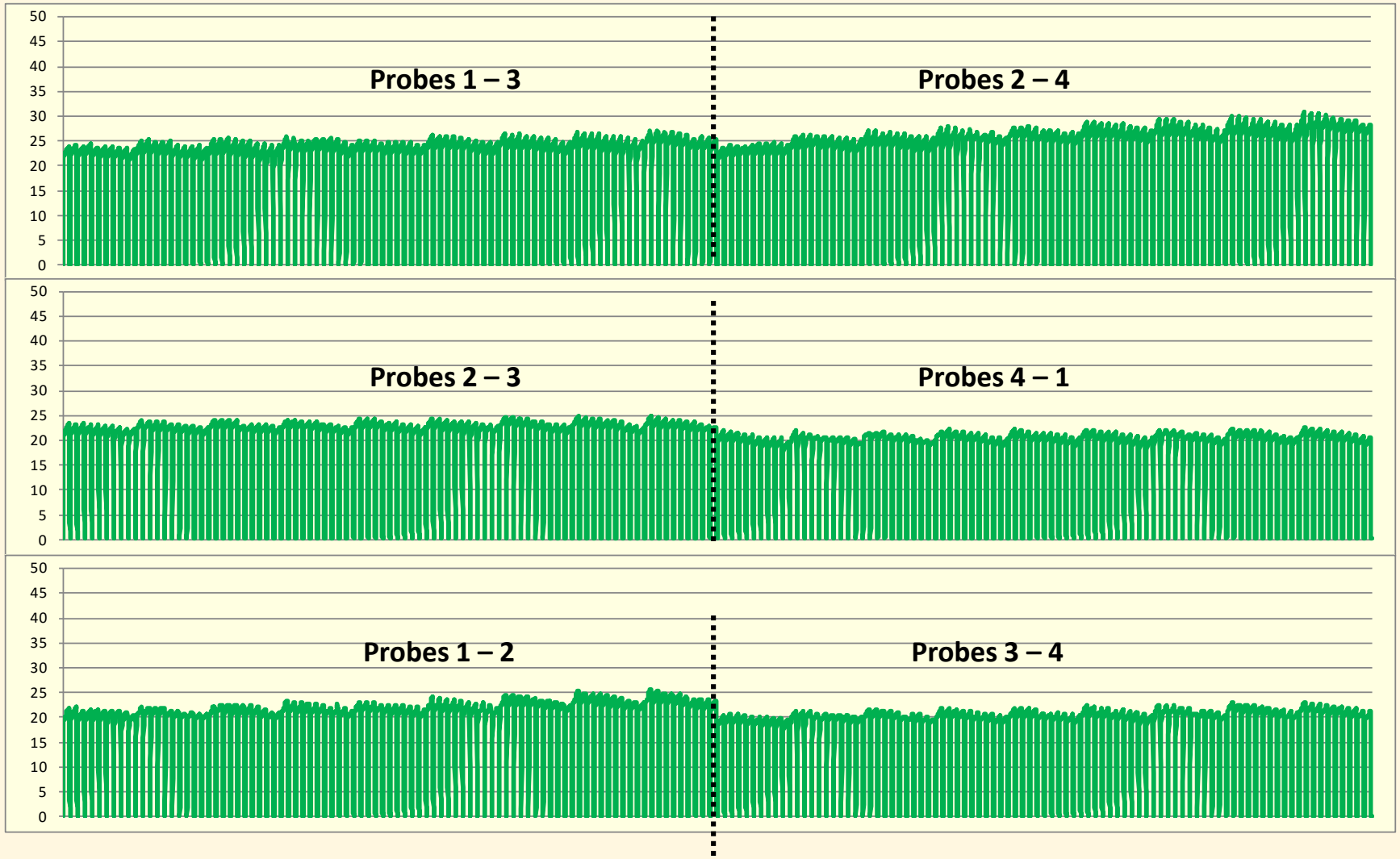


(A) An example of current draw (top in amps) and then change in resistance (bottom in ohms) from an **incomplete ablation** based on the lack of adequate change in ohms.

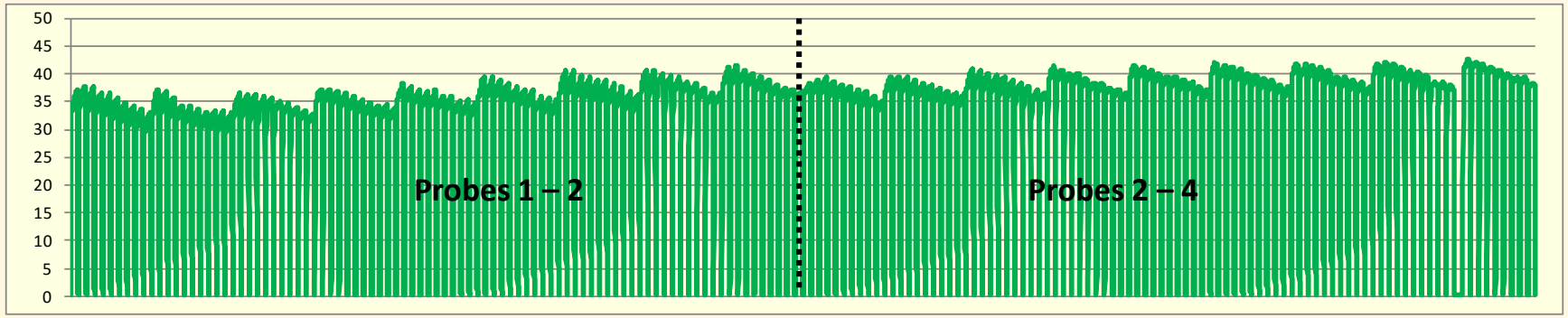


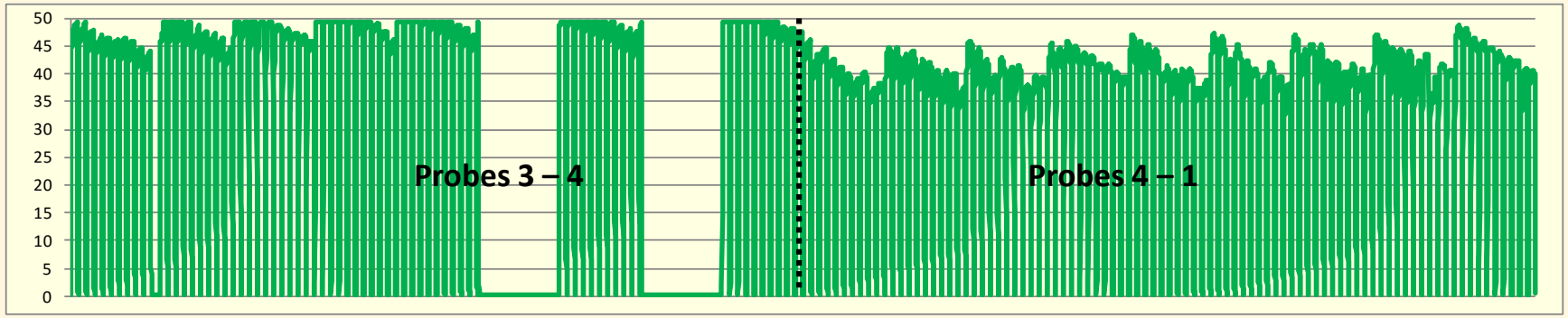
(A) An example of current draw (top in amps) and then change in resistance (bottom in ohms) from a **complete ablation** based on the adequate change in ohms.

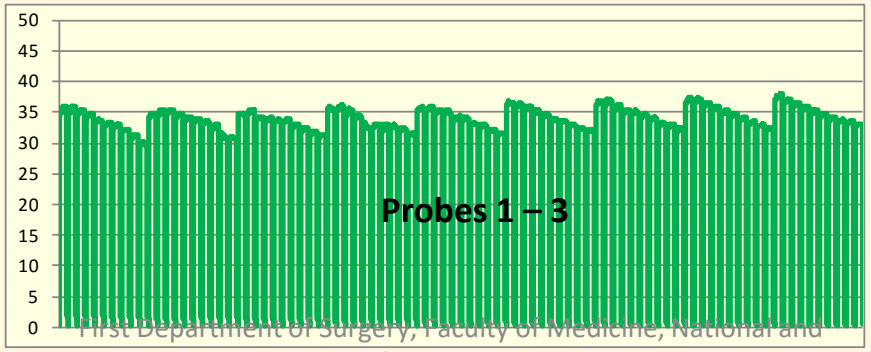
Martin et al. J Am Coll Surg 2014;218:179e187


50
45
40
35
30
25
20
15
10
5
0
Probes 1 – 3
Probes 2 – 4
Probes 2 – 3
Probes 4 – 1
Probes 1 – 2
Probes 3 – 4

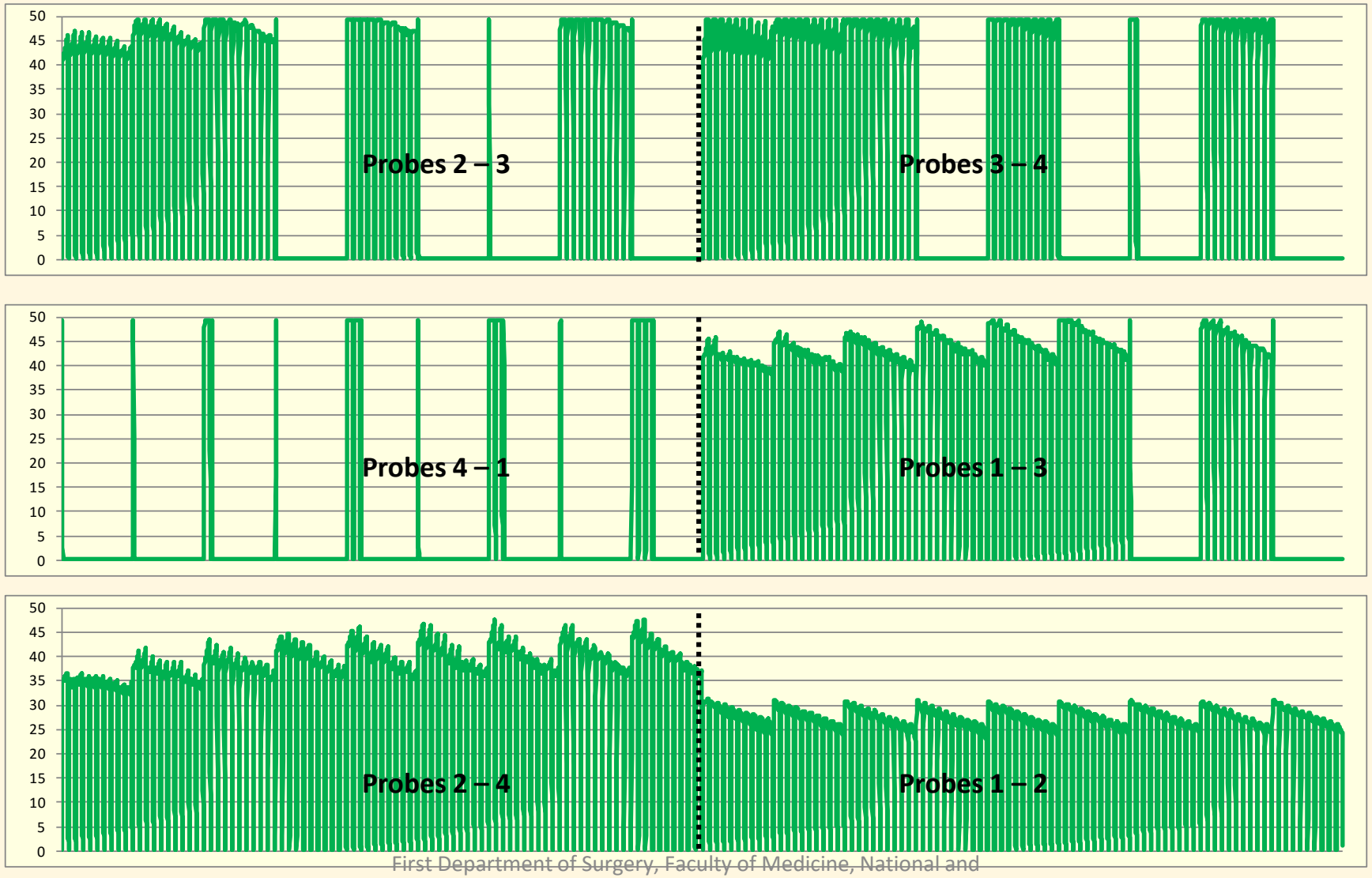
Case #2 – 1st Tx Current Results





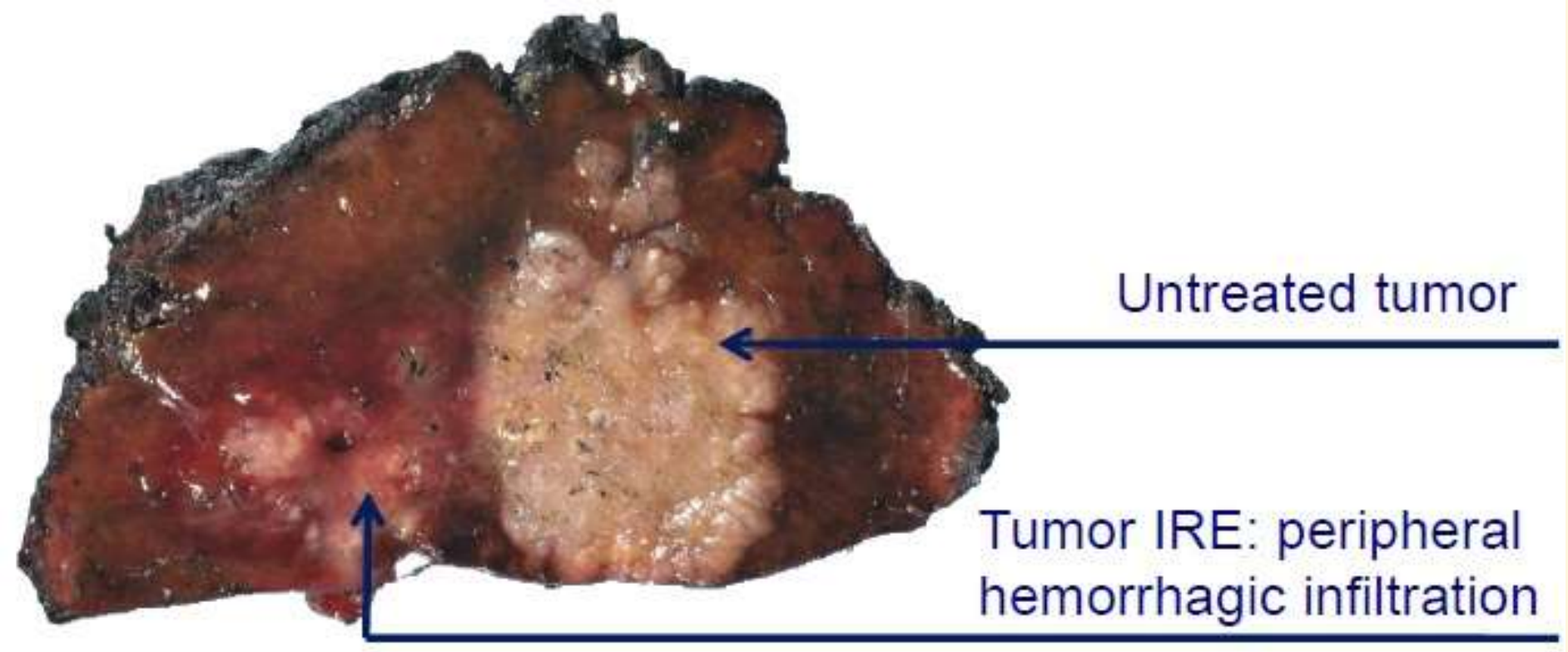


Case #2 – 2nd Tx Current Results



Histology of IRE

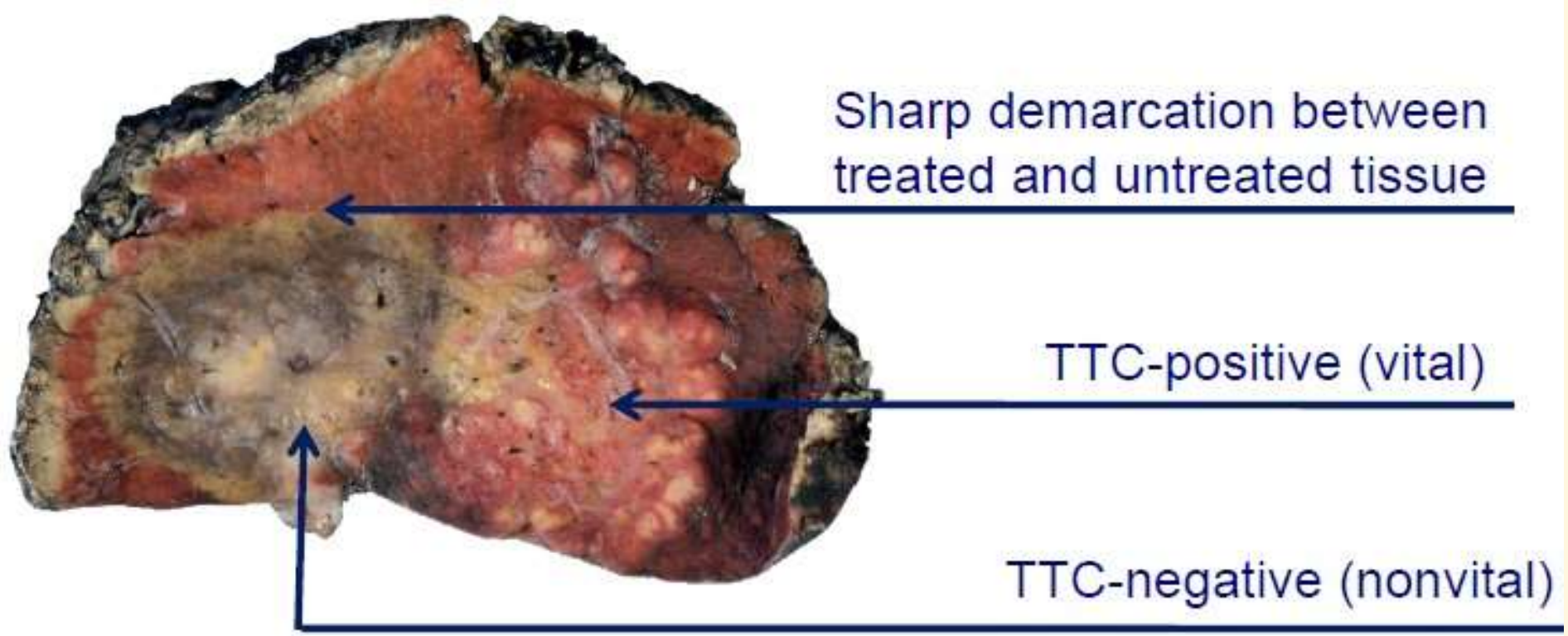
- Specimen directly after resection (1 hour post-IRE treatment)
- Macroscopy TTC Vitality Staining



1. Scheffer et al., Poster presented at CIRSE 2013

Histology of IRE

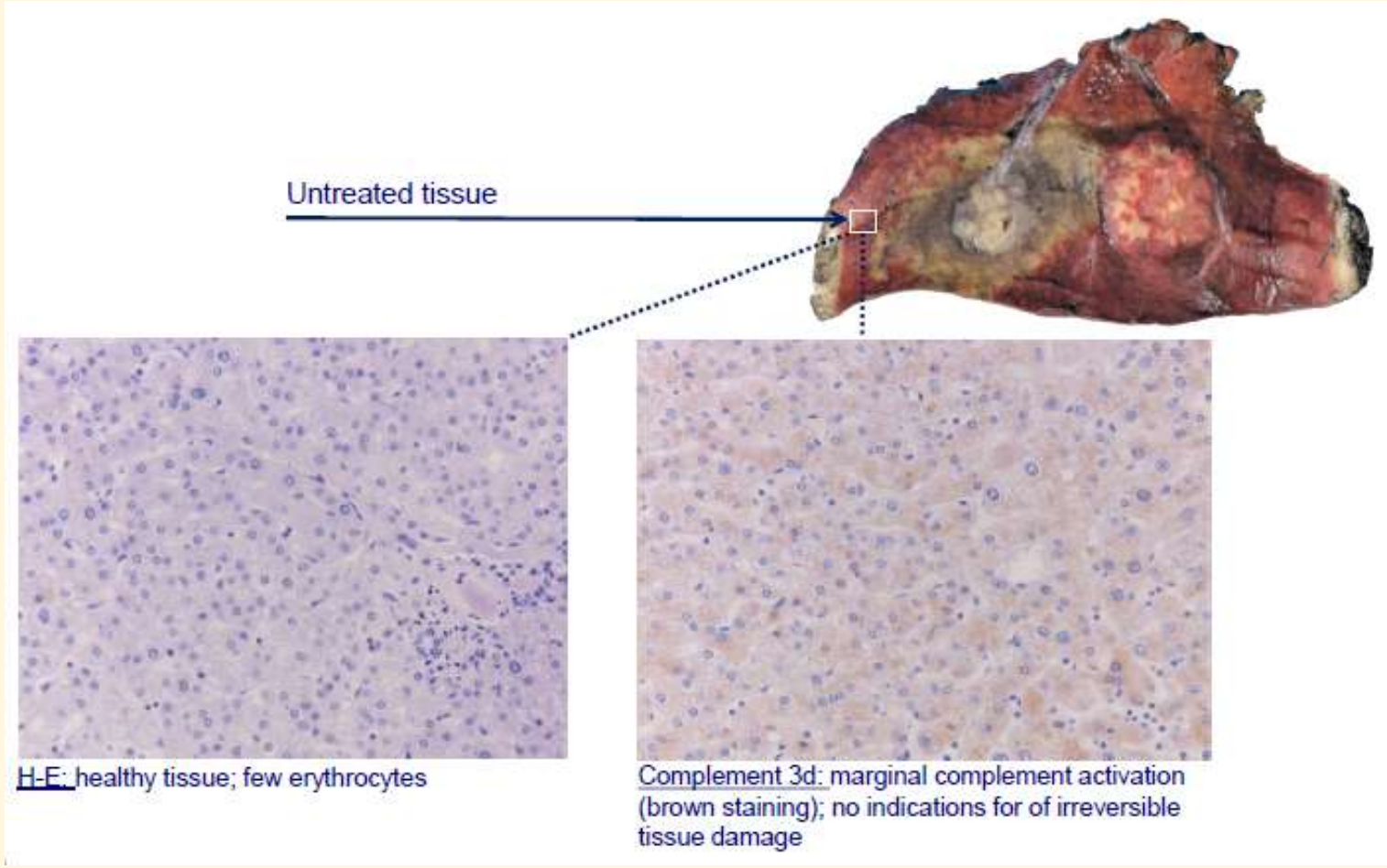
- Same specimen 24 hours after resection (25 hours post-IRE treatment)
- +TTC Vitality Staining – Vital tissue turns transparent TTC into red stain



1. Scheffer et al., Poster presented at CIRSE 2013

Histology of IRE

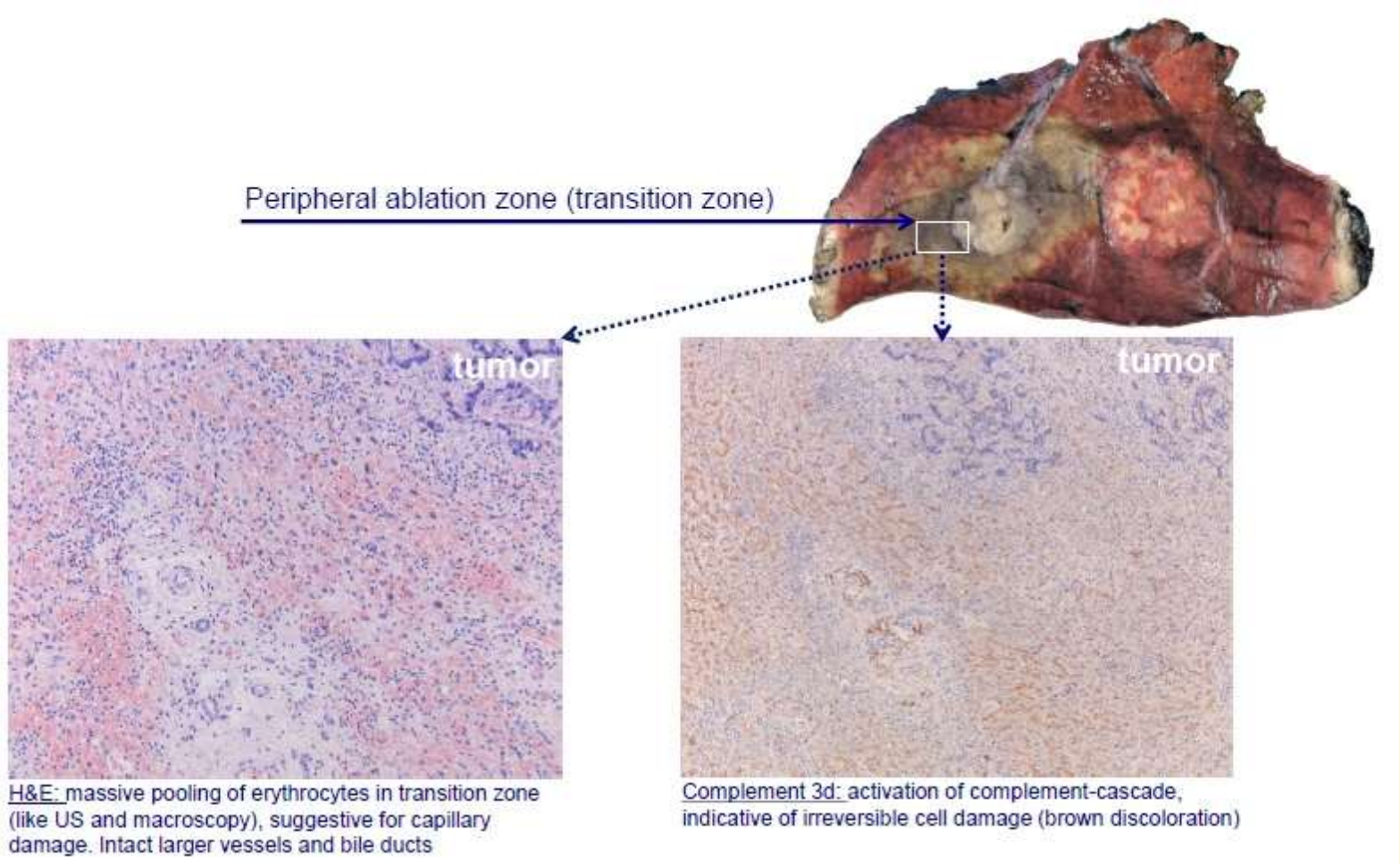
- Microscopy – H&E and complement 3D staining



1. Scheffer et al., Poster presented at CIRSE 2013

Histology of IRE

- Microscopy – H&E and complement 3D staining



1. Scheffer et al., Poster presented at CIRSE 2013

Safety of irreversible electroporation treatment for Liver metastatic disease in humans

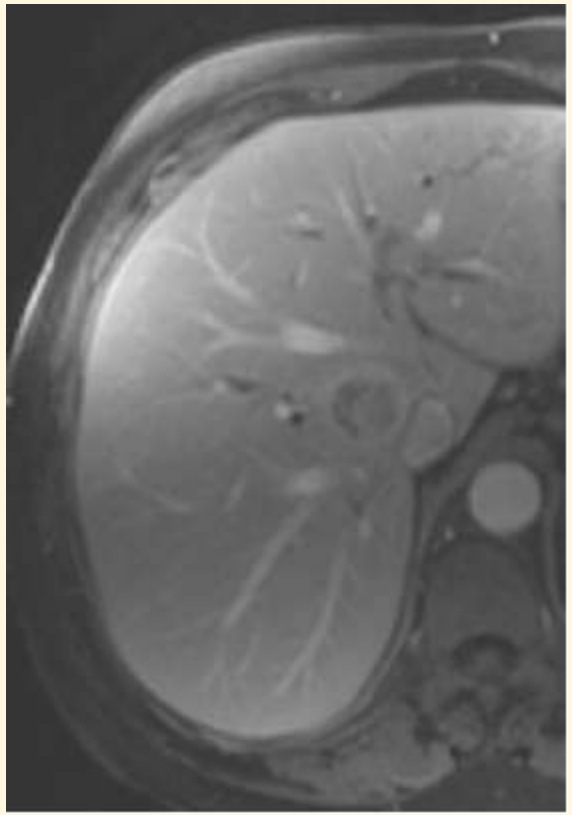
Silk Mikhail; Wimmer, Thomas; Getrajdman, George; Durack, Jeremy; Sofocleous, Constantinos T.; Solomon, Stephen B.

Interventional Radiology & Image Guided Therapies

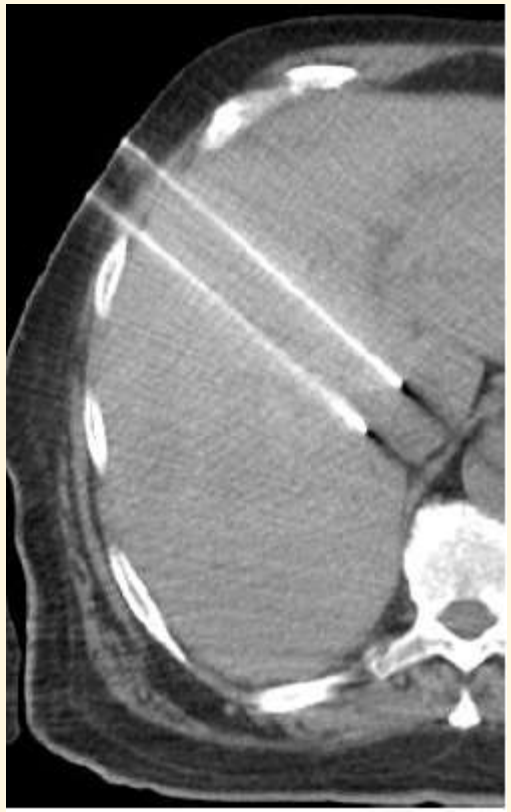
Memorial Sloan Kettering Cancer Center. New York, NY

Case close to bile duct and major vein

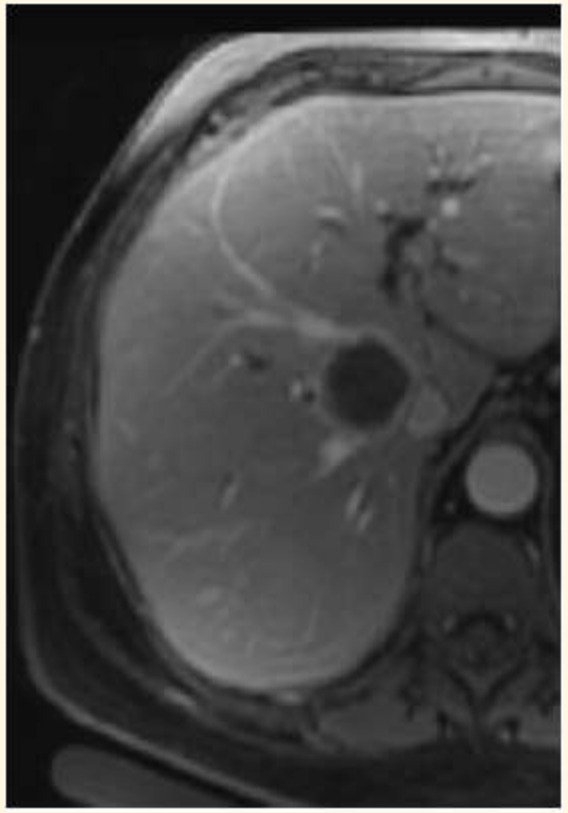
- Pre-Tx



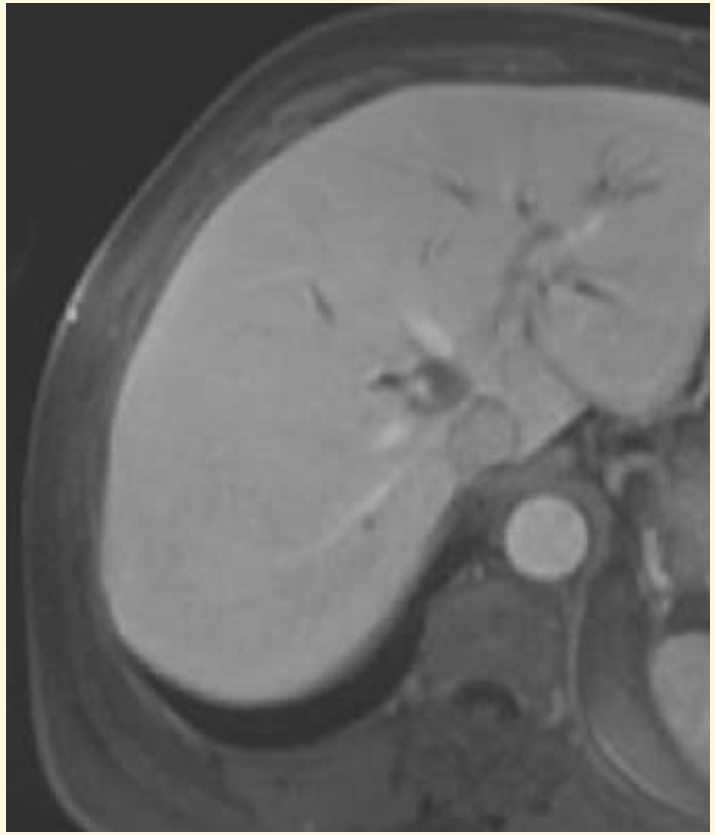
- Tx



- Post-Tx
  - 3 mo. f/u MRI

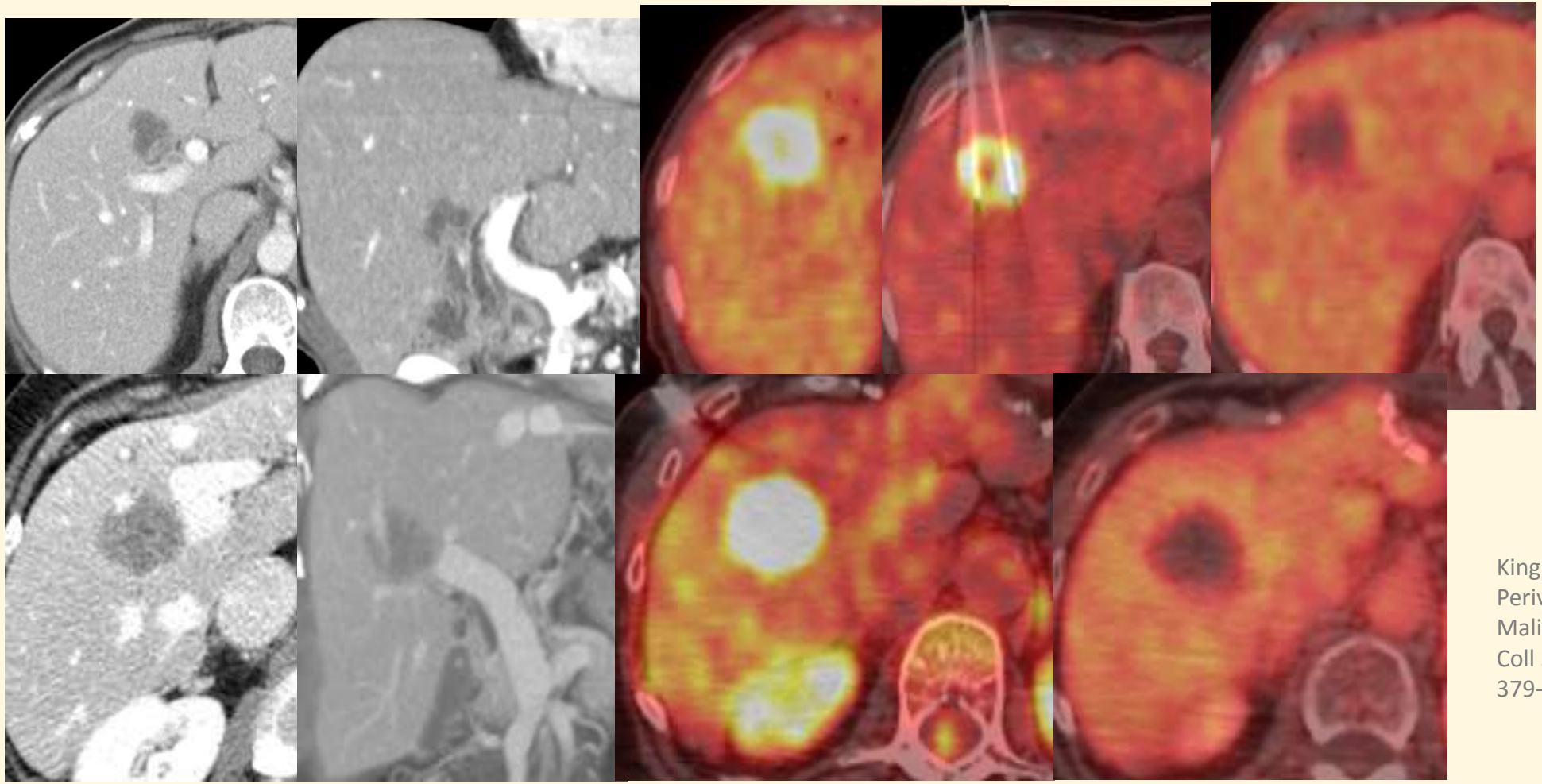


No tumor for +778 days



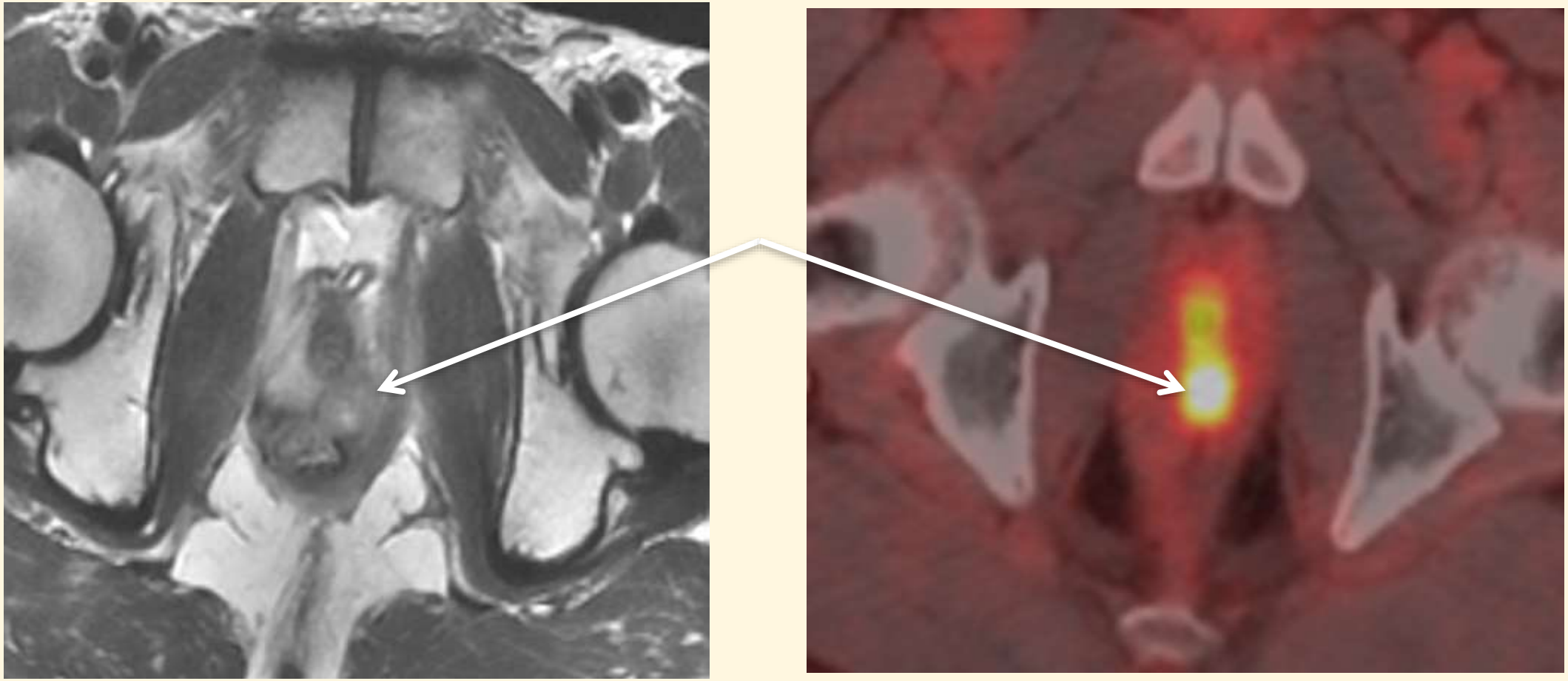
Perivascular/periductal Liver Metastases

28 patients/ 65 tumors: 1 arrhythmia; 1 PV thrombosis (3%)
6 months: 92% Complete Ablation

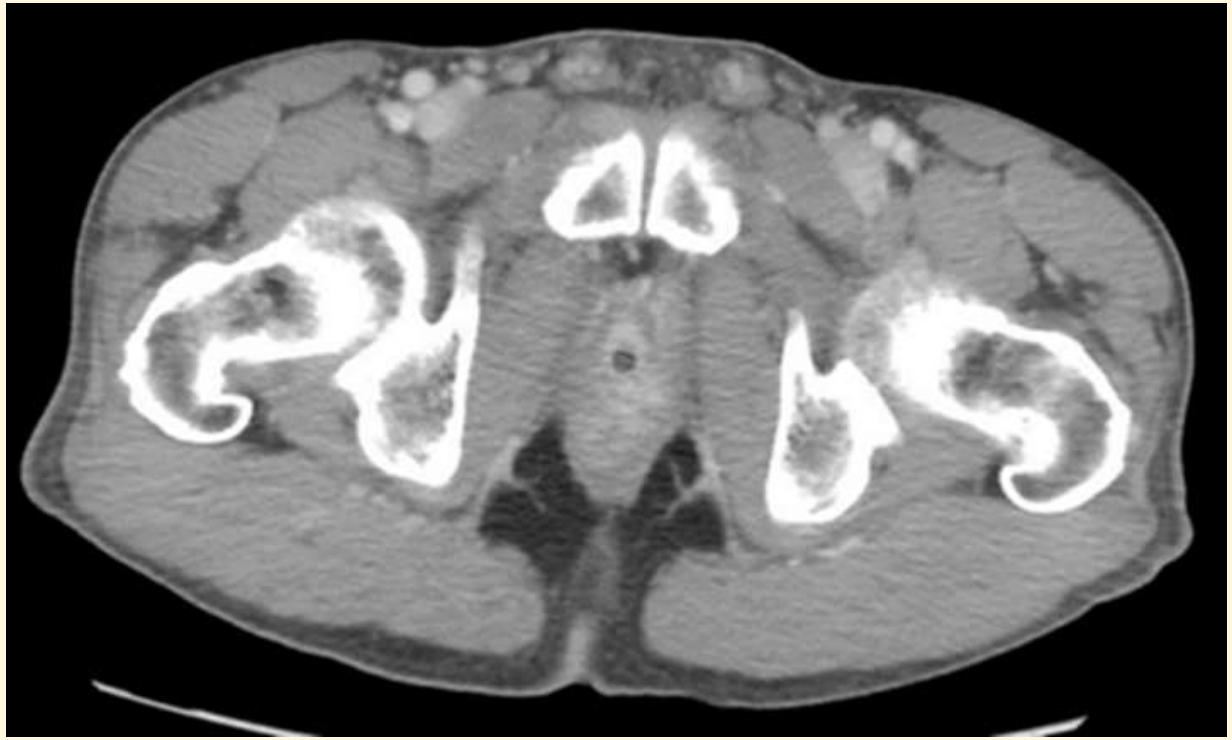


Kingham P et al: IRE for Perivascular Hepatic Malignant Tumors. J Am Coll Surg 2012; 215(3): 379-87

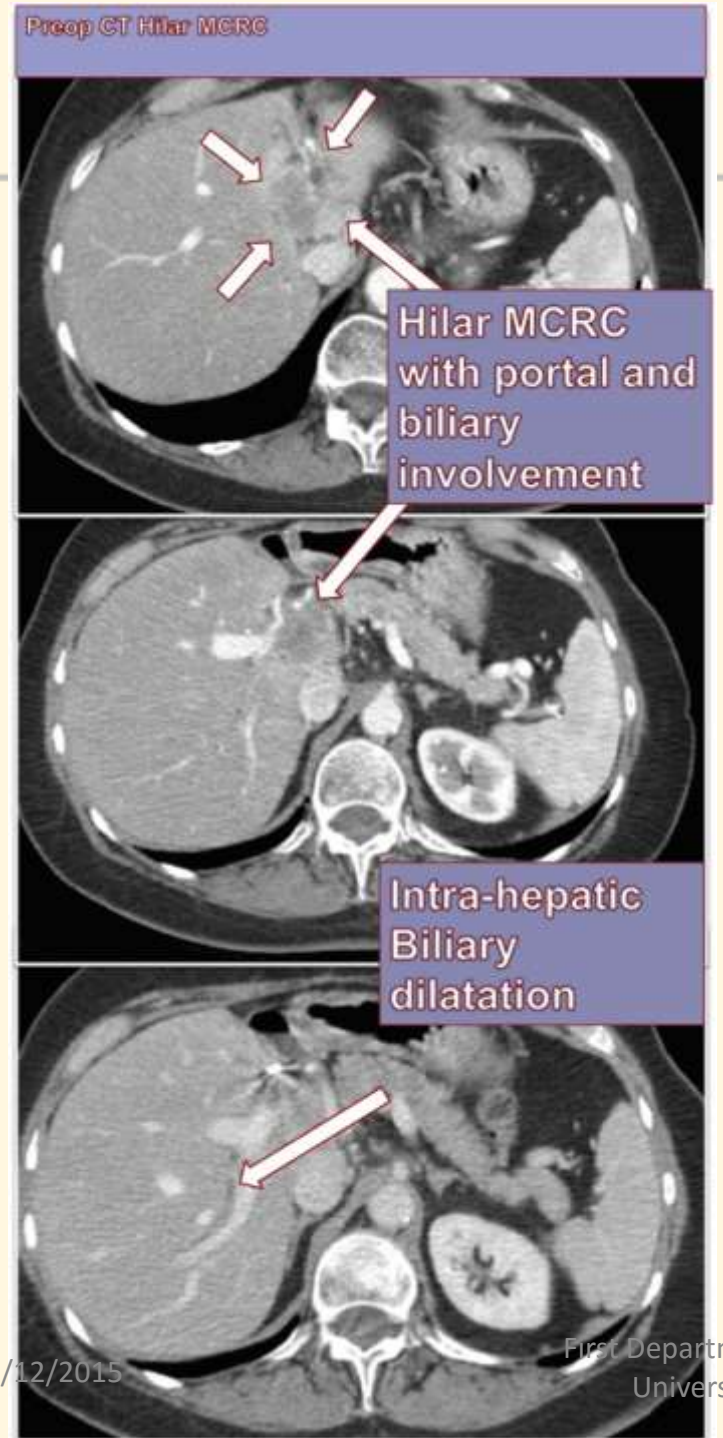
51 year old with rectal cancer recurrence near rectum

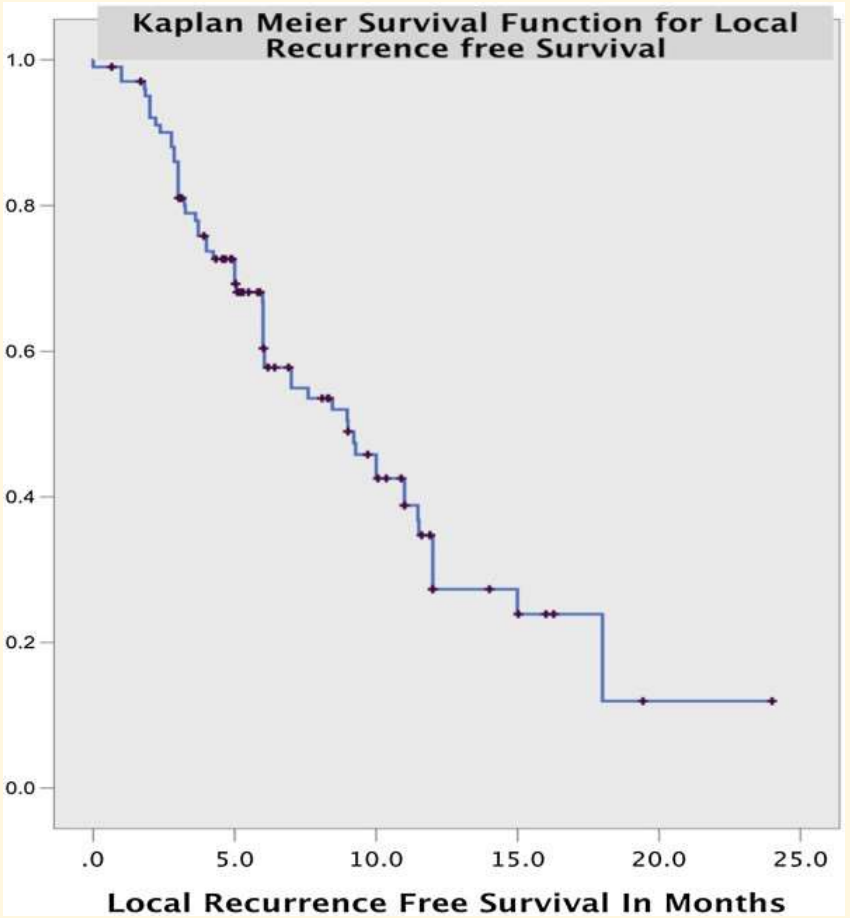


NO tumor for +565 days



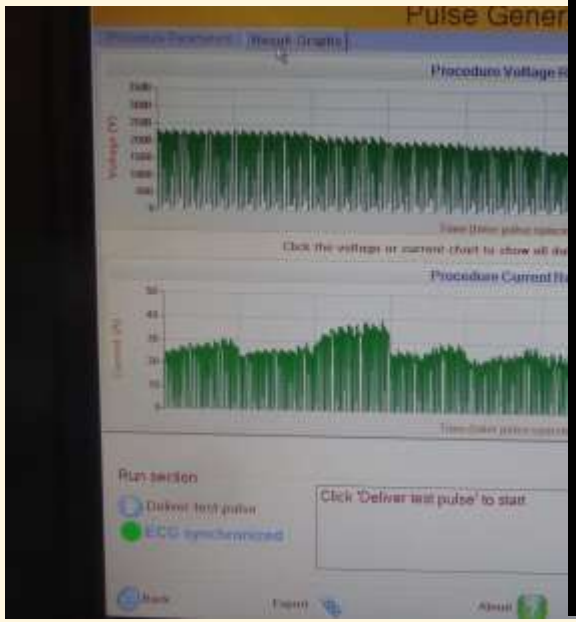
Mcrc

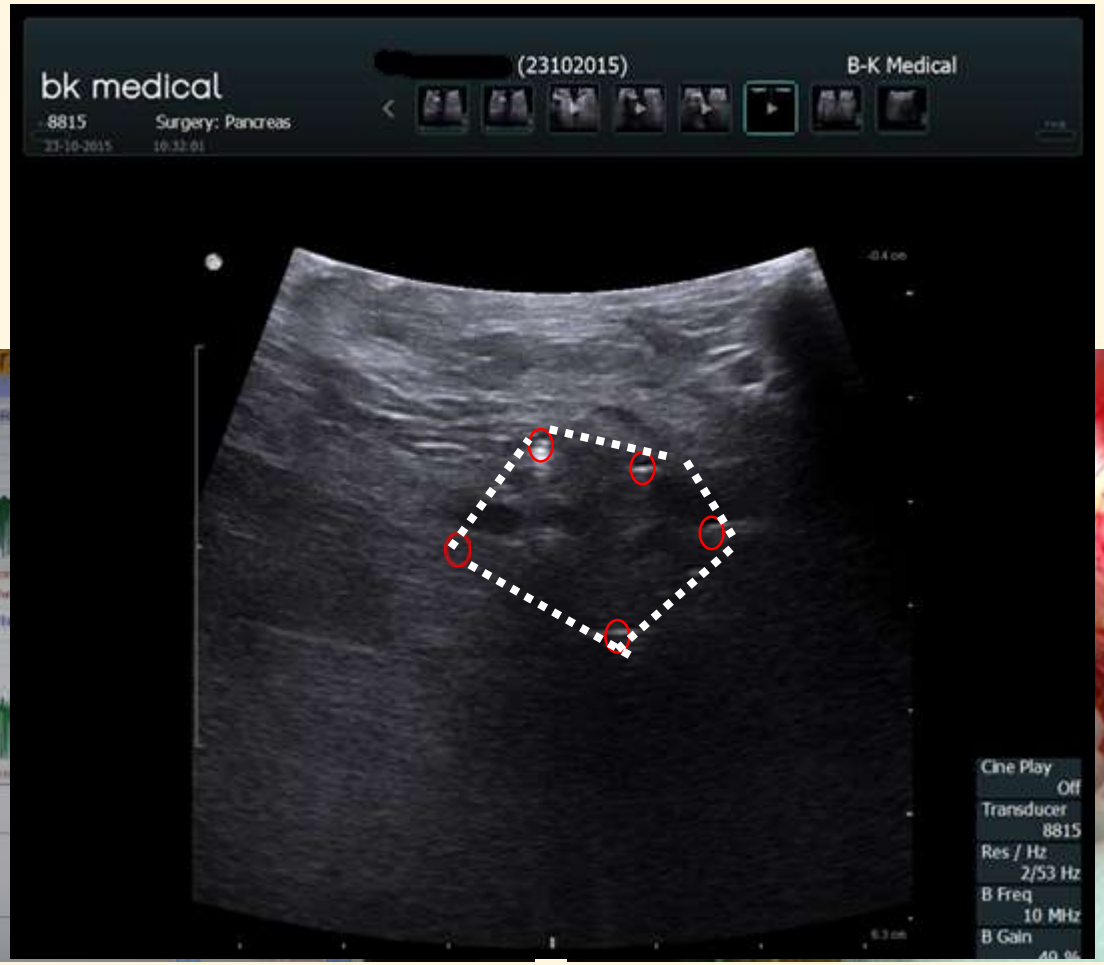




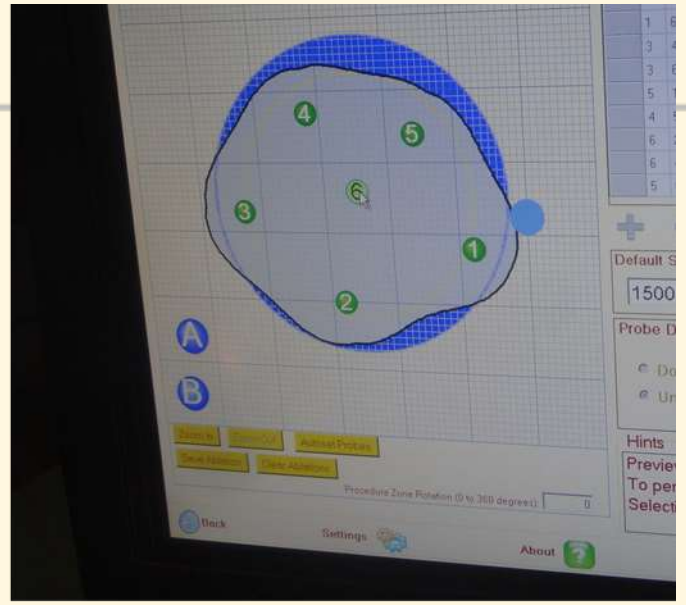
Martin RC et al. Irreversible electroporation of unresectable soft tissue tumors with vascular invasion: effective palliation. BMC Cancer. 2014 Jul 26;14:540.

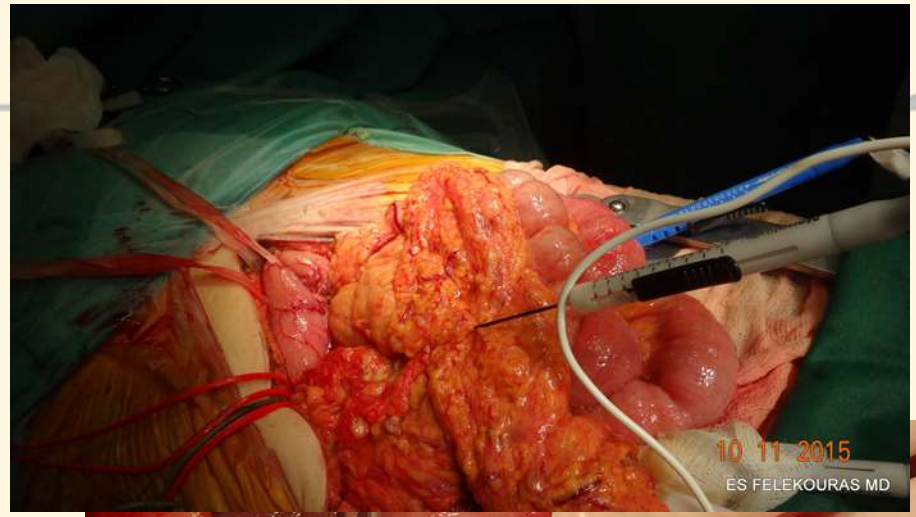
IRE in Greece



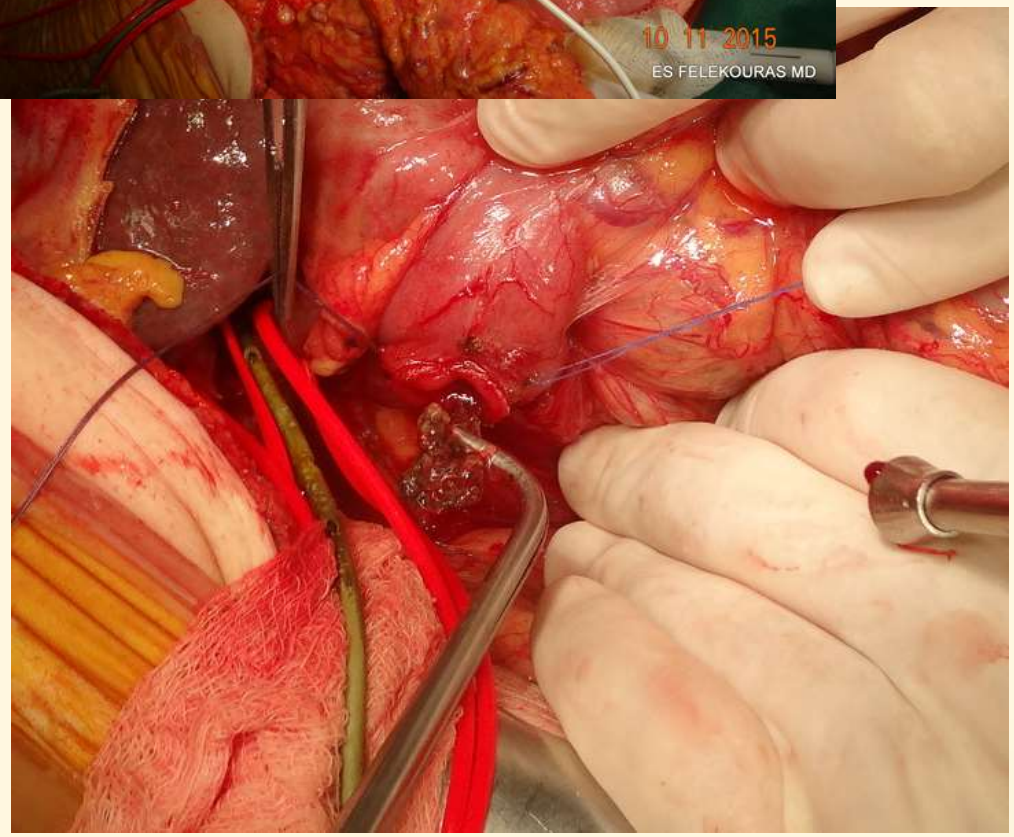


IRE


Default S
1500
Probe D
Hints
Previe
To per
Select
Settings
About


10 11 2015
ES FELEKOURAS MD


syngo CT 2012B
*10/16/1947, F, 68Y
10/16/2015
10:30:12.50
I No: 47
MIP THIN
<MIP Thin Collection>
Spin: 0
Tilt: 0
R
10cm
syngo CT 2012B
Spin: 0
Tilt: 0
10cm
10 11 2015
ES FELEKOURAS MD



IRE Summary

- Apoptotic induced cell death
- Non-thermal ablation
- No Heat Sink effect
- Precise ablations
- Preserves critical structures
- Might potentiate chemotherapy
- Compatible with CT/US and MRI (Pre & Post)
- Does not preclude other treatments
- Potential to extend Survival in (non-resectable) LAPC Patients
- Potential to downstage (non-resectable) LAPC Patients to resectability
- Safe in Pancreas

Applications: IRE
Where Thermal ablation is NOT feasible

- Pancreas: Locally advanced adenocarcinoma 100% success at 90 days.
  - Martin RC e al J Am Coll Surg 2012; 215(3): 361-9

- Perivascular Liver Tumors.
  - Kingham P et al: IRE for Perivascular Hepatic Malignant Tumors. J Am Coll Surg 2012; 215(3): 379-87

IRE as an Ablation Tool: Potential Advantages

- Non-Thermal:
  - Application in Locations non eligible for Thermal Ablation
  - Limit recurrences near vessels by avoiding the "heat sink" effect
- Cellular Kill Mechanism Avoids Damage to:
  - Extracellular Matrix. This may result in fewer complications:
  - Near Bile Ducts, Intestines, Ureters, Bronchi, Vital structures.