

NOVEL LOCAL ABLATIVE THERAPY FOR HEPATIC AND PANCREATIC MALIGNANCIES

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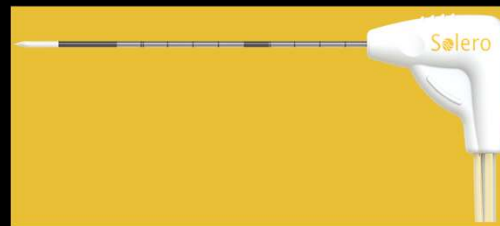
TYPES OF ABLATIVE TECHNIQUES

- **Thermal**
 - Microwave Ablation (MWA)
 - RFA: Radiofrequency Ablation
 - Cryo-Ablation
 - HIFU: High Intensity Focused Ultrasound
- **Non-Thermal**
 - Chemical Ablation
 - Irreversible Electroporation (IRE)
- **Approach:** Intra-operatively, Laparoscopically, Percutaneously
 - Percutaneous Approach: General anaesthetic or heavy sedation & Analgesia
- **Guidance:** US/CEUS, CT or MR

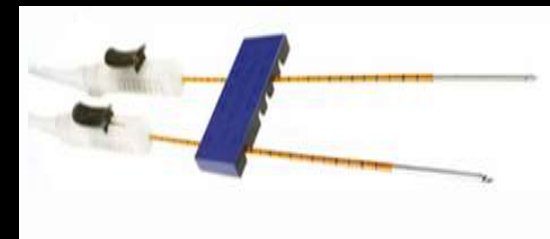
RFA



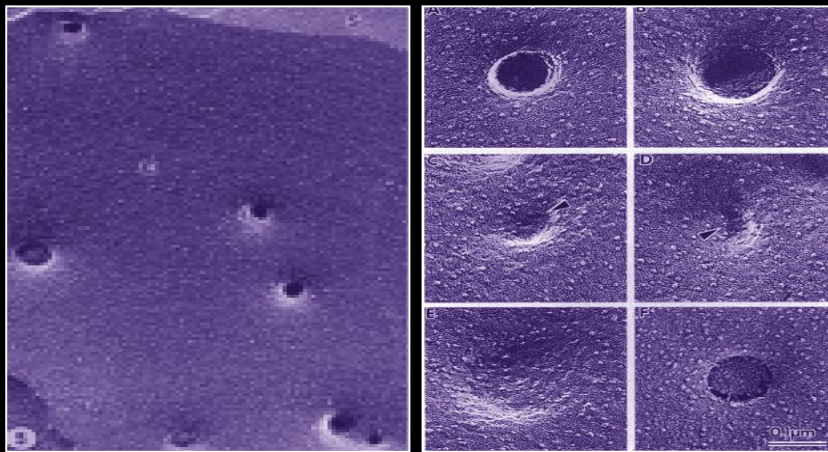
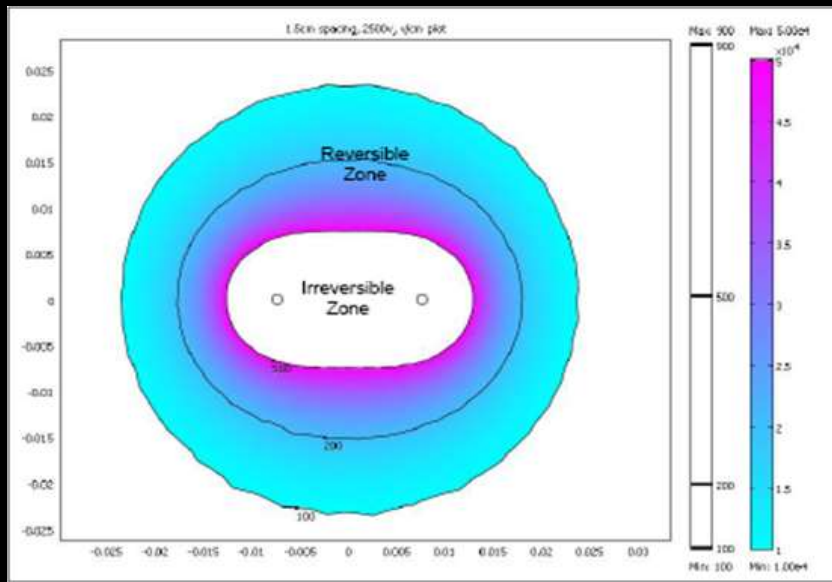
MWA



IRE



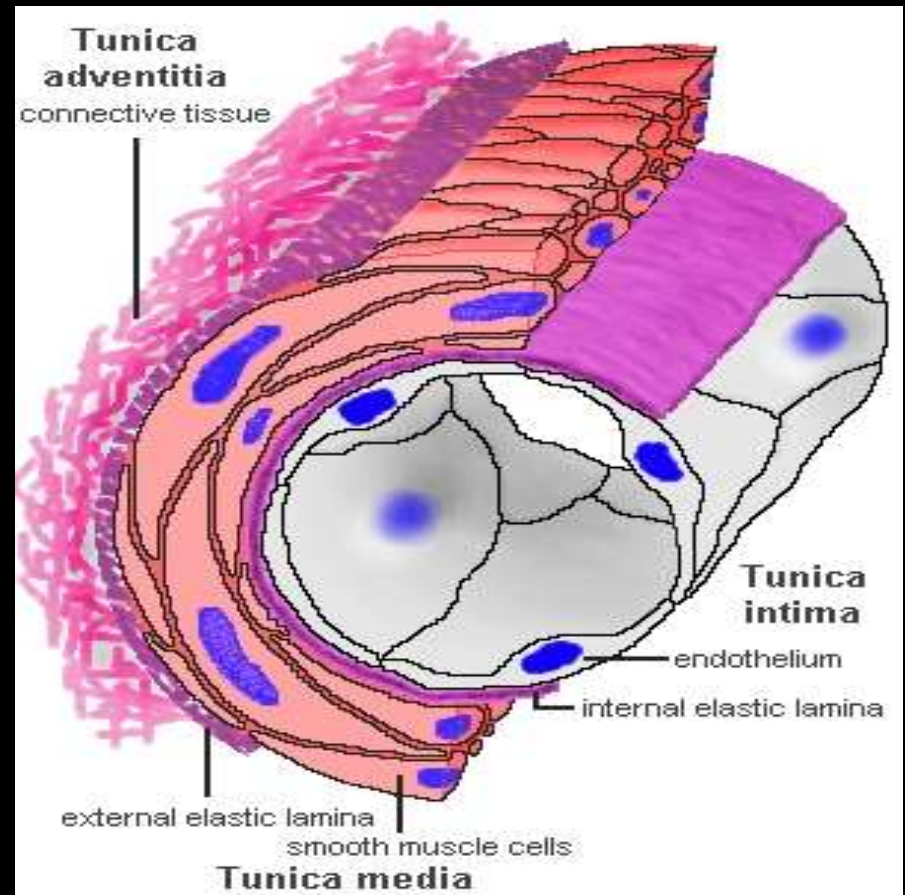
IRE



- Rapid series of short, electrical pulses.
- High voltage but low energy (non-thermal).
- Nano-sized defects ("pores") created in cell membrane.
- Cell death occurs (mimics natural cell death).

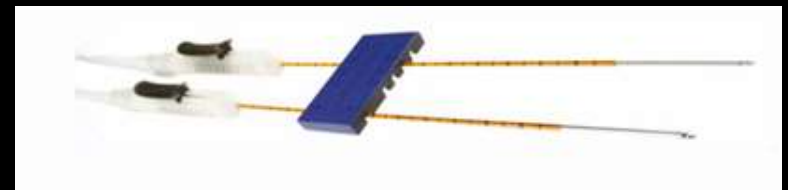
IRE: CELLULAR VS NON-CELLULAR TISSUE

- All cells in electroporation zone are irreversibly “porated”
- Collagenous structures are not affected
- Intact adventitia & lamina visible at 2 days with no smooth muscle cells present
- Endothelium largely repopulates at 2 days
- Smooth muscle repopulated at 2 weeks



IRE - Procedure

- General Anaesthetic
- Paralysed & ventilated
- ECG Synchronisation
- CT/US Guided Targeting
- 2 Needles at 2cm –2.5cm active
- 90 x 2 pulses delivery
- Ethanol Block



CT SCAN ROOM FOR IRE



INDICATIONS FOR ABLATION

Metastases - CRC

- Adjunct to liver resection
- Those unsuitable for resection: < 3 - 4 cms
 - inadequate surgical margins or liver reserve or co-existing morbidity
- Unsuitable for further chemotherapy: Cardio-toxicity, Neuropathy etc
- Neuro-endocrine Metastases – slow growing tumours
- Breast, Melanoma or Renal Metastases: Oligometastases

Hepatocellular Carcinoma (HCC)

- Patients with limited HCCs not suitable for transplant/ resection: 30-40%
- BCLC Stage A 1-4
- Patients awaiting Liver Transplant or Liver Resection: Single <5 cm or x3 < 3cm (Milan criteria)
- Large HCCs: BCLC Stage B1 and B2 – Combination techniques TACE/SIRT + MWA/RFA

IMAGING TASKS FOR ABLATION

- Staging:
 - Detection of “Occult” lesions
 - Characterisation
- Targeting
 - Occult lesions
 - Large lesions: multiple needle placements
- Peri-procedural monitor
 - Assessment of complete ablation
 - Assessment for potential complications
- Follow-up
 - Local Recurrence / New lesions

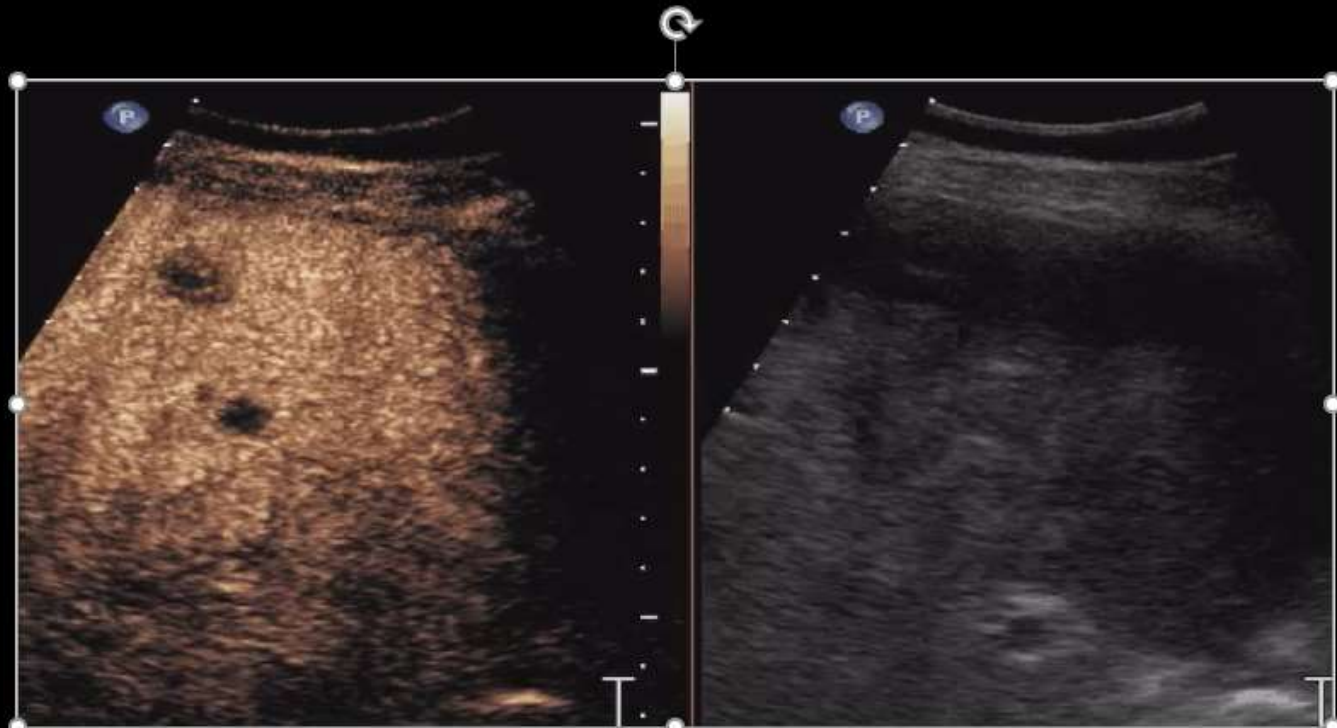
PROTOCOL FOR CONTRAST ENHANCED ULTRASOUND

- US Scanner
 - Non-Linear Imaging/Contrast mode
 - Low MI
 - Focal zone low down the screen
 - Adjust gain
 - Dual display with fundamental and contrast mode
- Small IV bolus 1.0 mL of SonoVue
- Systematic Sweeps over all phases
- Malignant lesions wash-out in portal and/or late phases
- Repeat 1.0 mL bolus injection if necessary

OCCULT METASTASES & EXTENT OF DISEASE



Baseline

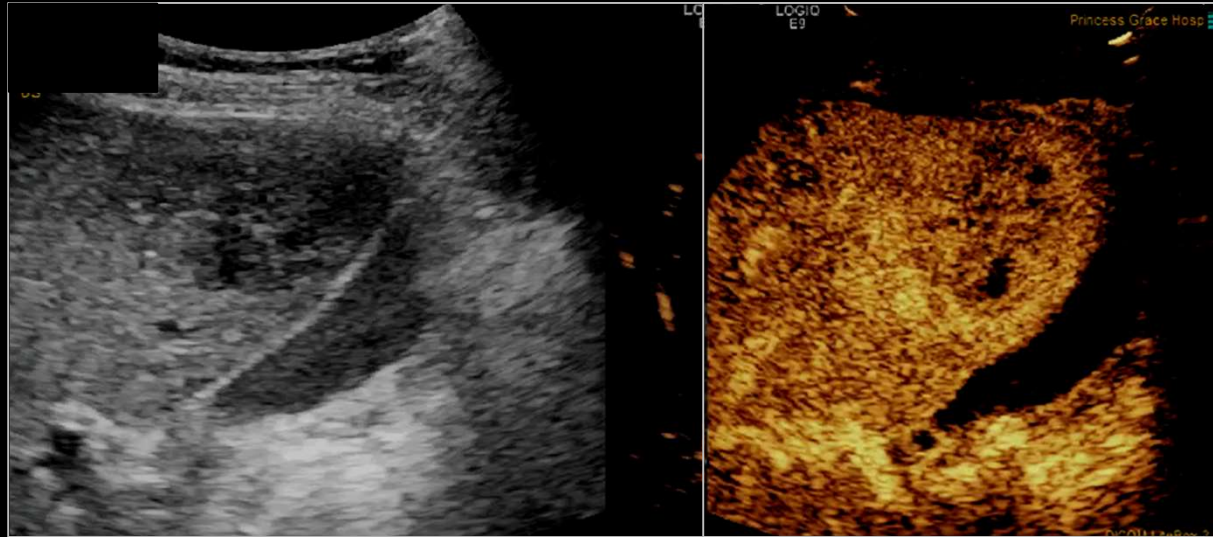


CEUS: Occult lesions clearly visualised

CHARACTERISATION: MET VS ABLATION ZONE



DELINEATION

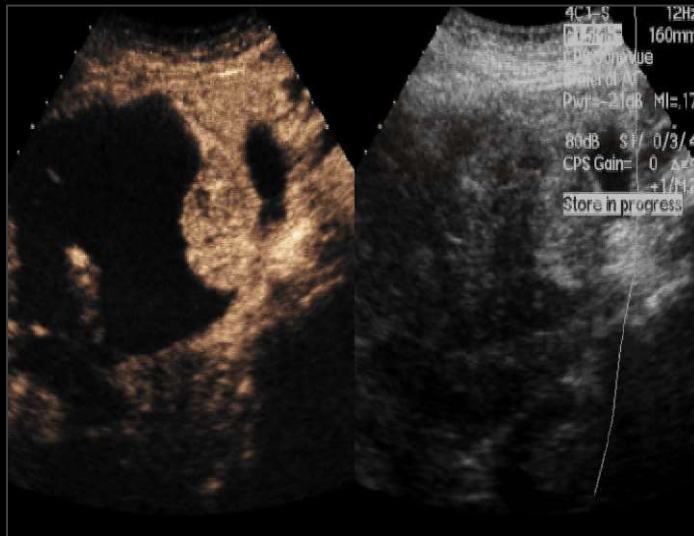


CEUS: Arterial Phase

Venous/ Late Phase

To determine appropriate ablation modality and ablation needle number/size

TARGETING RESIDUAL TUMOUR



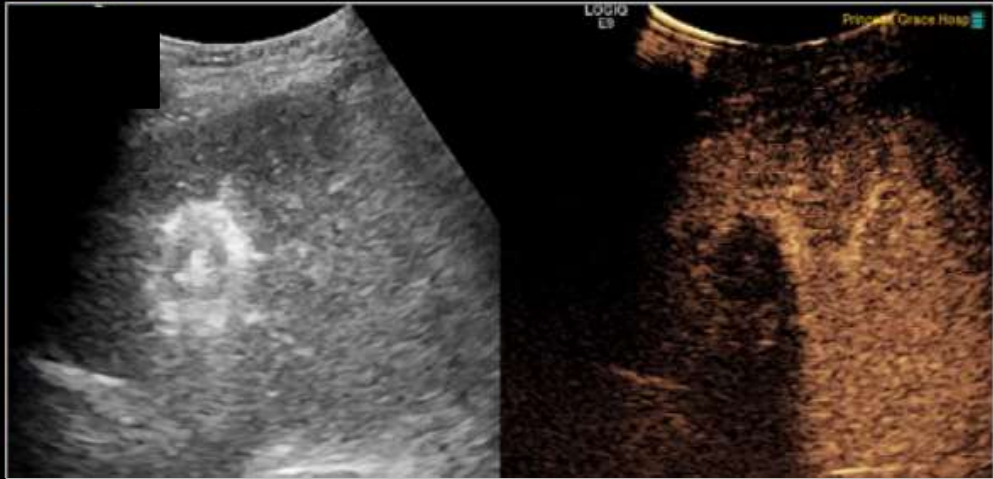
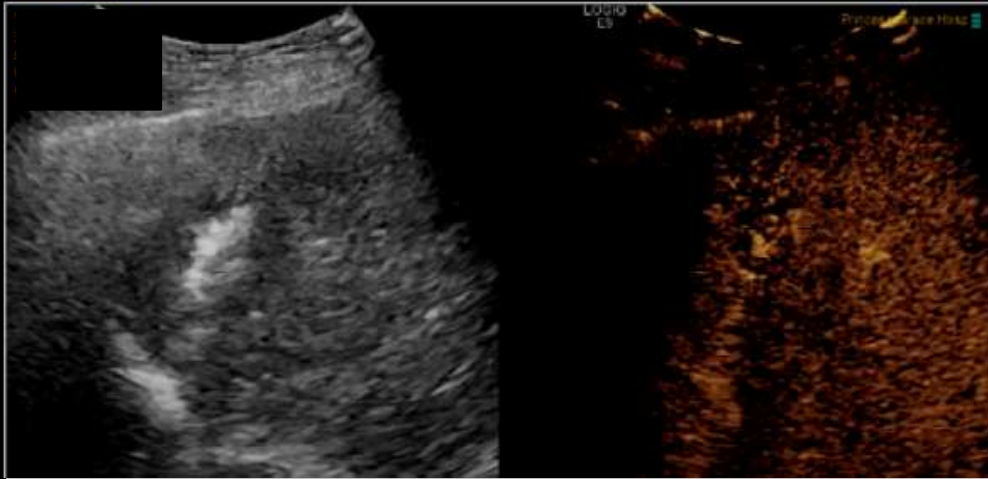
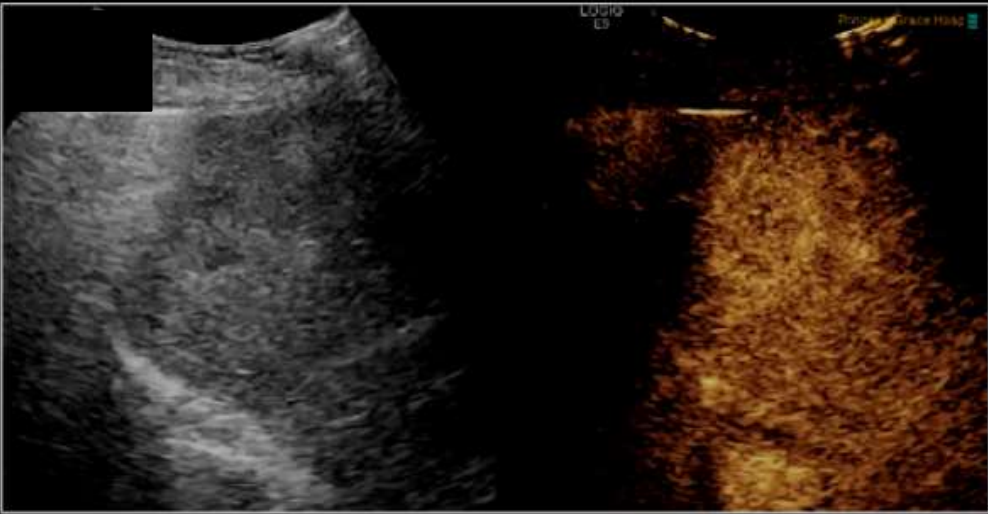
Post TACE, Pre RFA Targeting



Post TACE, Post RFA

- Meta-analysis: TACE-RFA improves overall survival- better prognosis for patients with intermediate- and large-size HCC. (Ni et al, 2013)
- TACE+RFA: most effective strategy for early-stage HCC. (Lan et al, 2016)
- Indicated for BCLC-B (1 and 2) HCC (Hirooka et al, 2018)

MWA: Pre, Targeting, Ablation & Post



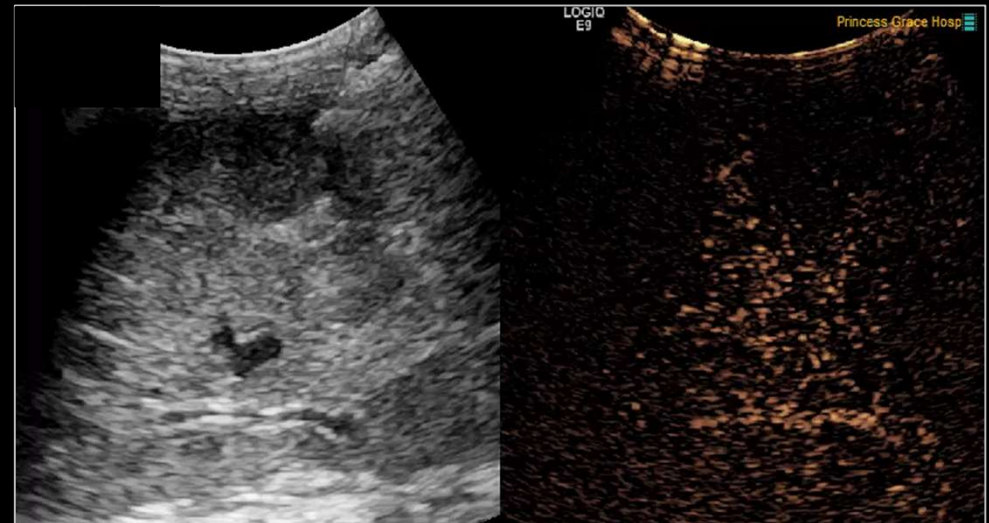
MWA

Post CEUS

RFA: PRE, TARGETING, ABLATING & POST



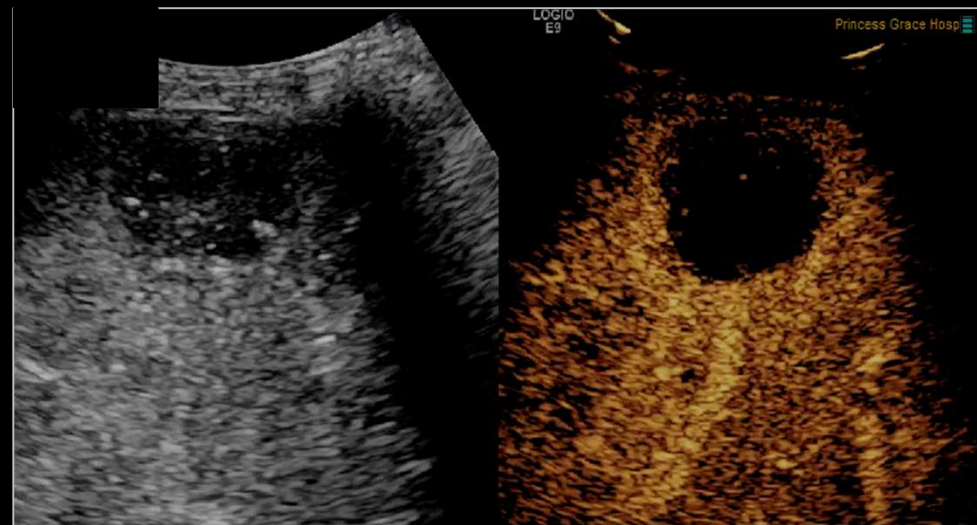
Pre CEUS



Targeting



RFA



Post CEUS

WHY IRE IN LIVER? - SAFER

Indications

- Hilar or Subcapsular Lesions
- Bile duct, GB, GIT, & Vessels

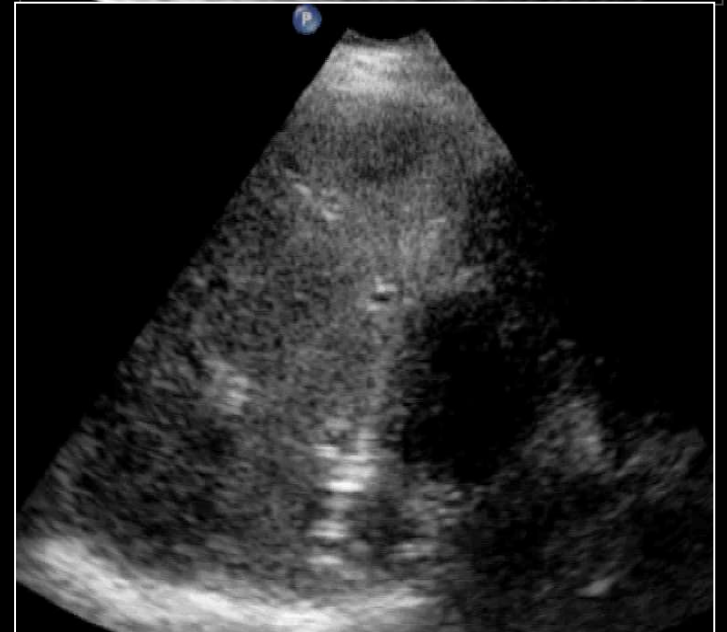
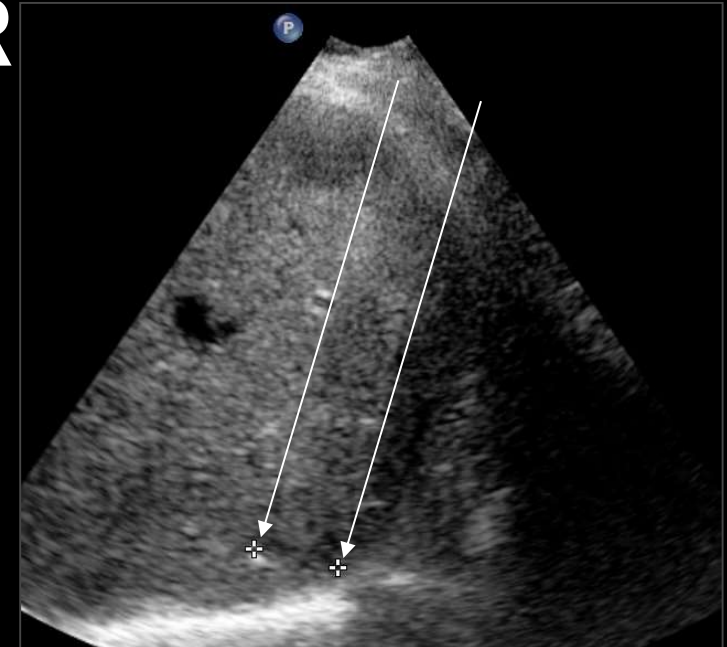
Thompson et al, 2011
Narayanan et al, 2014
Scheffer et al 2014

Effectiveness

- Long-Term Survival: 5yr OS 49.2%
- Useful technique: outcome HCC > CLM

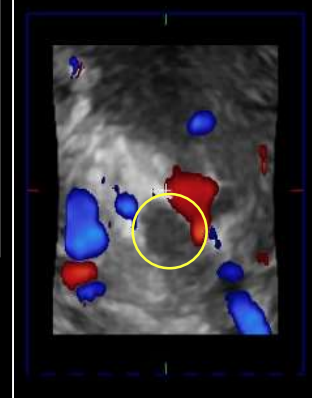
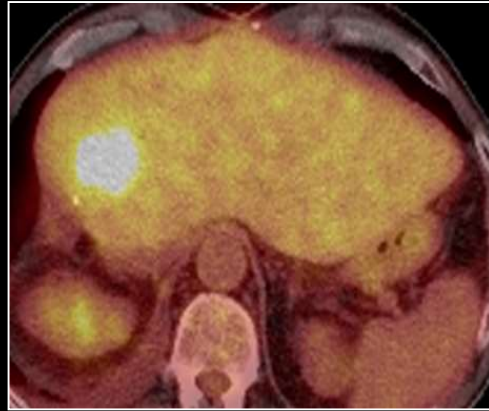
Schicho et al, 2019

Mafeld et al, 2019

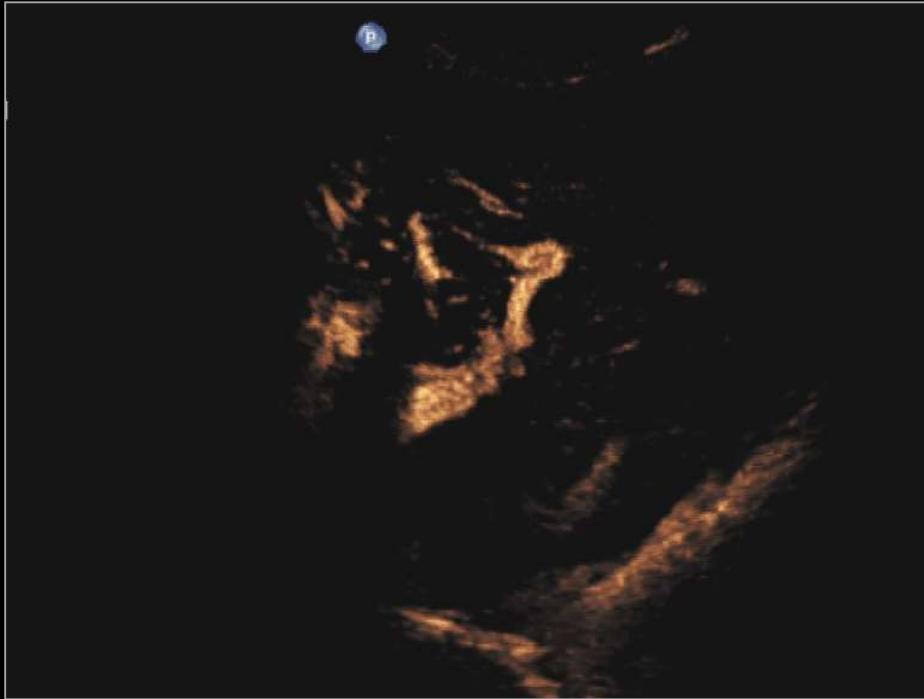


CRC Liver Metastasis – IRE Targeting & Ablating

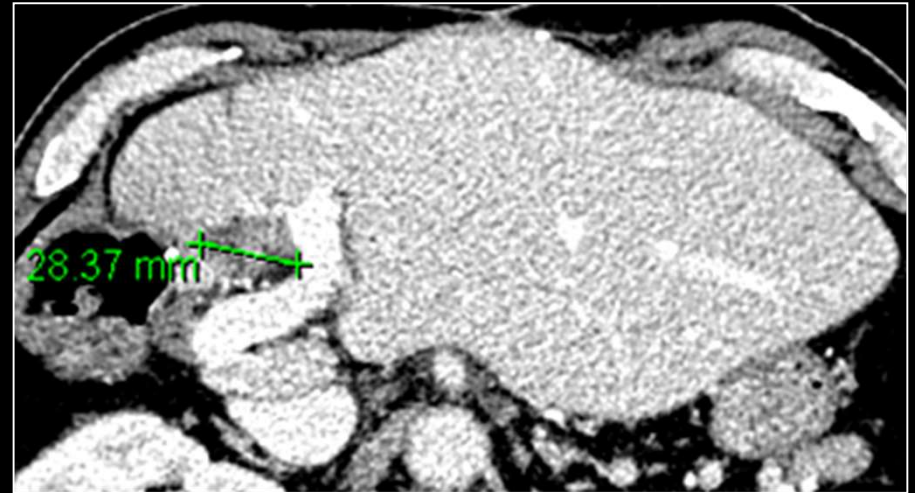
CRC METASTASIS BY PORTAL VEIN



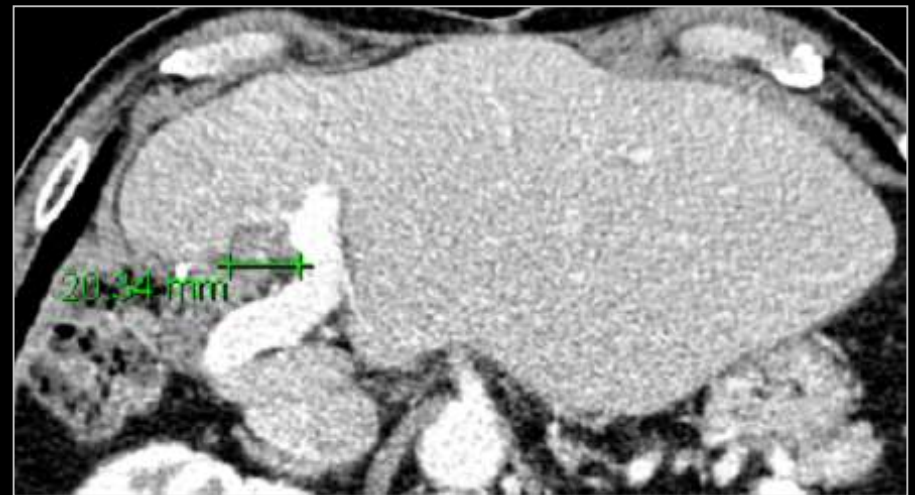
POST IRE ABLATION



Post IRE CEUS

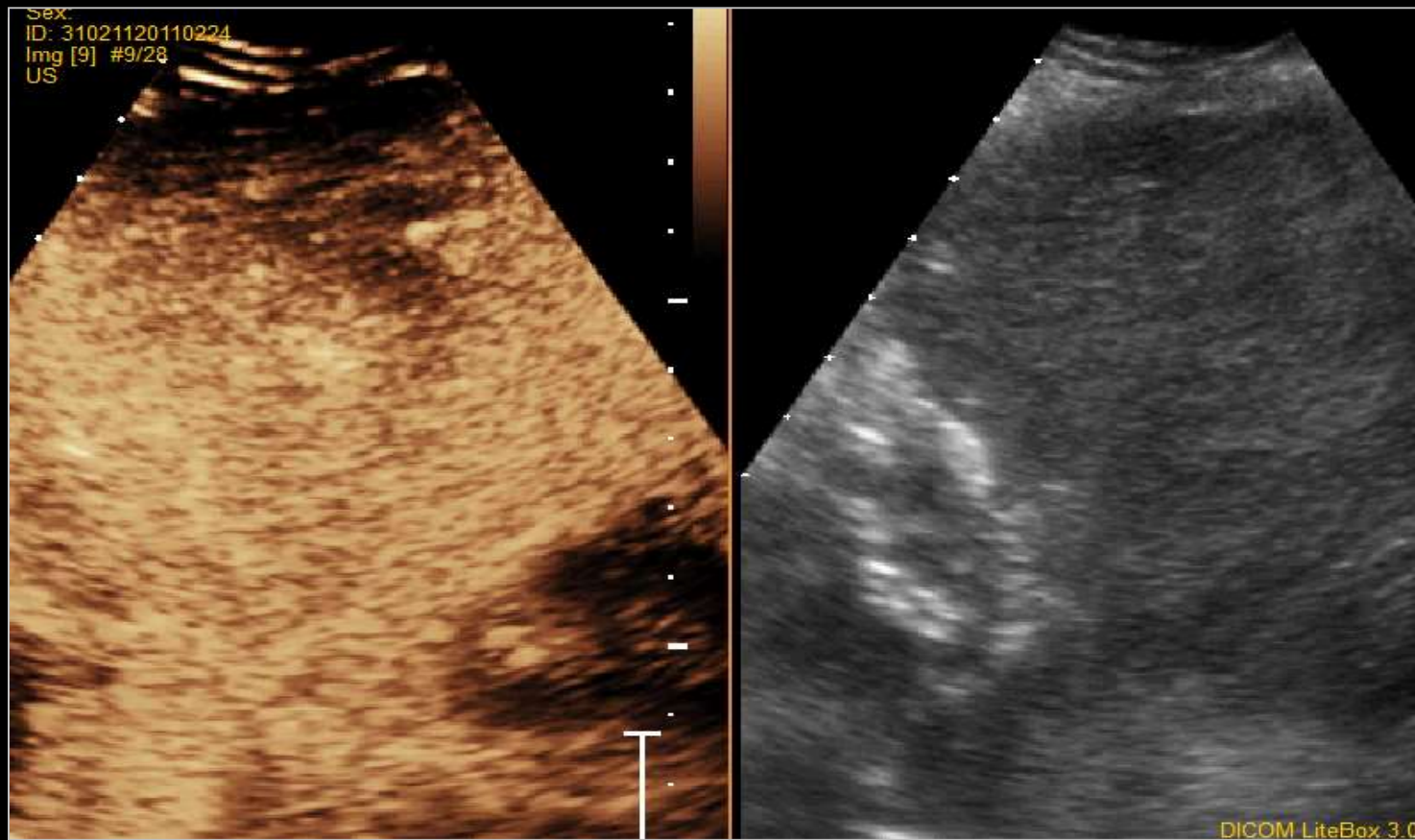


Pre IRE CT: 28.4mm

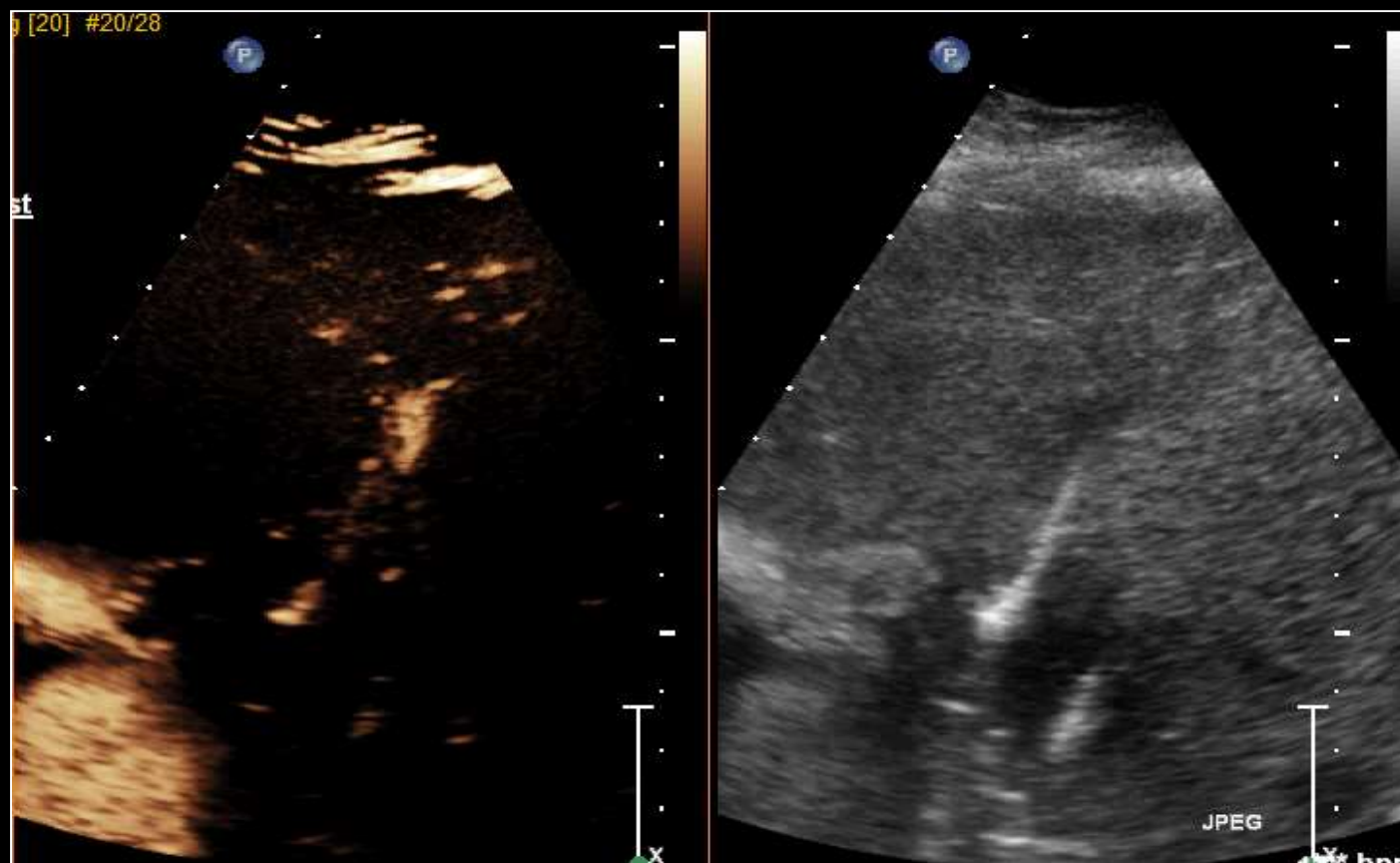


Post IRE CT: 20.0mm

PRE-IRE OF METASTASIS



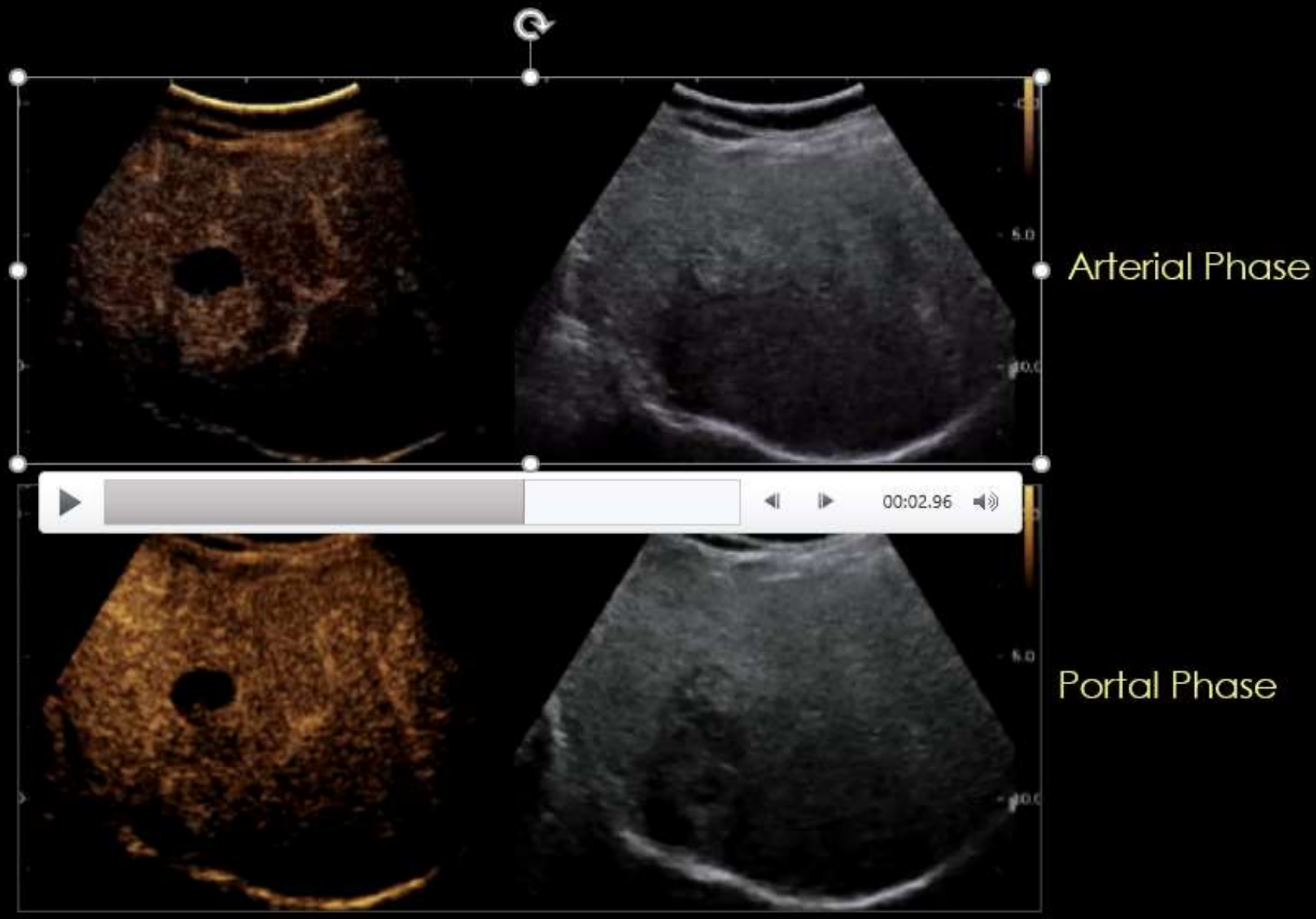
IRE ABLATION OF METASTASIS



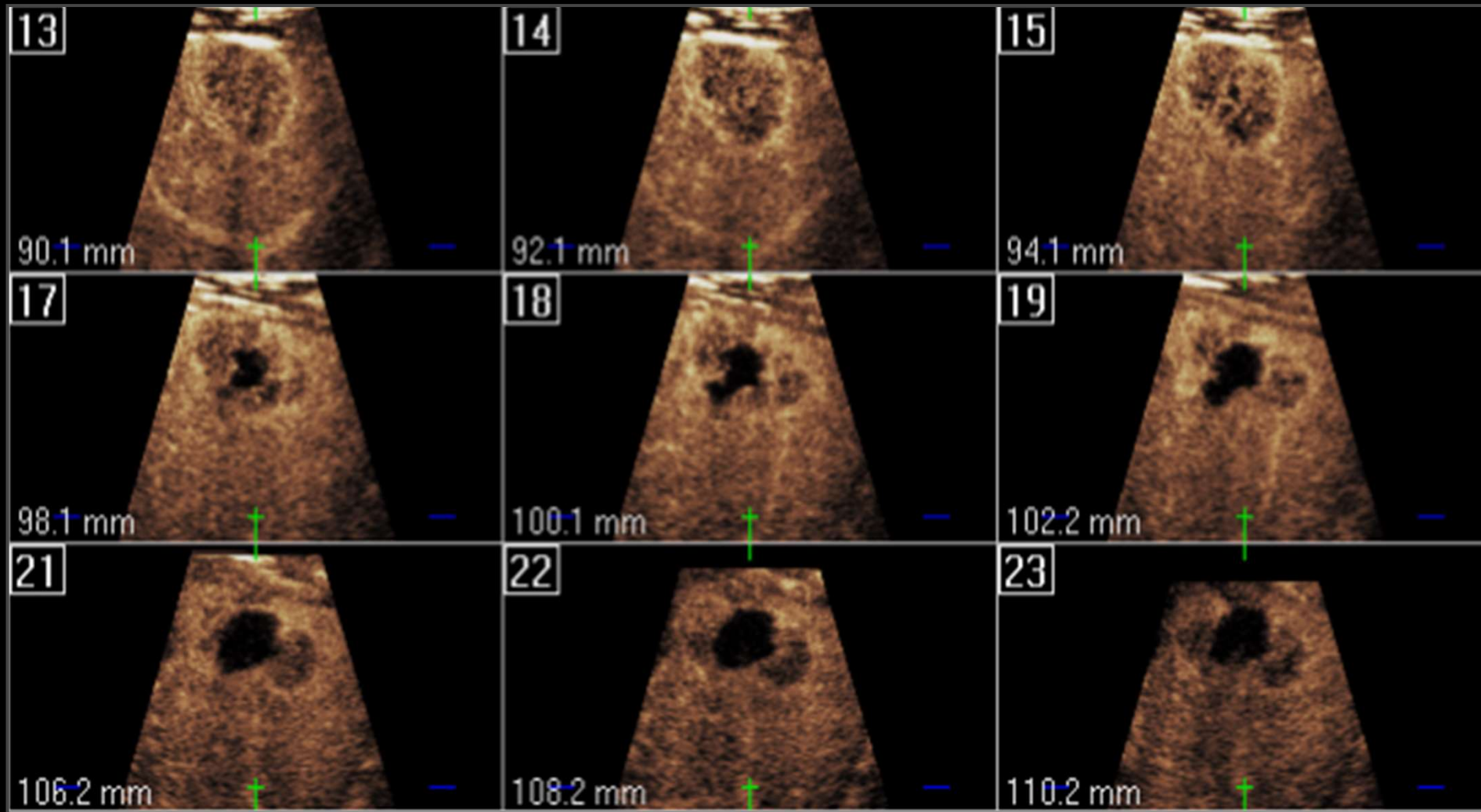
POST IRE CEUS: 6 WEEKS



LOCAL RECURRENCE AFTER RFA



3D CE-US: RECURRENT METASTASIS



MONITORING OF RESPONSE:

RFA / MWA

Complete Coagulation

Volume larger
Loss of enhancement
Sharp margin

Residual Disease

Diameter unchanged
Margin ill-defined
Maintains enhancement in arterial phase and wash-out in portal and late phases

IRE

Complete Coagulation

Smaller Volume-involution
Loss of enhancement
Ill-defined margin

Residual Disease

Diameter unchanged
Margin ill-defined
Enhancement in arterial phase and wash-out in portal and late phases

SURVEILLANCE POST ABLATION

- Colorectal Ca and HCC: CEUS at 4-6 weeks
- Colorectal Ca
 - CT scan: 3-4 months for the first year
 - CT scan 6 monthly for 2 years
 - CT yearly after
- HCC
 - MRI scan: 3-4 months

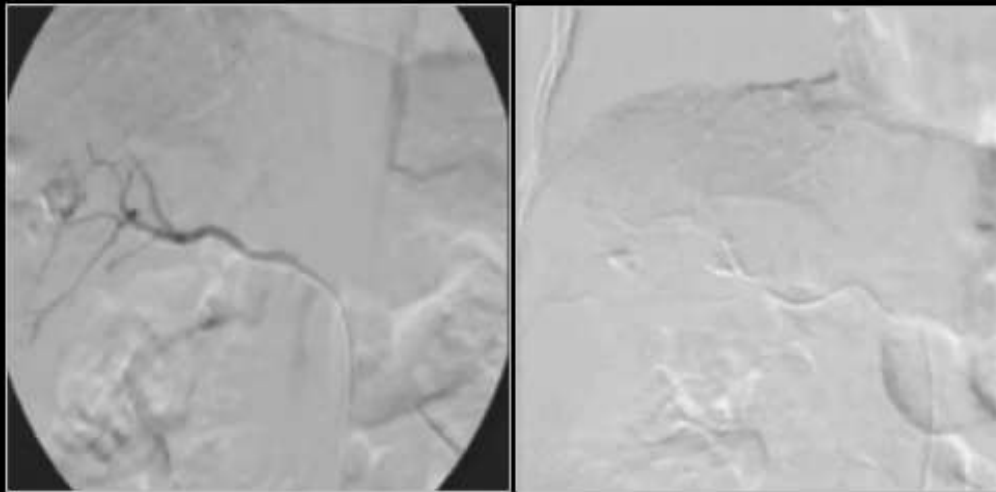
COMPLICATIONS



Sub-capsular Haematoma



Active Haemorrhage



Angio –Pre and Post embolisation



Post embolisation

LIVER METASTASES:

Resection vs Ablation

- Resection is superior to Ablation *(Abdalla et al, 2004, Park et al, 2008)*
- RCT: MWA equally effective as Resection *(shibata et al, 2000)*
- 2017 Meta-analysis from Dutch group: Data is still limited *(Meijerink et al, 2017)*
- Ablation is comparable to Resection *(Ashowo et al, 2003, Lee et al, 2008, Reuters et al 2009)*
- RFA is superior to Resection (<3cm): incremental cost-effective ratio (ICER) of –
£270K per QALY gained *(Loveman et al 2014)*

Chemotherapy + RFA vs Chemotherapy

- EORTC-CLOCC randomised Trial: 119 CRC patients; <10 lesions & no EHD *(Ruers et al, 2017)*

	Chemotherapy + RFA	Chemotherapy	p
OS median (m)	45.6	40.5	0.01
PFS median (m)	16.8	9.9	0.025
5-year OS (%)	43.1	30.3	NS

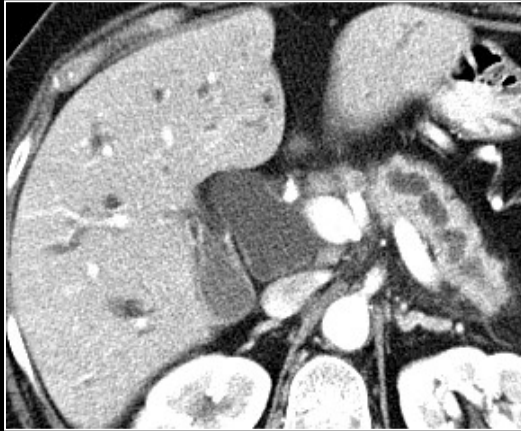
- Limited study – RFA and RFA+PH included

NATURAL HISTORY OF PANCREATIC CA

- Fourth leading cause of cancer-related death
- Incidence 96,000/y in EU:
 - 80,000/y deaths
- Incidence in UK: 8875/y
 - 8600/y Deaths
- Overall 5-year survival < 5%.

- 10 -15% - Suitable for Resection
 - Resection - Whipple: Median OS: <2 years;
33% morbidity & 5% mortality
- 30-35% - Locally advanced disease
- 50-65% - Disseminated disease

PANCREATIC CARCINOMA: RFA



Pre RFA CT



Pre RFA CT



Pre RFA

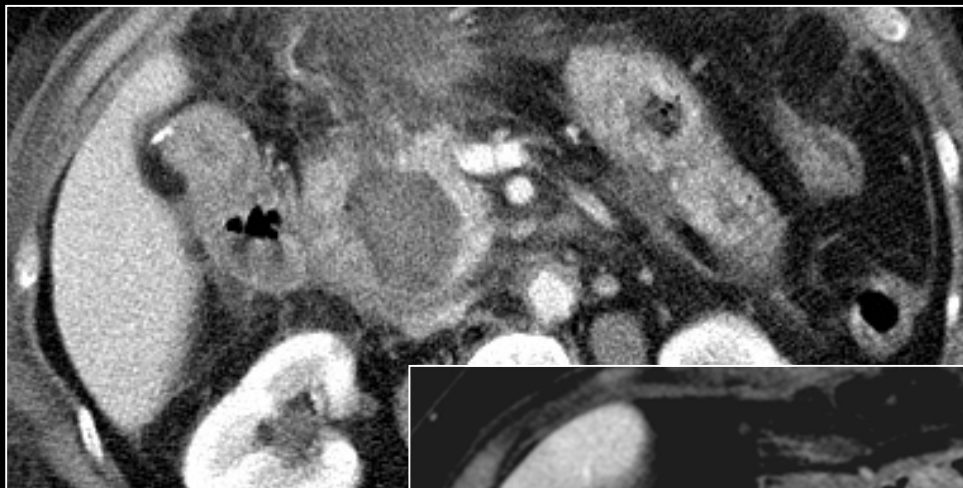


RFA

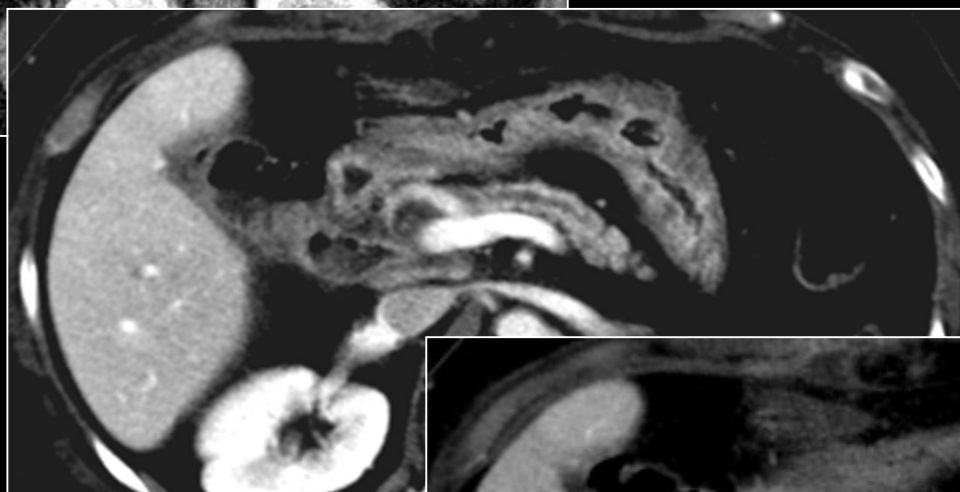


Post RFA

PANCREATIC CA: POST RFA



5th day Post RFA



14th day Post RFA



6 months Post RFA

MATERIALS & METHODS

111 Patients: Locally advanced Pancreatic Carcinoma N=75
Liver Metastases N=36
3 months Chemotherapy: Pre & Post IRE

Follow-up: Clinical examination
CT/MRI/PET at 2-3 months
CEUS 4 weeks and 2-3 months

End-points:

Primary: Safety and Efficacy

Secondary: Progression Free Survival: PFS

Overall survival: OS

From Day of IRE

From Day of presentation

SELECTION CRITERIA:

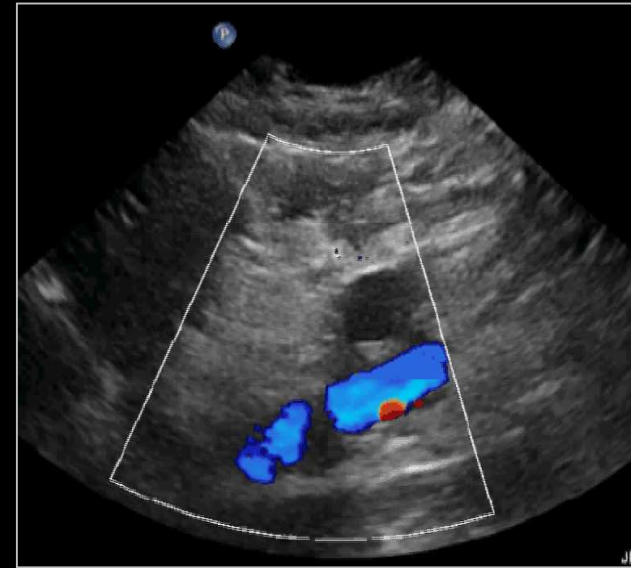
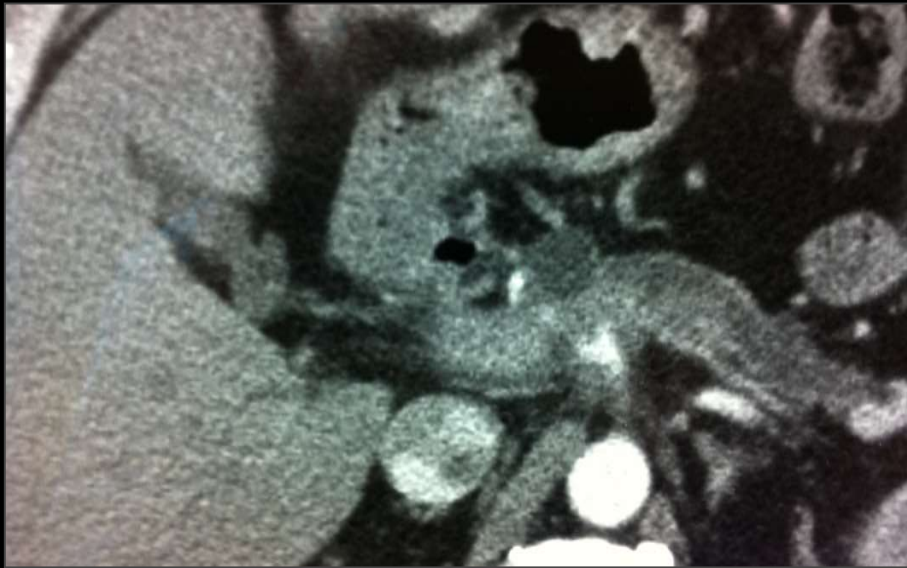
INCLUSION

- Unresectable Pan Ca: <4cm (3.4+/-1.2) biopsy or FNA proven
- Able to tolerate any Standard First-line chemotherapy regime
 - (FOLFIRINOX- 37% Gemcitabine + Capecitabine- 33%, Gemcitabine + other- 29%)
- ECOG PS 0 or 1

EXCLUSION

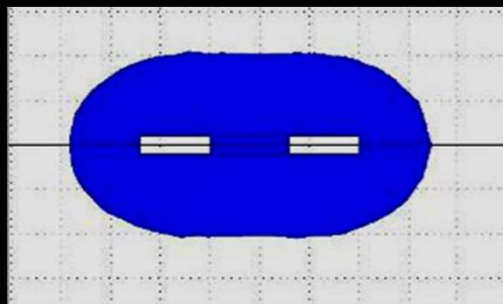
- Recent Myocardial Infarction
- History of Epilepsy or Cardiac Arrhythmia
- Presence of Implanted Pacemaker
- Underlying Sepsis
- Widespread peritoneal or lung disease
- Duodenal or stomach invasion/Bleeding
- ECOG PS > 2
- Unable to give informed consent

Pancreatic Ca: US Guided IRE Bipolar Needle

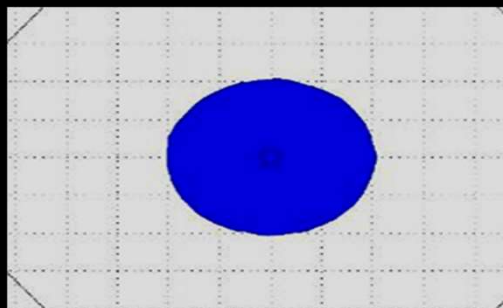


Pancreatic Ca: US guided IRE Bipolar Needle

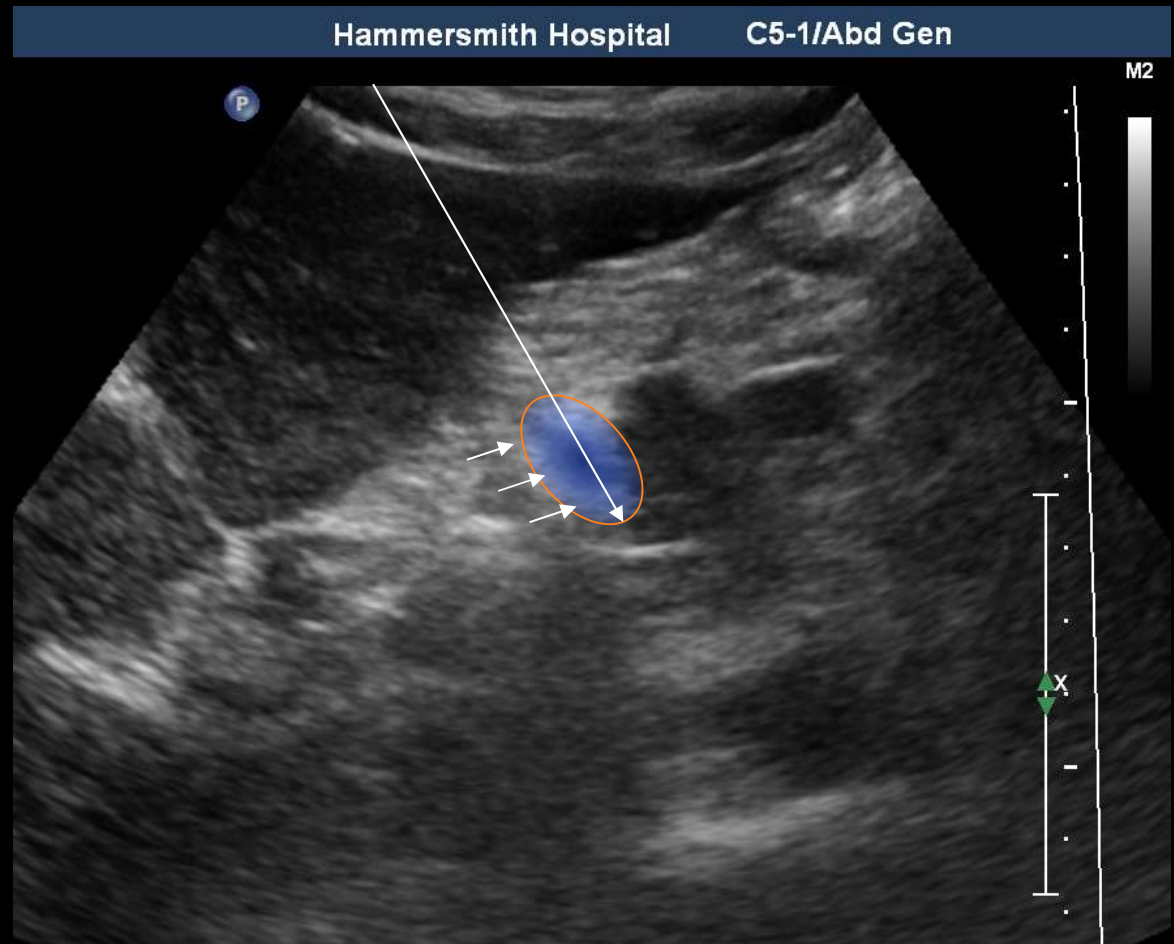
- 2 cm Tx Zone @ 2,750 volts



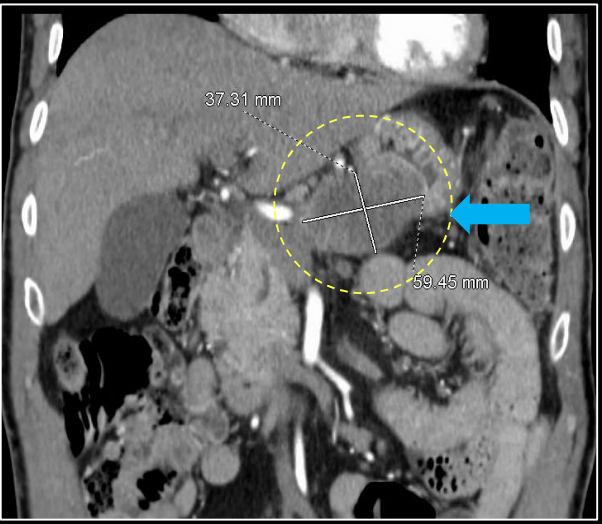
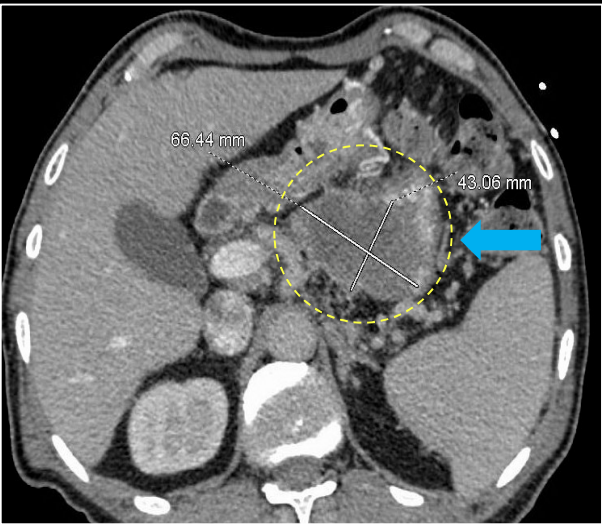
Coronal



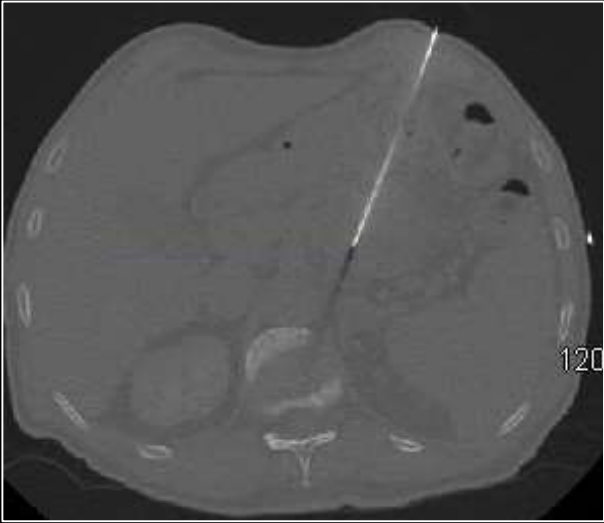
Axial



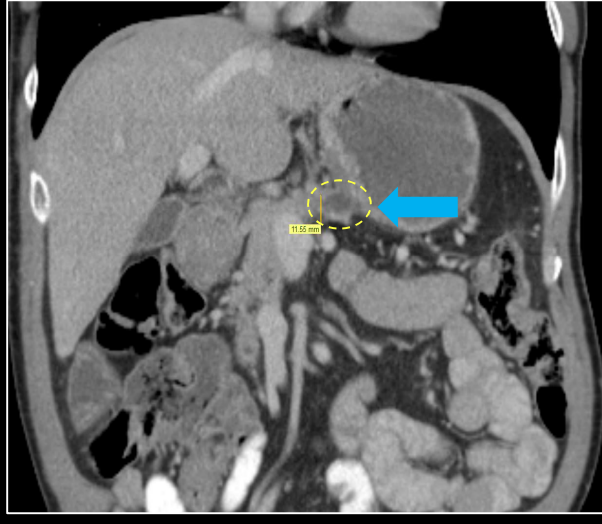
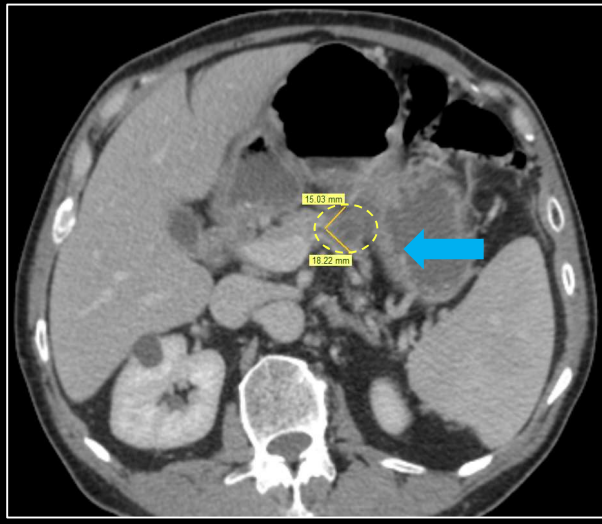
PRE IRE



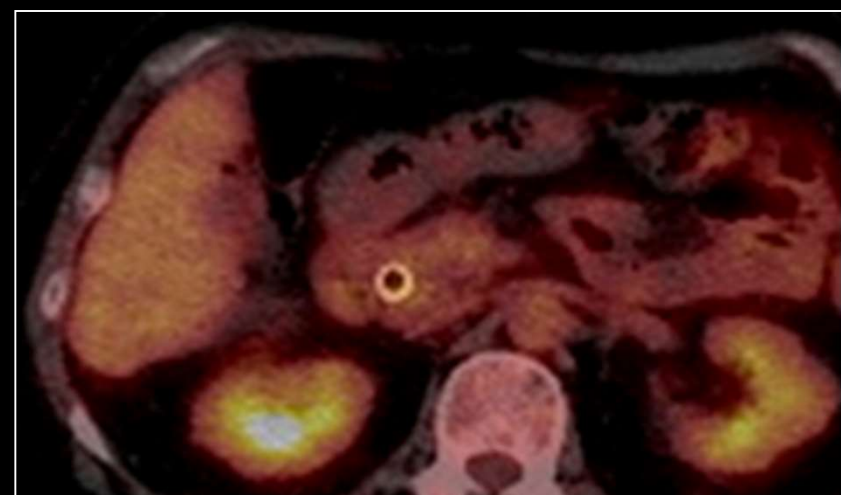
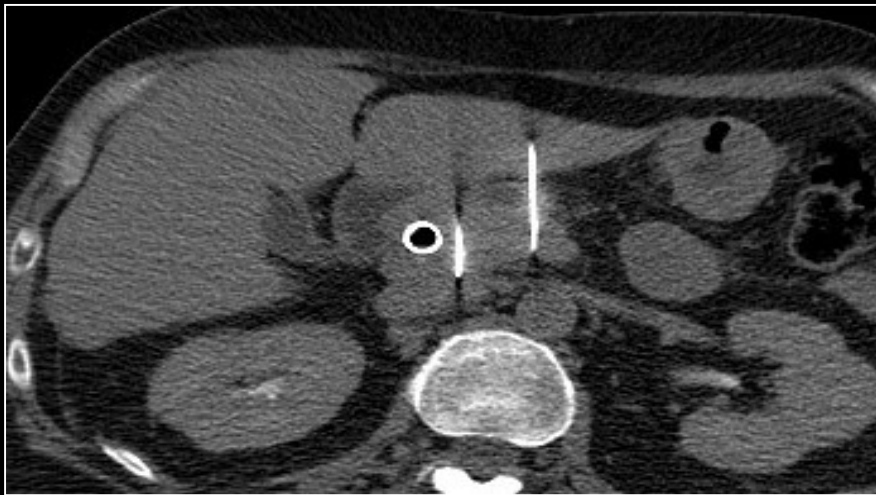
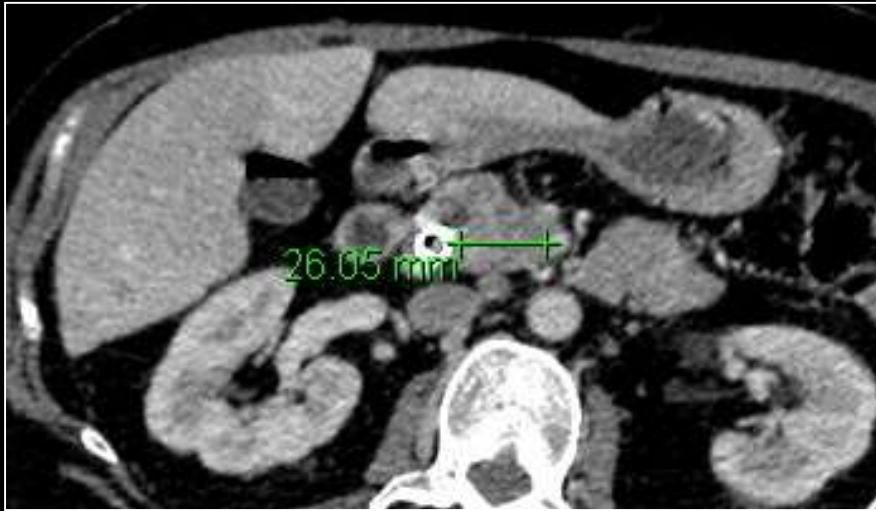
IRE Needling



POST IRE

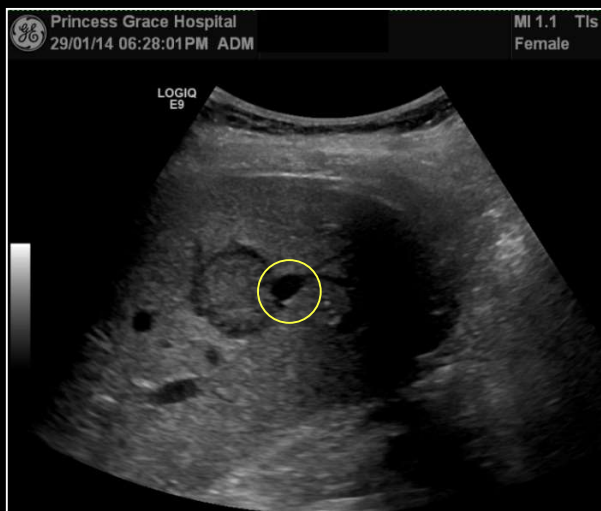


PRE IRE & POST IRE

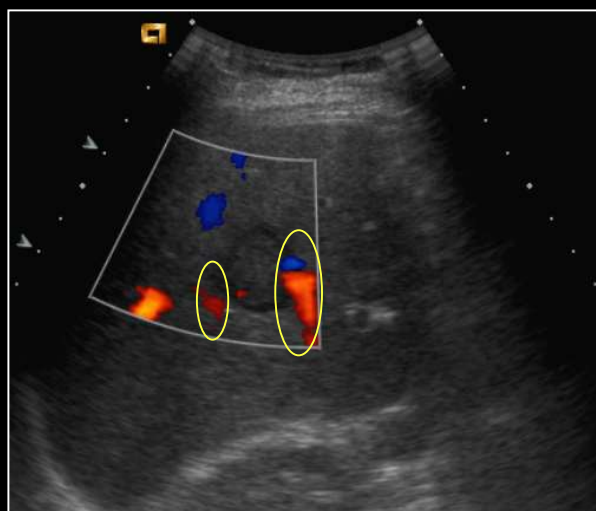


Post IRE PET Negative at 1 year

BASELINE IRE OF PANCREATIC LIVER METASTASIS

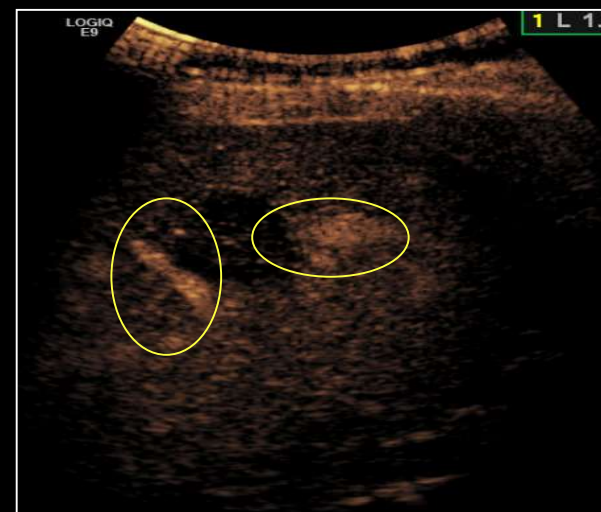


Baseline US



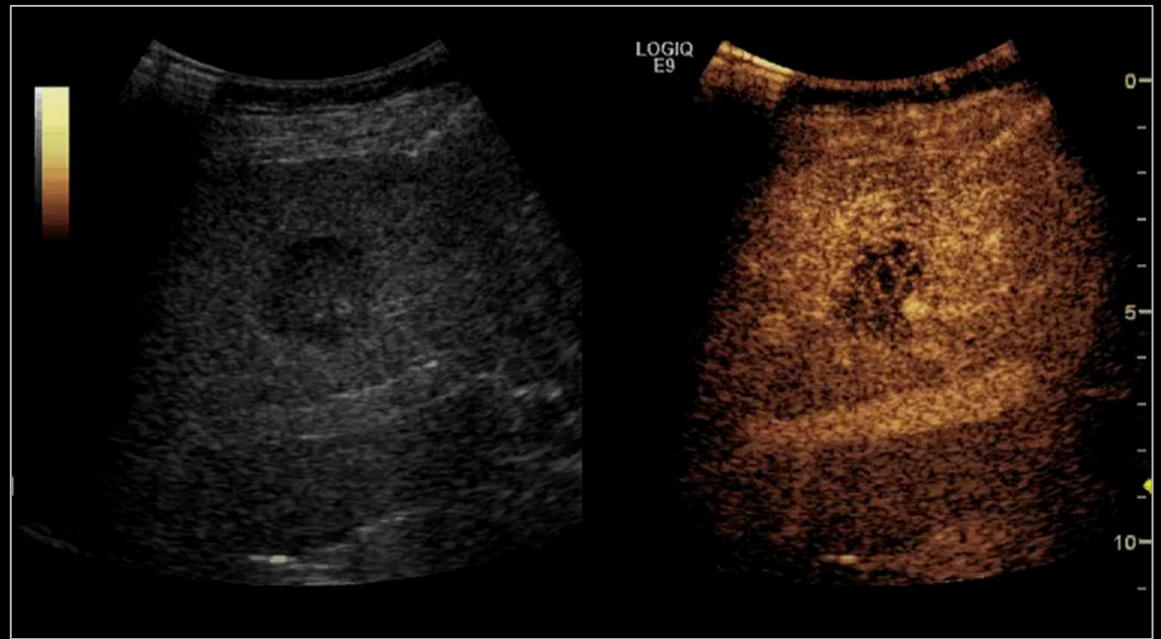
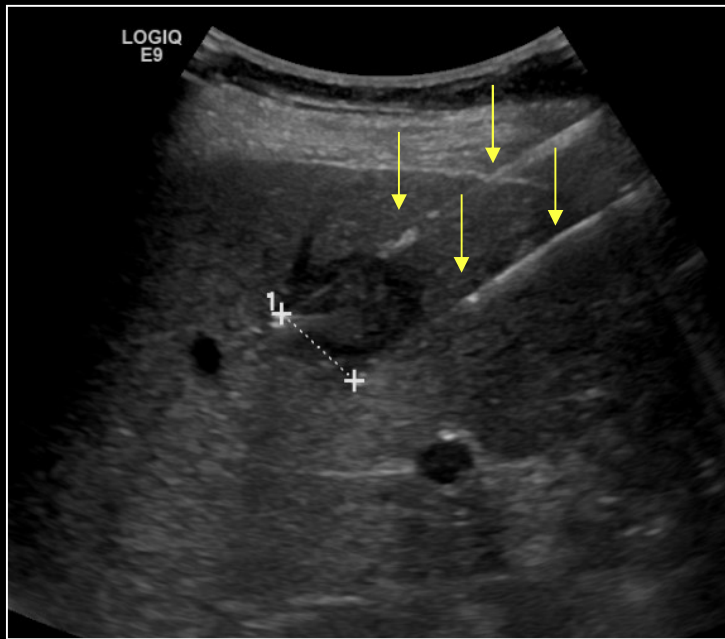
Baseline CDUS

Vessels Involved



Baseline CEUS

IRE NEEDLE TARGETING OF METASTASIS

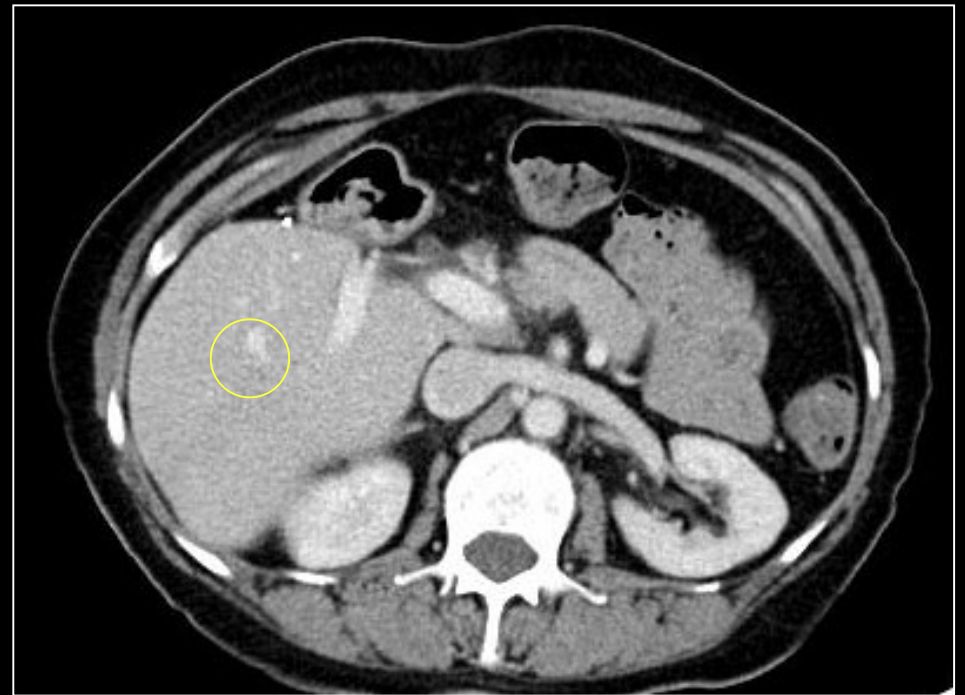


2 IRE Needles at 2cm
separation in proximity to
2 main vessels

CT SCAN 9/12 POST IRE ABLATION



Significant Involution

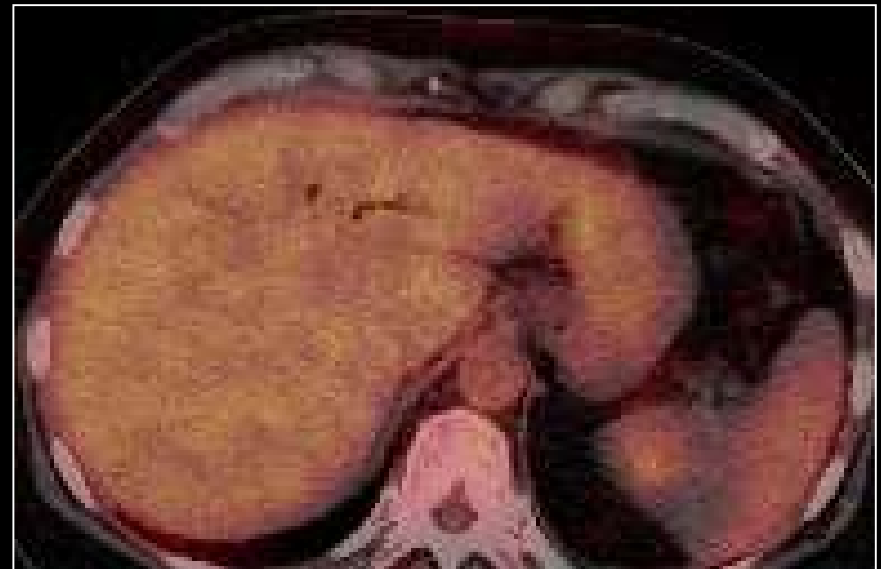


PANCREATIC LIVER METASTASES ABLATION

PRE MWA ABLATION



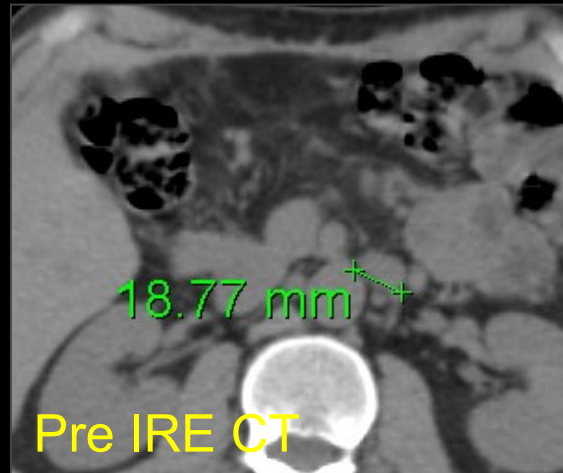
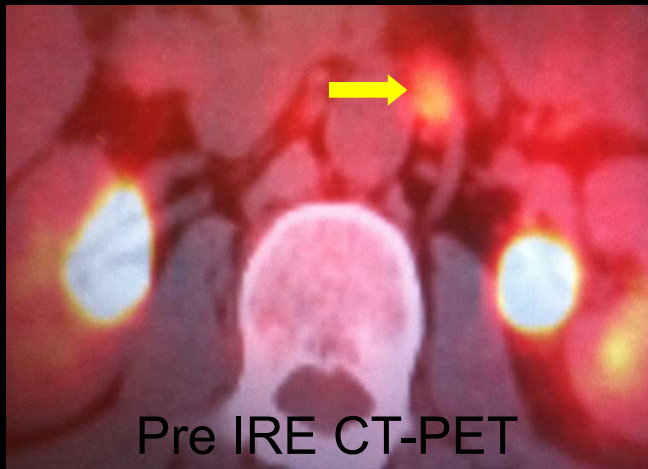
POST CT-PET -VE AT 1 YEAR



IRE LOCAL RECURRENCE POST WHIPPLES



PARA-AORTIC NODAL METASTASIS



IRE Targeting 2nd Electrode

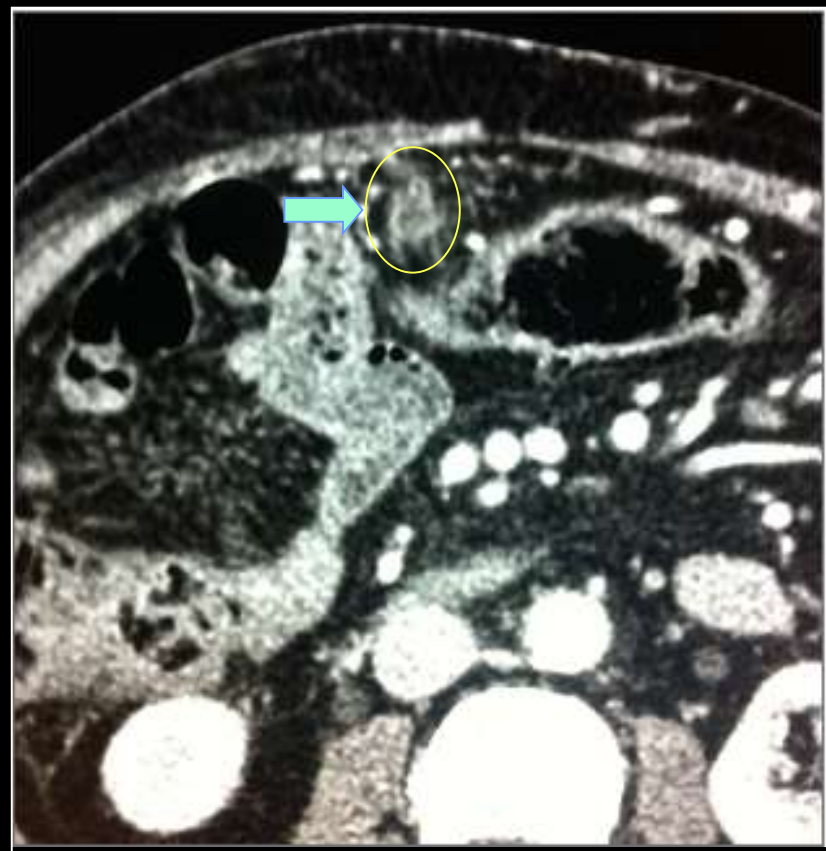
Post IRE CT

Post IRE CT-PET

PERITONEAL METASTASIS: INVOLUTION AT 4 WEEKS

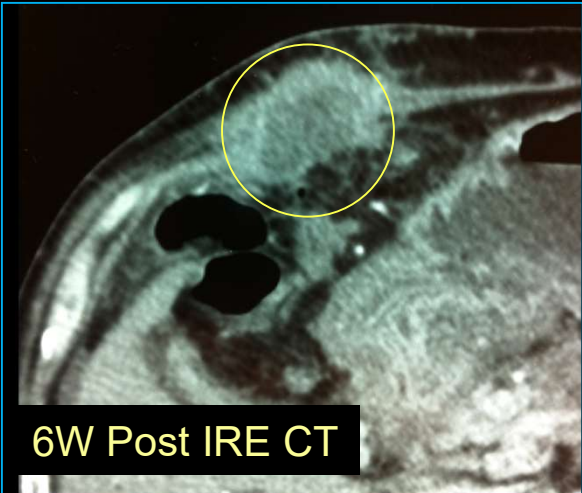
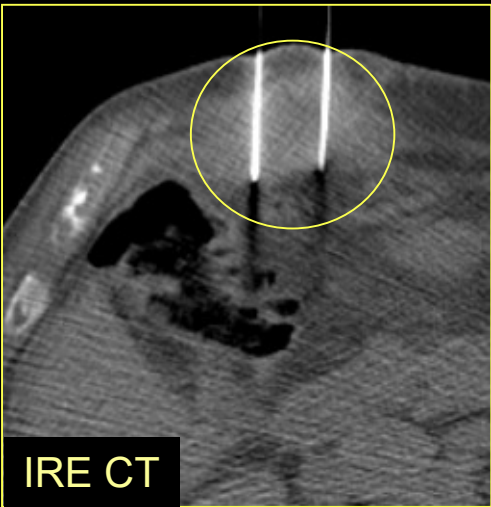
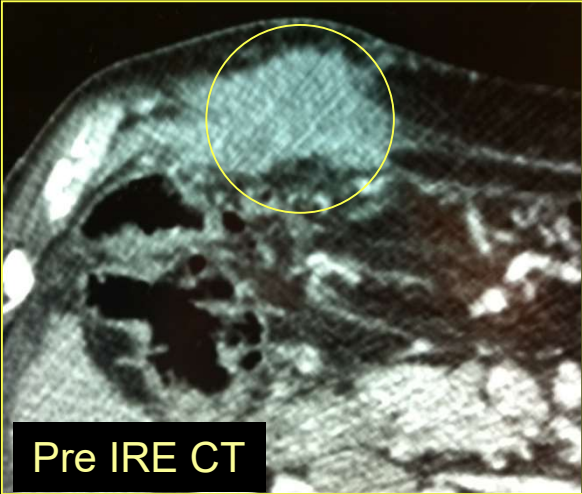


Pre IRE CT



Post IRE CT

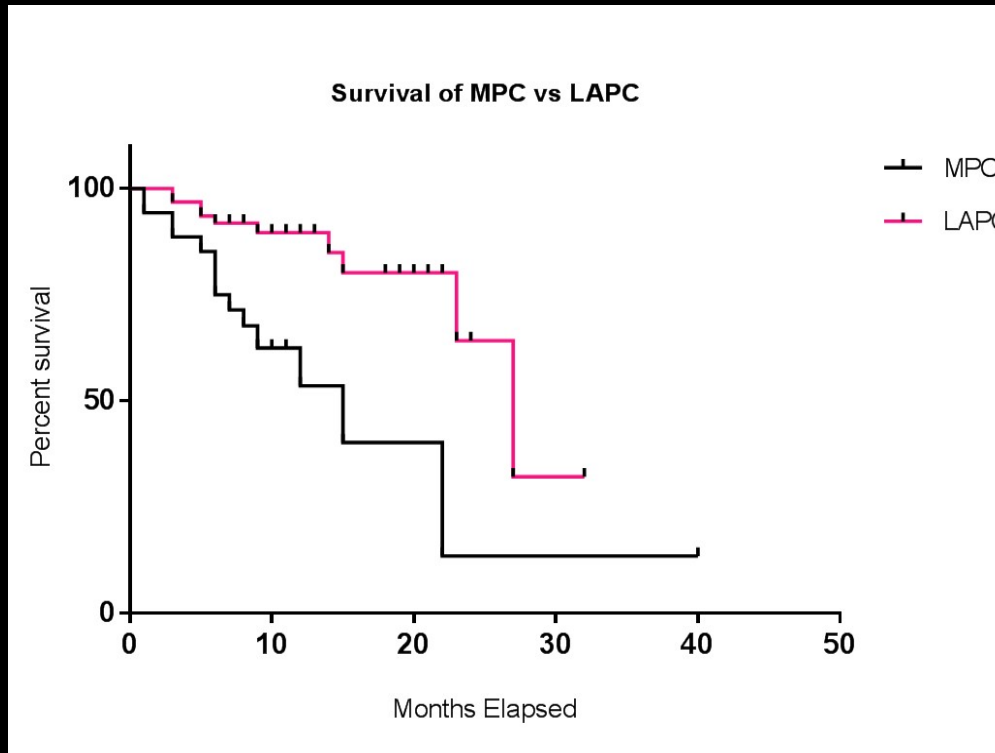
IRE OF ABDOMINAL WALL METASTASIS



RESULTS: OUTCOME OF IRE FOR LAPC

Criteria	Outcome
Overall local tumour response at 3-6 months	
- Partial response	23 (31%)
- Stable	50 (66%)
- Progressed	2 (3%)
Over 2 Years: Recurrence	38%
- Liver metastases	25%
- Peritoneal metastases	10%
- Laparotomy cutaneous scar metastases	3%
Median follow-up (months (range))	11.7 (3-45)
Survival from time of IRE (months (95%CI)):	
Median progression free survival	15 (13.7 – 16.3)
Median overall survival	27 (21.1 – 32.8)

SURVIVAL OF ADVANCED & LOCALLY ADVANCED PANCREATIC CA



MPC & LAPC Combined:
OS: 23 m from Day of IRE
OS: 27 m from Diagnosis

MPC:
OS: 15m From Day of IRE
OS: 19m From Diagnosis

LAPC:
OS: 27m From Day of IRE
OS: 31m From Diagnosis

Historical Data: From Diagnosis
MPC: Gem Abraxane: Median OS: 6 m
LAPC: Gemcitabine: Median OS: 7 - 11 m

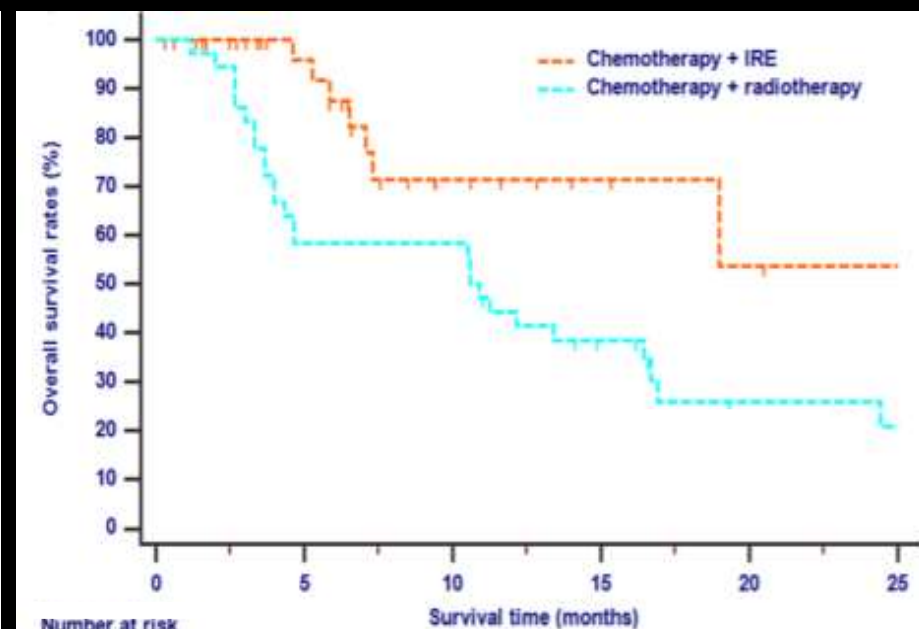
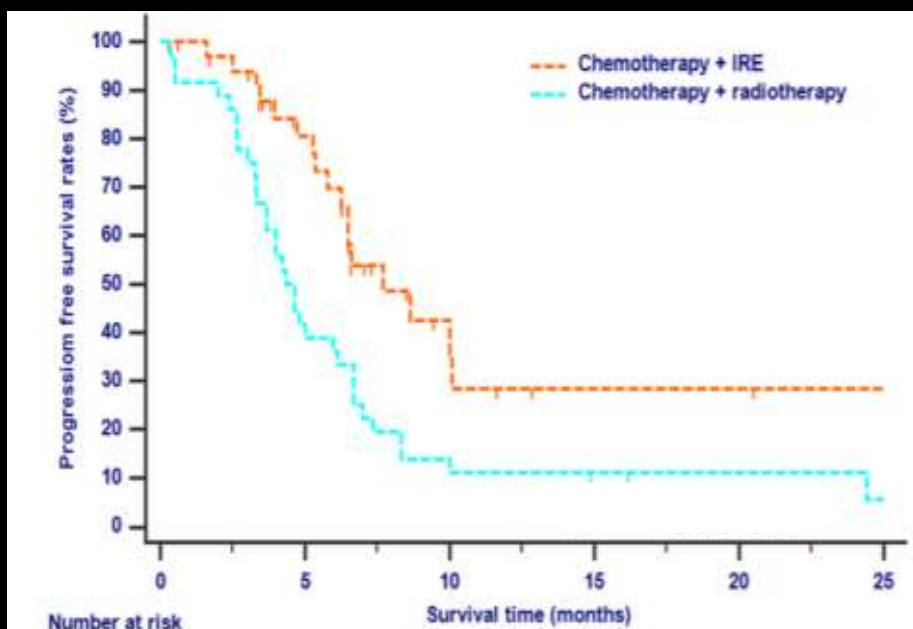
CLINICAL STUDIES: IRE IN PANCREATIC CANCER

Authors	N	Stage/Size	Median OS (months)	Method	Complications
Veldhuisen et al, 2020	52	LAPC < 4.5cm	17.2	Percutaneous	37%
Holland et al, 2019	152	LAPC < 5.5cm	30	Percutaneous	18% / 13%
Liu et al, 2019	54	LAPC (n: 28) MPC (n: 24)	LAPC: 20 MPC 14	Percutaneous	44% / 3%
Leen et al, 2018	75	LAPC < 5cm MPC (n: 36)	LAPC: 27 MPC: 15	Percutaneous	25% / 8%
Huang et al, 2018	70	LAPC < 5cm	22	Open	23% / 4%
Martin et al, 2015	200	LAPC	24.9	Open	36%
Kruger et al, 2015	50	LAPV < 3cm	12	Open	46% / 20%

LAPC & MPC: IRE ALONE VS IRE + CHEMO

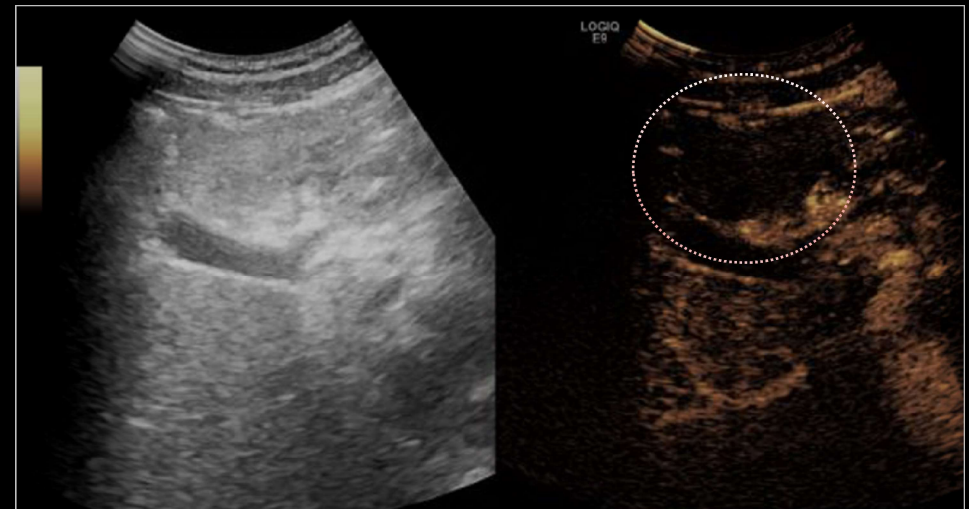
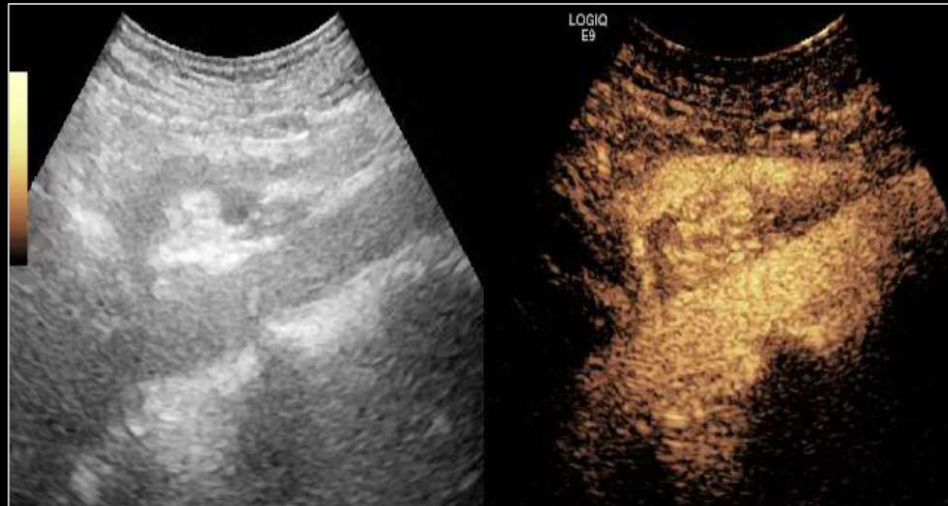
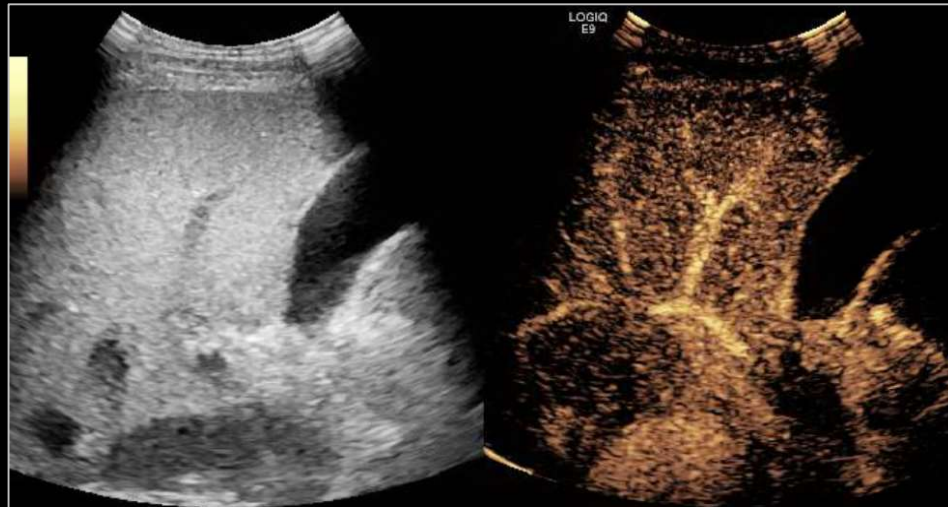
	Survival	IRE Alone	IRE + Chemo	
LAPC	PFS	13.9m	16.1m	<i>P</i> =0.04
	OS	16.2m	20.3m	<i>P</i> =0.04
		IRE Alone	IRE + Chemo	
MPC	PFS	9.45m	11.7m	<i>P</i> =0.04
	OS	11.6m	13.6m	<i>P</i> =0.04

LAPC: CHEMO-IRE VS CHEMO-RAD

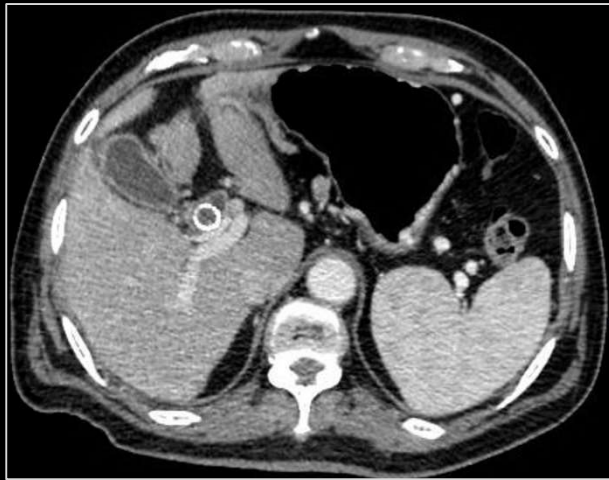


	Chemo IRE	Chemo Rad	P
PFS	7.7m	4.7m	P=0.045
OS	21.6m	10.6m	P= 0.011

HAEMATOMA POST IRE



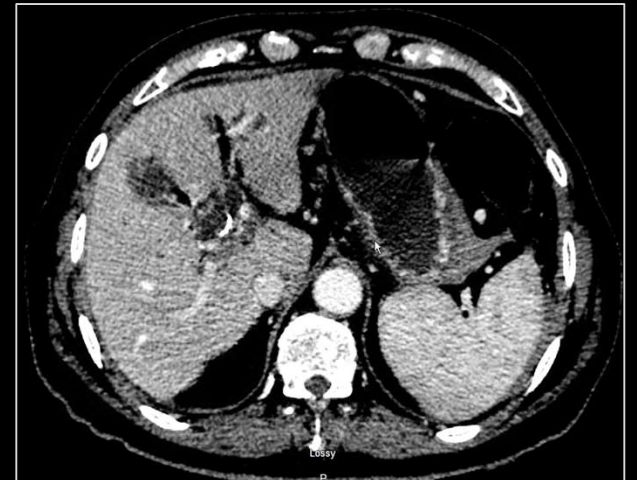
PORTAL VENOUS THROMBOSIS POST IRE



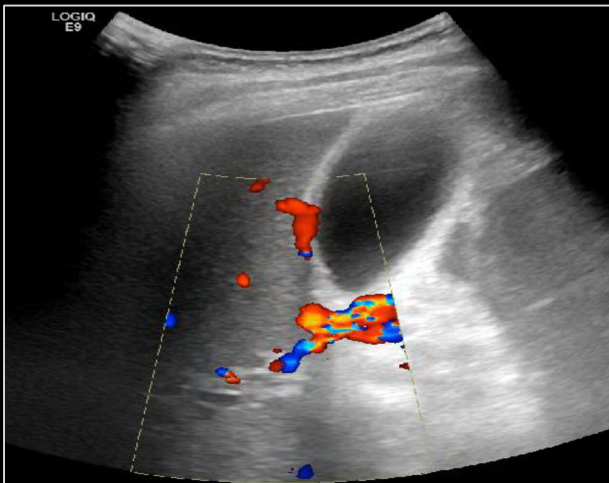
Pre IRE CT



IRE



Post IRE CT



Post IRE CDUS



Post IRE CT



Post IRE CEUS

SUMMARY: ABLATION WITH IRE

- Safe technique
- Locally effective
- In combination with systemic treatment prolongs Overall Survival