Chemoembolization, Radioembolization and Focal Ablation in Oncology

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The Medical Educator Consortium

13th Annual New Orleans Summer Cancer Meeting
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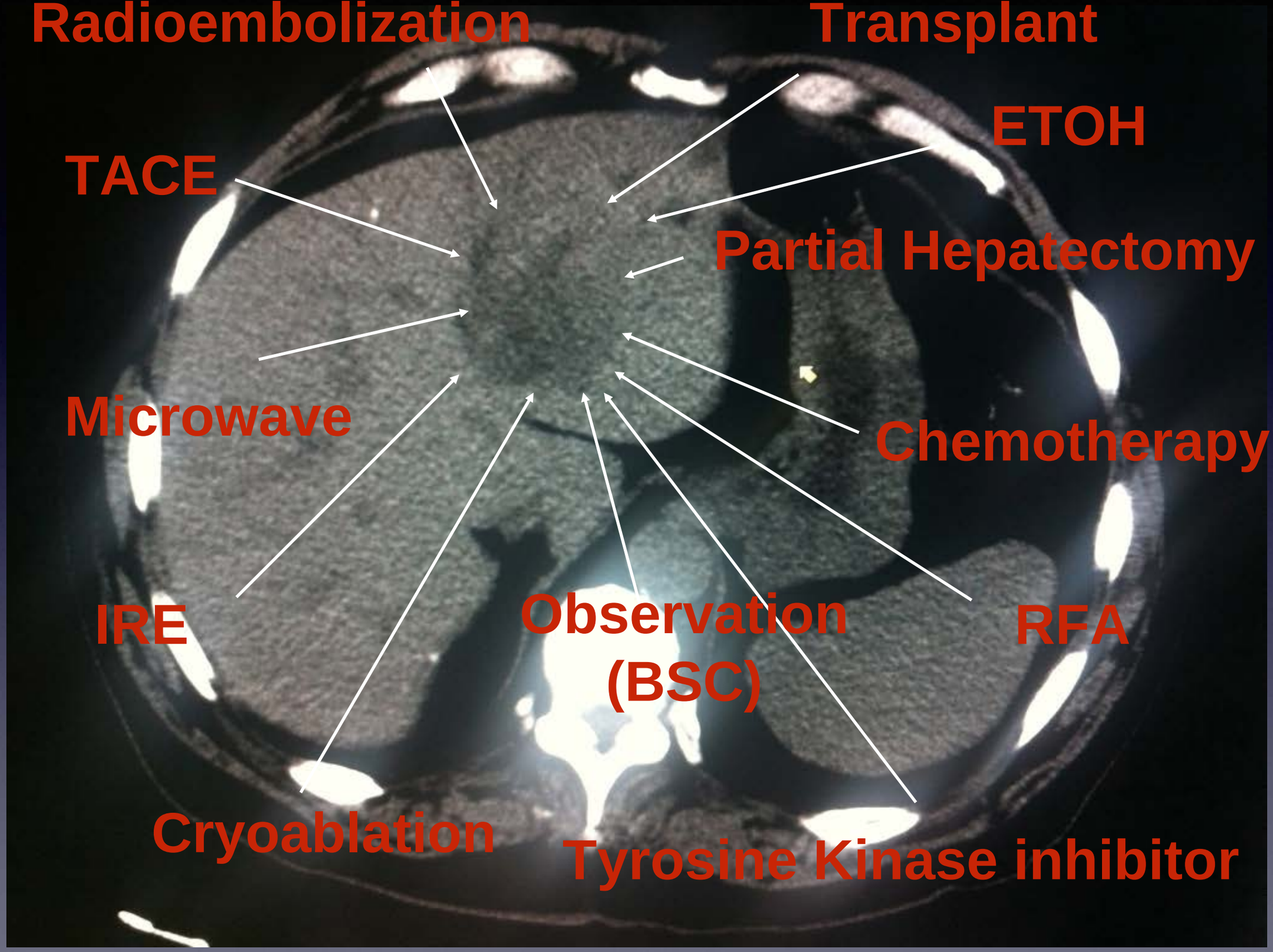
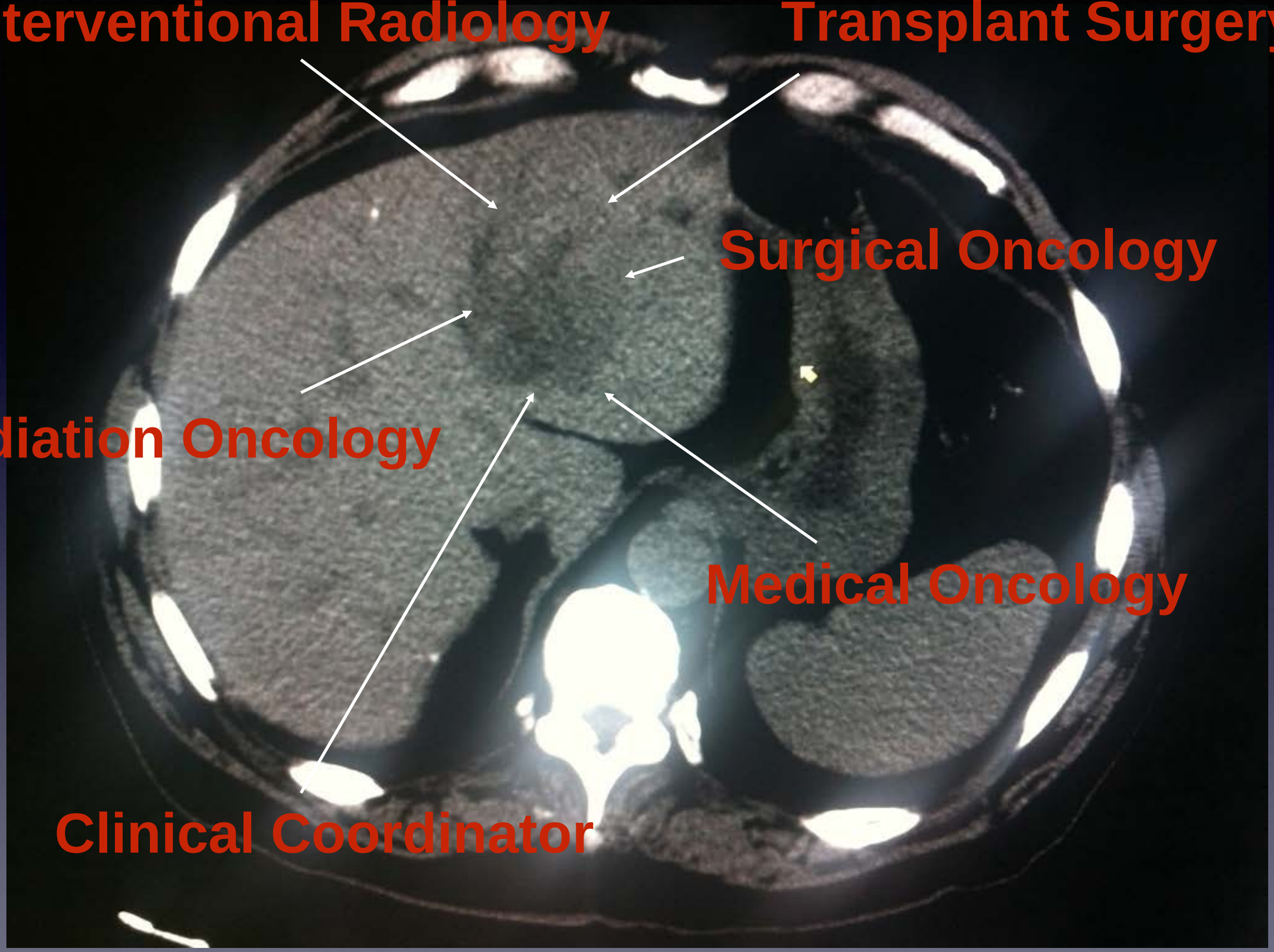
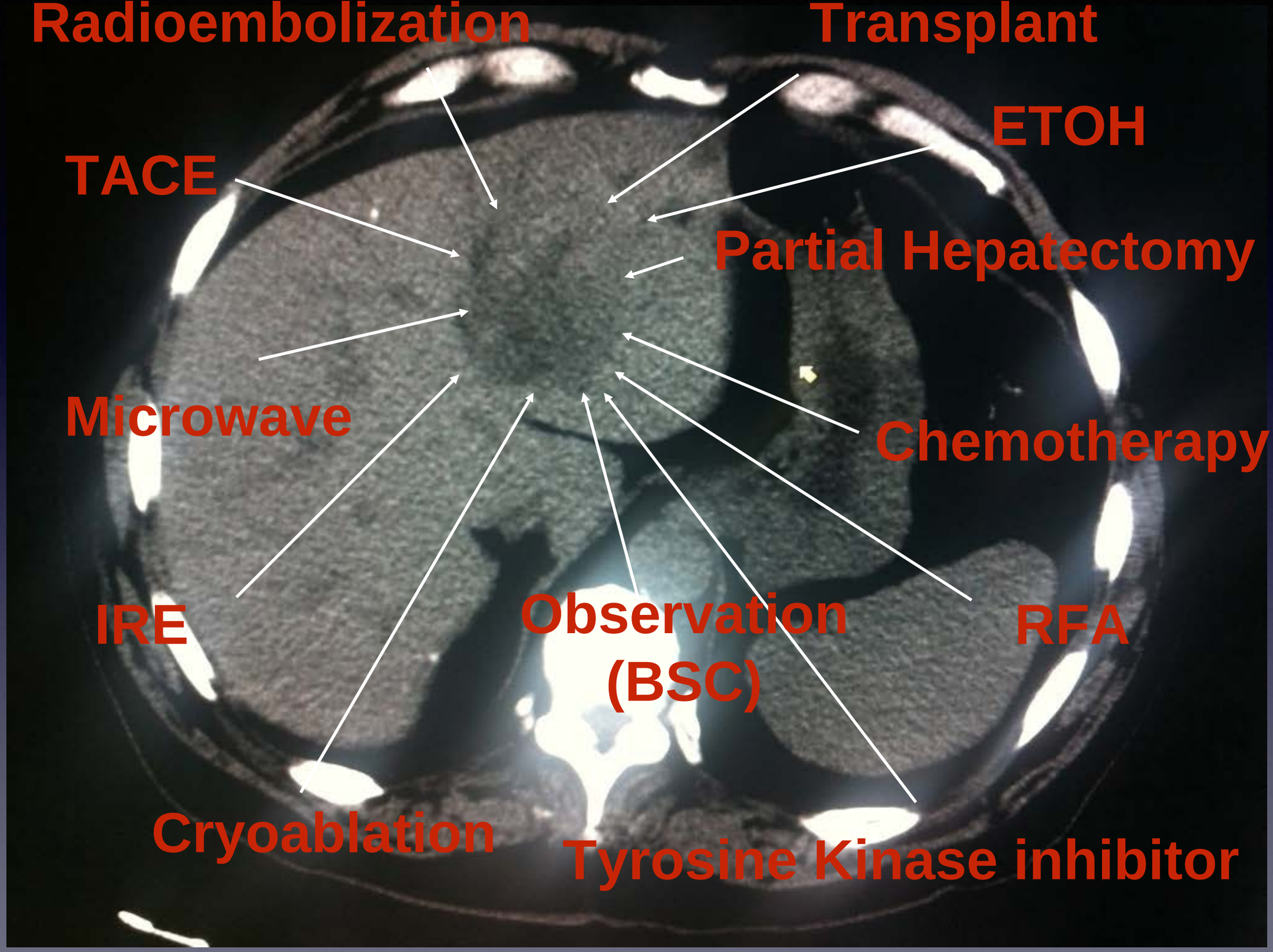
Interventional Oncology

- Concepts
- Tools
- Data

- 76 yo man with ETOH cirrhosis
- ECOG Grade 2
- Child-Pugh Score 6, Class A
- HCC in the Left Lobe of the Liver


Radioembolization
Transplant
ETOH
TACE
Partial Hepatectomy
Microwave
Chemotherapy
IRE
Observation
(BSC)
RFA
Cryoablation
Tyrosine Kinase inhibitor


Interventional Radiology
Transplant Surgery
Surgical Oncology
Radiation Oncology
Medical Oncology
Clinical Coordinator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Treatment Options

Surgery	Local	Regional	Systemic
Partial Hepatectomy	Thermal Ablation	TACE	Chemotherapy
Transplant	Non-Thermal Ablation	TARE	Tyrosine Kinase Inhibitors

Interventional Radiology

Treatment Options

Loco-regional

Surgery	Local	Regional	Systemic
Partial Hepatectomy	Thermal Ablation	TACE	Chemotherapy
Transplant	Non-Thermal Ablation	TARE	Tyrosine Kinase Inhibitors

Surgical Resection

- 1st line
- For those who are candidates
- Preserved liver function
- (Level IIA Evidence)

Surgical Resection

- Perioperative morbidity and mortality <5% in select patients.
- 5 year survival > 50%
- May be as high as 70% in patients with:
  - Early stage
  - Preserved liver function (Child-Pugh A)

Goal of Resection

- Negative surgical margins of 0.5 cm to 1cm (R0)
- Preservation of Liver Function

RO	Negative margins
R1	Microscopic residual tumor
R2	Gross residual tumor

Candidates for Surgical Resection

- Child-Pugh A (maybe B)
- Milan Criteria
  - Solitary tumor $\leq$ 5 cm
  - No more than 3 tumors $\leq$ 3 cm
- No vascular invasion
- No evidence of portal hypertension
- No major Comorbidities
- No Extrahepatic Metastases

Candidates for Surgical Resection

- Only 5 - 10% of HCC patients are resectable[1]

[1]Llovet, JM. Current treatment Options for Gastroenterology. 2004;7:431-441

Transplant

- 4 year Overall Survival (OS): 85%
- Relapse Free Survival (RFS): 92%

Transplant

- Significant Heart, Lung, CNS, or other systemic disease
- Systemic infection
- Malignancy outside liver
- Active ETOH or Drug use
- Portal vein thrombosis
- Psychiatric
- Obesity
- Lack of sufficient social support
- Other severe comorbid conditions

Transplant

- Significant H[illegible]3, or other systemic di[illegible]
- Systemic [illegible]
- Maligna[illegible]de liver
- Active [illegible]Drug use
- Portal v[illegible]bosis
- Psychiat[illegible]
- Obesity
- Lack of sufficie[illegible]
- Severe comorbid condi[illegible]

Transplant

- Patients on Transplant list: 114,436
- Waiting list for livers: 13,835

Organ Procurement and Transplant Network data as of July 2018

- 76 yo man with cirrhosis presented with mass in the Left Lobe of the Liver.
- ECOG Grade 2.
- Child-Pugh Score 6, Class A

- Evaluated by Transplant Team
- Evaluated by Hepatobiliary Surgeon

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Loco-regional Therapy

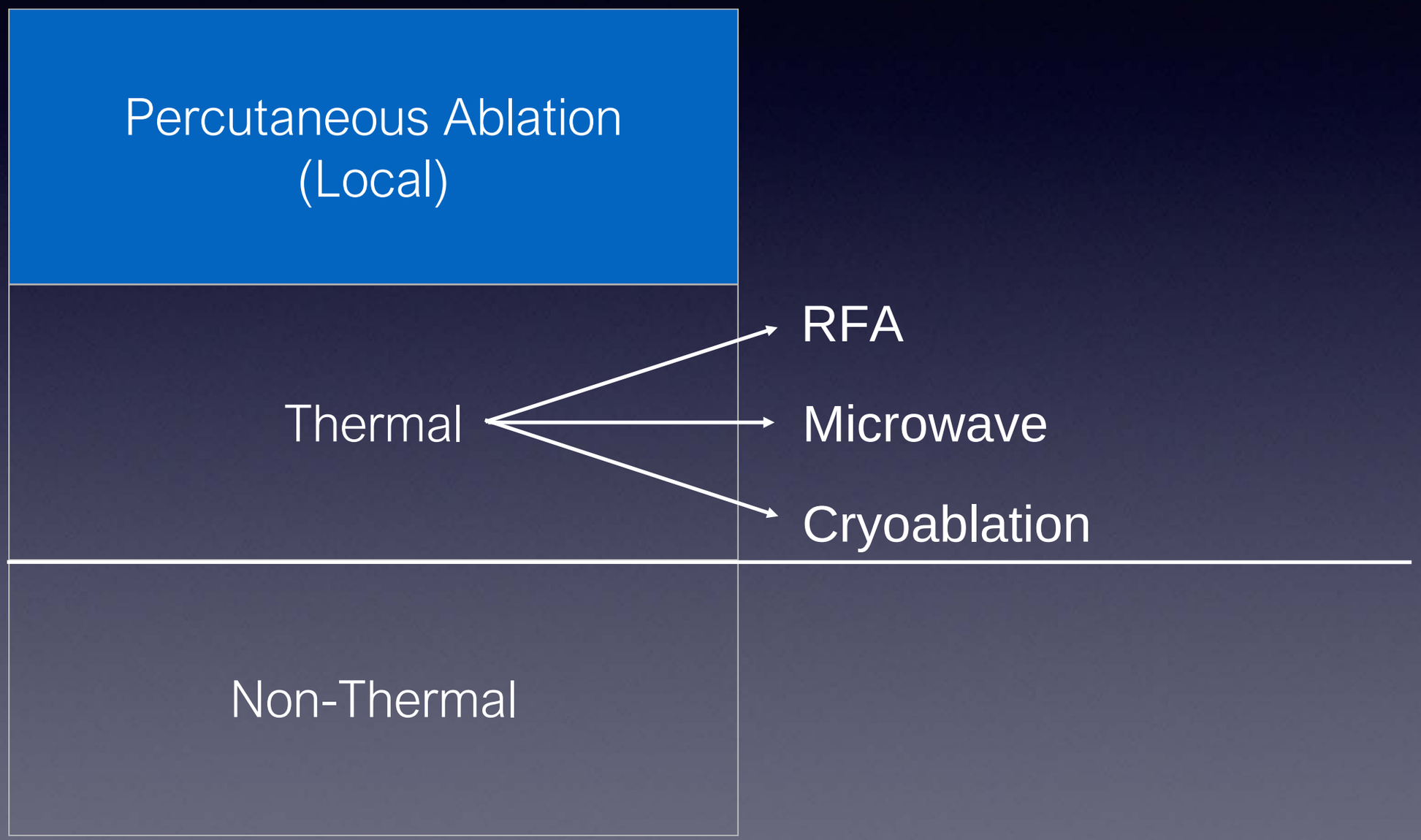
Percutaneous Ablation (Local)	Regional
Thermal	Transarterial Chemoembolization (TACE)
Non-Thermal	Transarterial Radioembolization (TARE)

Loco-regional Therapy

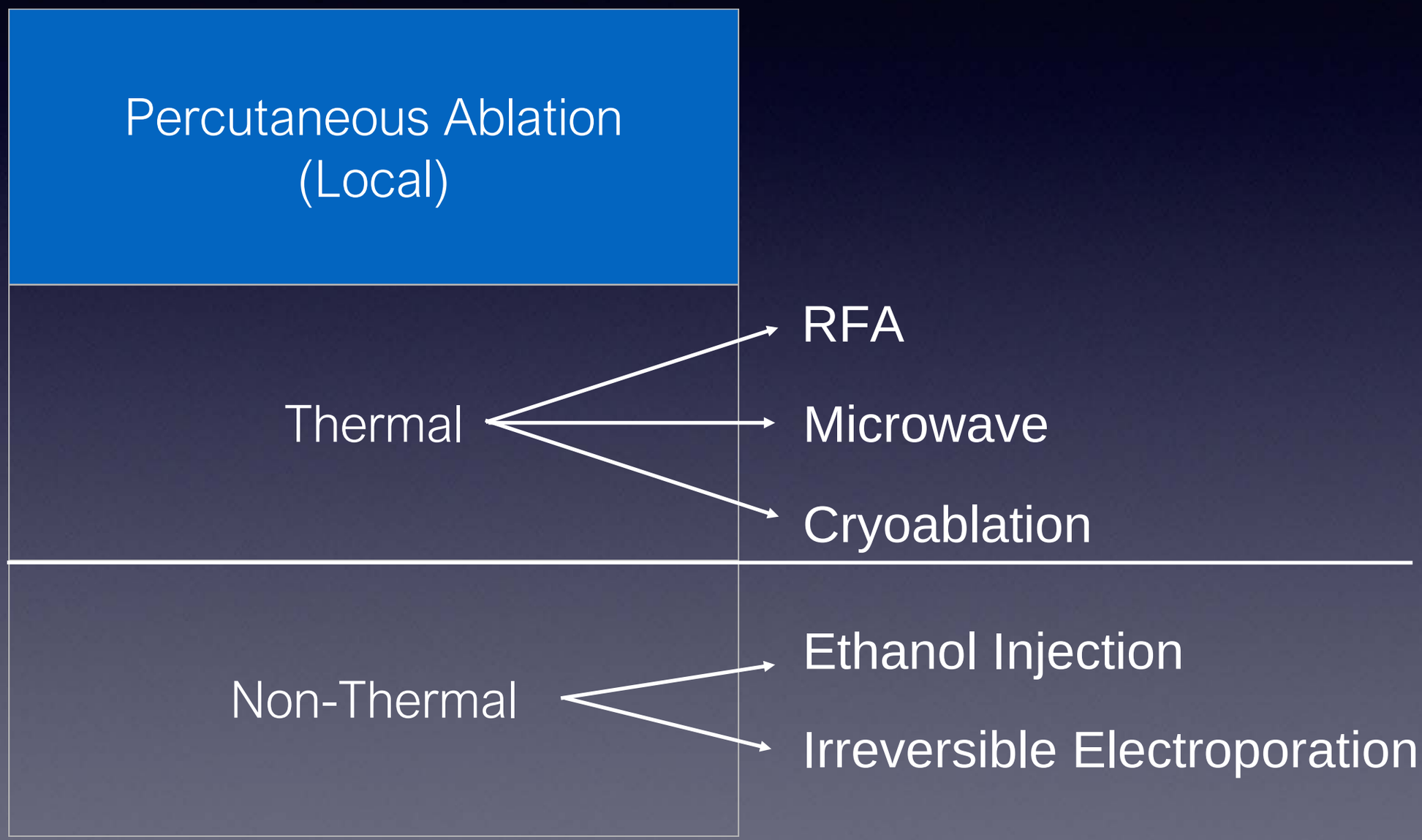
Percutaneous Ablation (Local)

- Thermal
- Non-Thermal

Loco-regional Therapy



Loco-regional Therapy



Percutaneous Ethanol Injection

- Dehydrated 98% ethyl alcohol by volume (196 proof)
- Preferentially permeates softer tumor
- Effective, especially for tumors < 2cm in size
- Inexpensive

Percutaneous Ethanol Injection

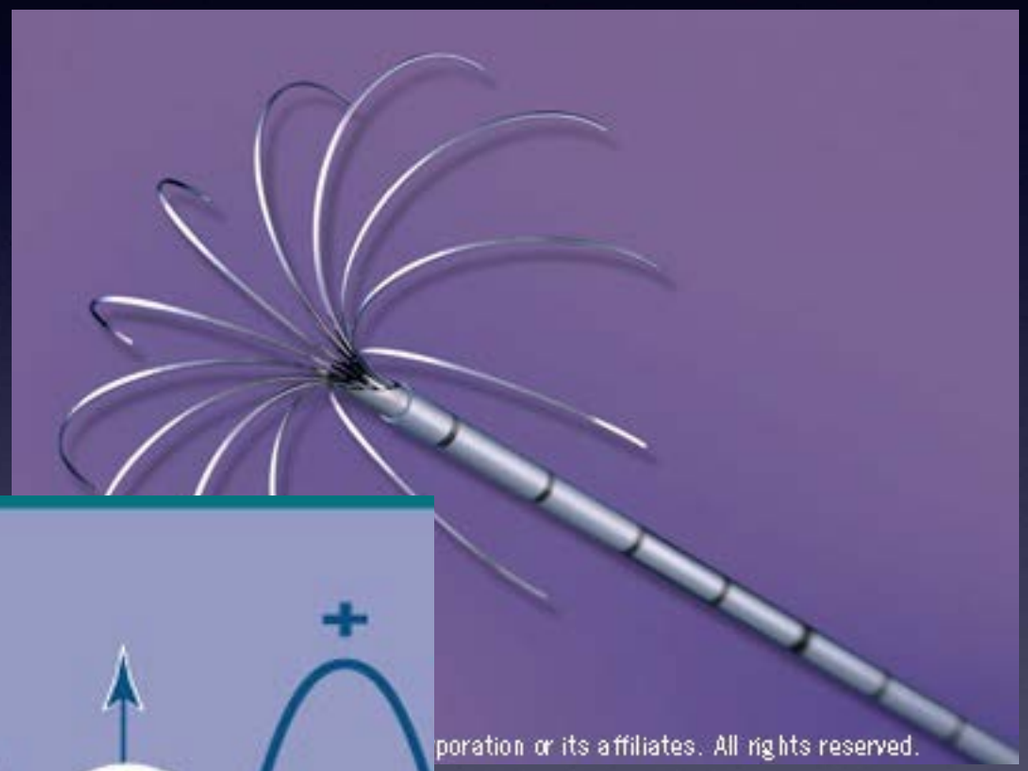
- Effects of RF Ablation are more predictable

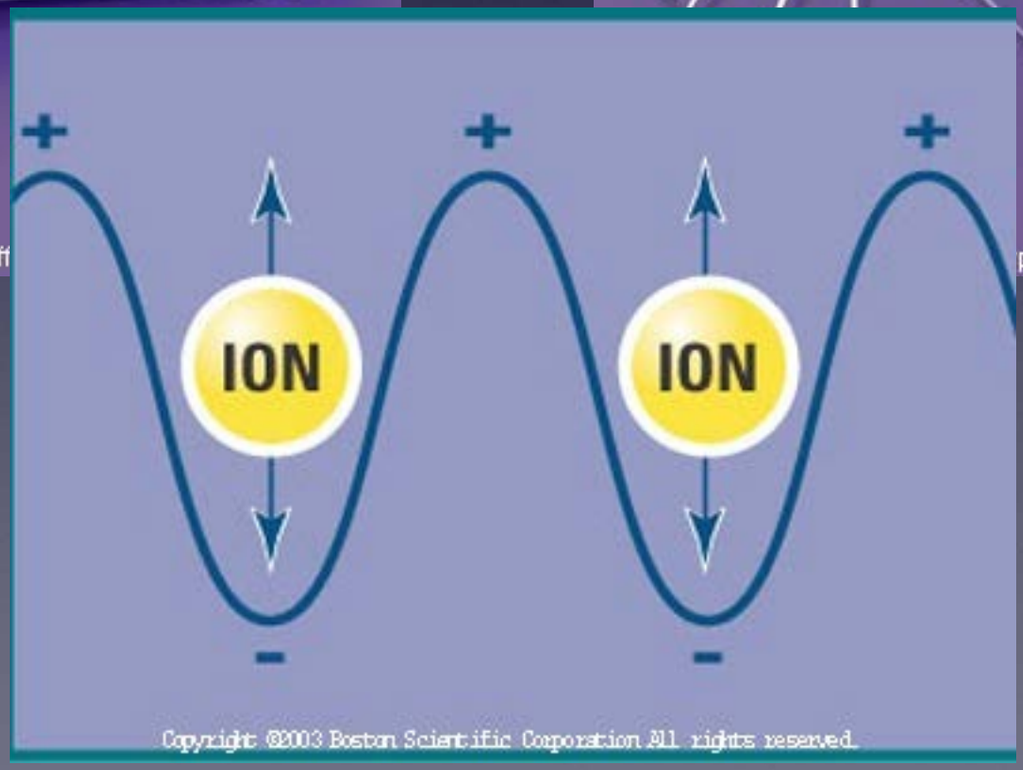
Level I evidence

Radiofrequency Ablation
RFA

Radiofrequency Ablation
RFA

Radiofrequency Ablation
RFA





Radiofrequency Ablation
RFA


May 2008

RFA

- Goal is to achieve an ablation zone of 0.5 cm to 1 cm

Chen, et al., “A Prospective Randomized Trial Comparing Percutaneous Local Ablative Therapy and Partial Hepatectomy for Small Hepatocellular Carcinoma,” Annals of Surgery, 2006; 243(3):321-328.

- Randomized 180 patients
- Solitary HCC < 5 cm
- 71 Local Ablation
- 69 Surgical Resection

Chen, et al., “A Prospective Randomized Trial Comparing Percutaneous Local Ablative Therapy and Partial Hepatectomy for Small Hepatocellular Carcinoma,” Annals of Surgery, 2006; 243(3):321-328.

Overall Survival	1 Year	2 Year	3 Year	4 Year
Ablation	95.8%	82.1%	71.4%	67.9%
Resection	93.3%	82.3%	73.4%	64%

RFA

- 5 Year OS in early stage HCC 50% - 64%
- Most favorable for tumors ≤ 3cm
- For tumors ≤ 2cm, 5 year OS 97%

RFA

- For small, solitary, early-stage HCC, RFA offers similar survival rates to surgical resection and may represent an equivalent alternative to surgical resection as 1st line treatment.

Livragui et. al, “Sustained complete response and complication rates after radiofrequeny ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice,” Hepatology 2008; 47:82-89.

RFA

- Rates of successful ablation decrease as tumors exceed 3cm

- “Heat Sink” can decrease rate of complete tumor necrosis to < 50%

- Subcapsular Location increases risk of incomplete ablation and tumor progression

Microwave Ablation

- Similar to RFA
- Shifted on Electromagnetic Spectrum (2.45 GHz)
- Oscillation of water molecules
- Can reach 150 degrees Celsius

Microwave Ablation

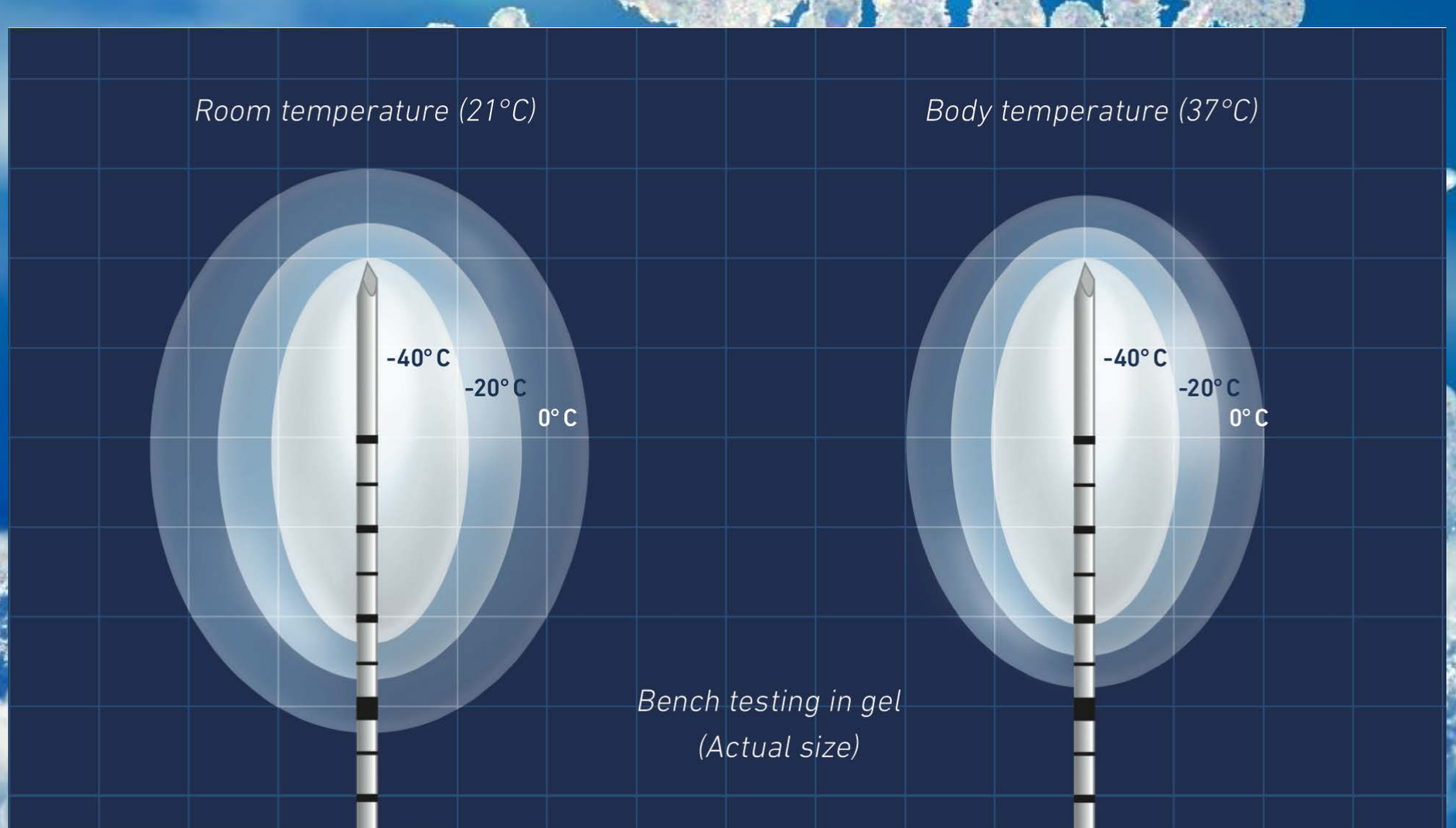
Advantages	Dissadvantages
Higher Temperature (150ºC vs. 100ºC)	Not as much published research compared to RFA
Not prone to “Heat Sink”	

Cryoablation

- Thermal Ablation
- Cold instead of heat

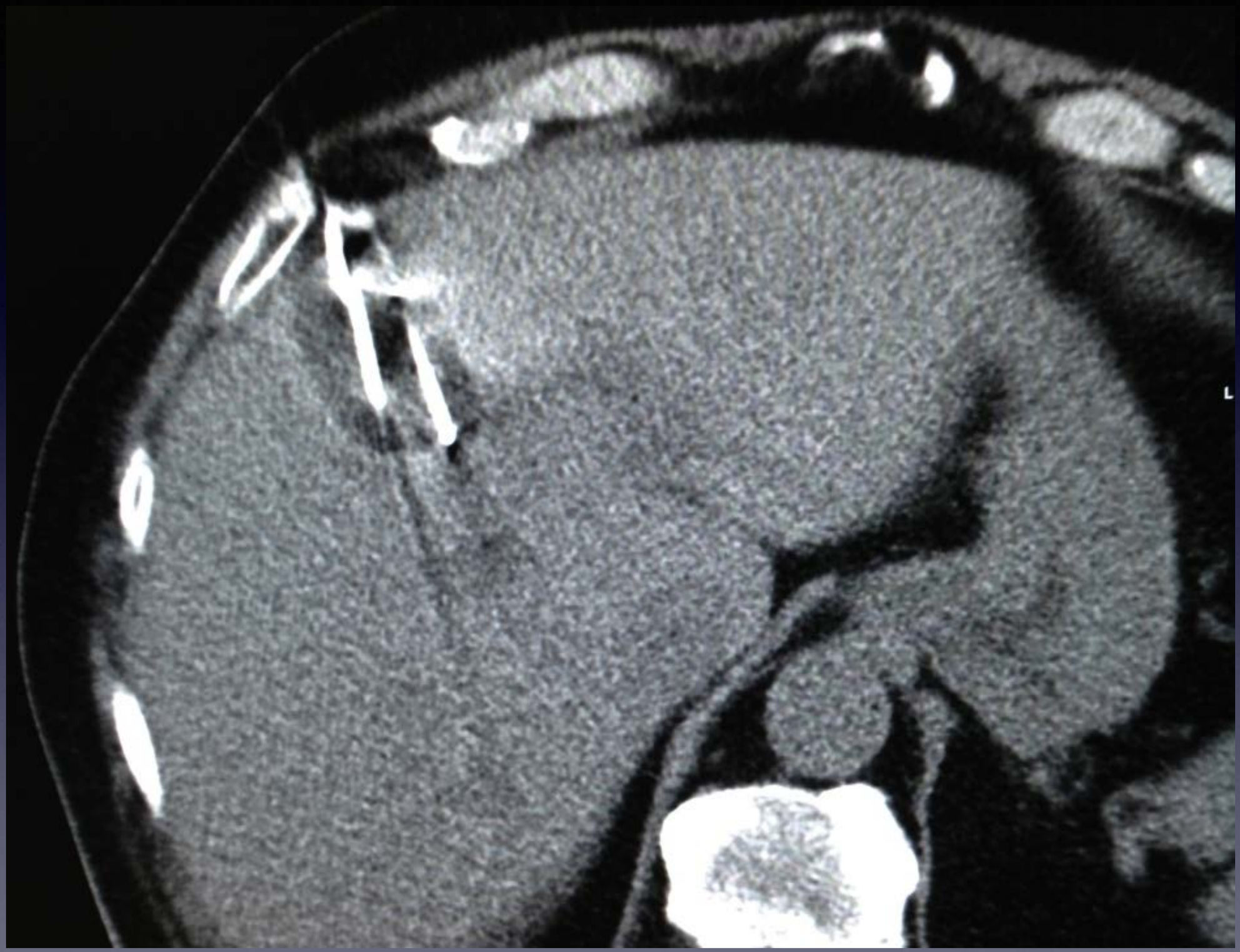
Cryoablation

- Argon
- -40º C / F



Cryoablation

- Cause cell death by:
  - intracellular ice formation
  - cell dehydration
  - rupture of cell membrane



Yang, et al: “Outcomes of ultrasound-guided percutaneous argon-helium cryoablation of hepatocellular carcinoma,” J Hepatology and Pancreatic Science (2012) 19:674-684

- 408 tumors
- 300 patients
- Mean Diameters 1.9cm to 15cm

Yang, et al: “Outcomes of ultrasound-guided percutaneous argon-helium cryoablation of hepatocellular carcinoma,” J Hepatology and Pancreatic Science (2012) 19:674-684

- 185 tumors *completely* ablated
  - 1.9 cm to 7 cm with mean diameter of 5.6 cm
- 223 tumors *incompletely* ablated
  - 5 cm to 15 cm with mean diameter of 7.2 cm

Yang, et al: “Outcomes of ultrasound-guided percutaneous argon-helium cryoablation of hepatocellular carcinoma,” J Hepatology and Pancreatic Science (2012) 19:674-684

- OS of patients with 1 to 3 HCC < 3cm:
  - 1 year: 91%
  - 2 year: 85%
  - 3 year: 65%
  - 5 year: 54%

Yang, et al: “Outcomes of ultrasound-guided percutaneous argon-helium cryoablation of hepatocellular carcinoma,” J Hepatology and Pancreatic Science (2012) 19:674-684

- Most common causes of death:
  - Variceal Bleeding: 36.3%
  - Liver Failure: 26.2%
  - Tumor recurrence and metastasis: 23.2%

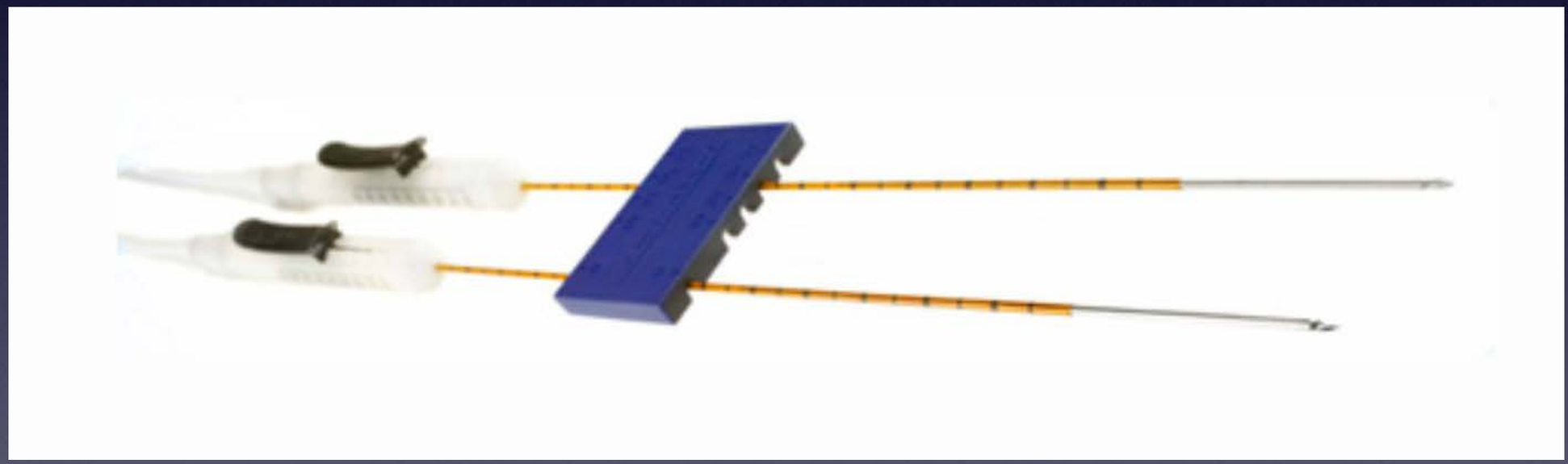
Yang, et al: “Outcomes of ultrasound-guided percutaneous argon-helium cryoablation of hepatocellular carcinoma,” J Hepatology and Pancreatic Science (2012) 19:674-684

- Complications:
  - Majority minor
  - Severe in 19 (6.3%)
    - Hemorrhage
    - Intestinal fistula
    - Severe Liver Damage and Liver Failure

Cryoablation in Liver

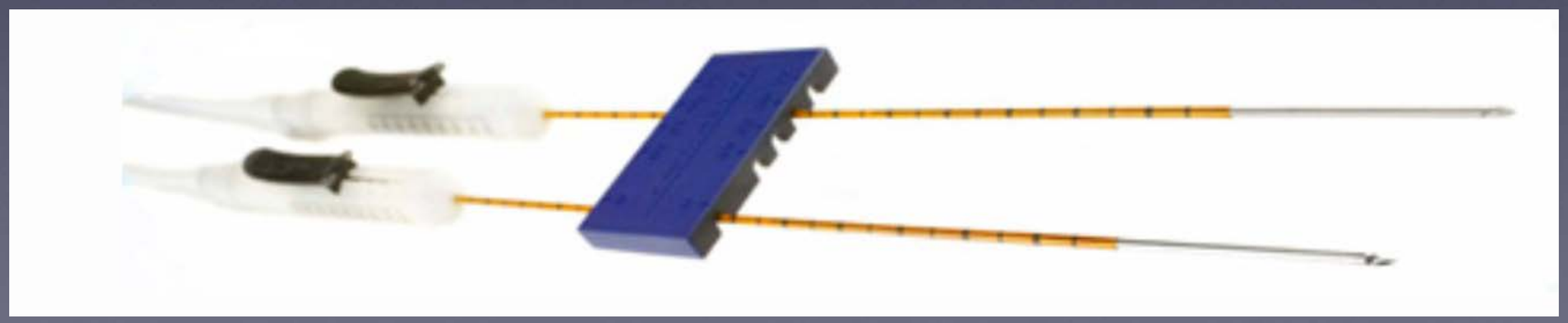
- Relatively safe and effective
- Tumors < 5 cm
- Child-Pugh A (maybe B)

Irreversible Electroporation



Irreversible Electroporation

- Electrical current causes micro perforations “nanopores” through cell membrane



Irreversible Electroporation

Pros	Cons
Not susceptible to “Heat Sink”	Minimal data in clinical literature

Percutaneous Ablation

- Very favorable response profile
- Should be considered for patients who are not candidates for surgical resection
- Ablation alone may be curative for lesions < 3cm
- Prolong survival for lesions 3 cm - 5 cm

- 75 years old man with incidental finding of a solid, enhancing, 2.2 cm, left kidney mass.

Renal Cell CA

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1-T2	N1	M0
	T3	N0-1	M0
IV	T4	N2	M0
	Any T	Any N	M1

Renal Cell CA

Primary Tumor (T1)	
T1a	< 4cm
T1b	>4cm but <7cm

Renal Cell CA

- Stage T1a RCC (tumors <4cm) are curable
- Nephron Sparing Partial Nephrectomy replaced Radical Nephrectomy as Standard of Care

How does Thermal Ablation compare with Surgery?

Thermal Ablation

- T1 lesions (<7cm)
  - Similar distance recurrence free survival rates
  - Increased risk of local recurrence
    - (T1b: 4 - 7cm)
  - American Urological Association: Thermal Ablation as alternative to surgery in high risk patients

Percutaneous Ablation Versus Partial and Radical Nephrectomy for T1a Renal Cancer: A Population-Based Analysis

- *Talenfeld, et al.*, Annals of Internal Medicine, June 2018

- Population based SEER cancer registry data linked to Medicare claims

- 4310 patients

- Median follow up of 52 months

Percutaneous Ablation Versus Partial and Radical Nephrectomy for T1a Renal Cancer: A Population-Based Analysis

- 5-year RCC specific survival rate
  - 95% PA
  - 98% PN
  - 95% RN

Percutaneous Ablation Versus Partial and Radical Nephrectomy for T1a Renal Cancer: A Population-Based Analysis

- 5-year OS
- 77% PA
- 86% PN
- 75% RN

Percutaneous Ablation Versus Partial and Radical Nephrectomy for T1a Renal Cancer: A Population-Based Analysis

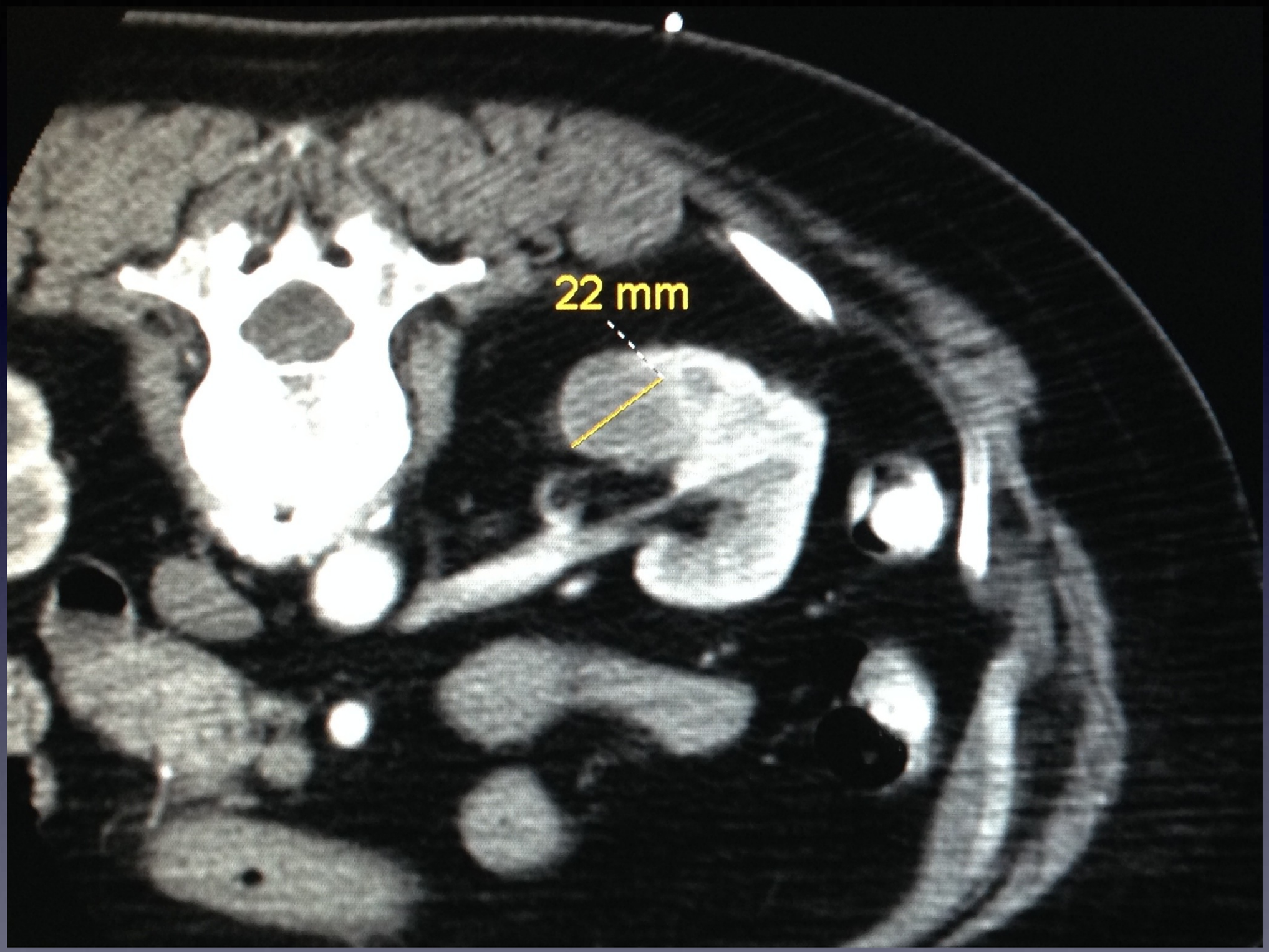
- Non-neurological Complications at 30 days
  - 6% PA
  - 29% PN
  - 30% RN

Percutaneous Ablation Versus Partial and Radical Nephrectomy for T1a Renal Cancer: A Population-Based Analysis

- 10% of PN – Intraoperative conversion to RN
- 7% of PA – Additional PA within 1 year

Percutaneous Ablation Versus Partial and Radical Nephrectomy for T1a Renal Cancer: A Population-Based Analysis

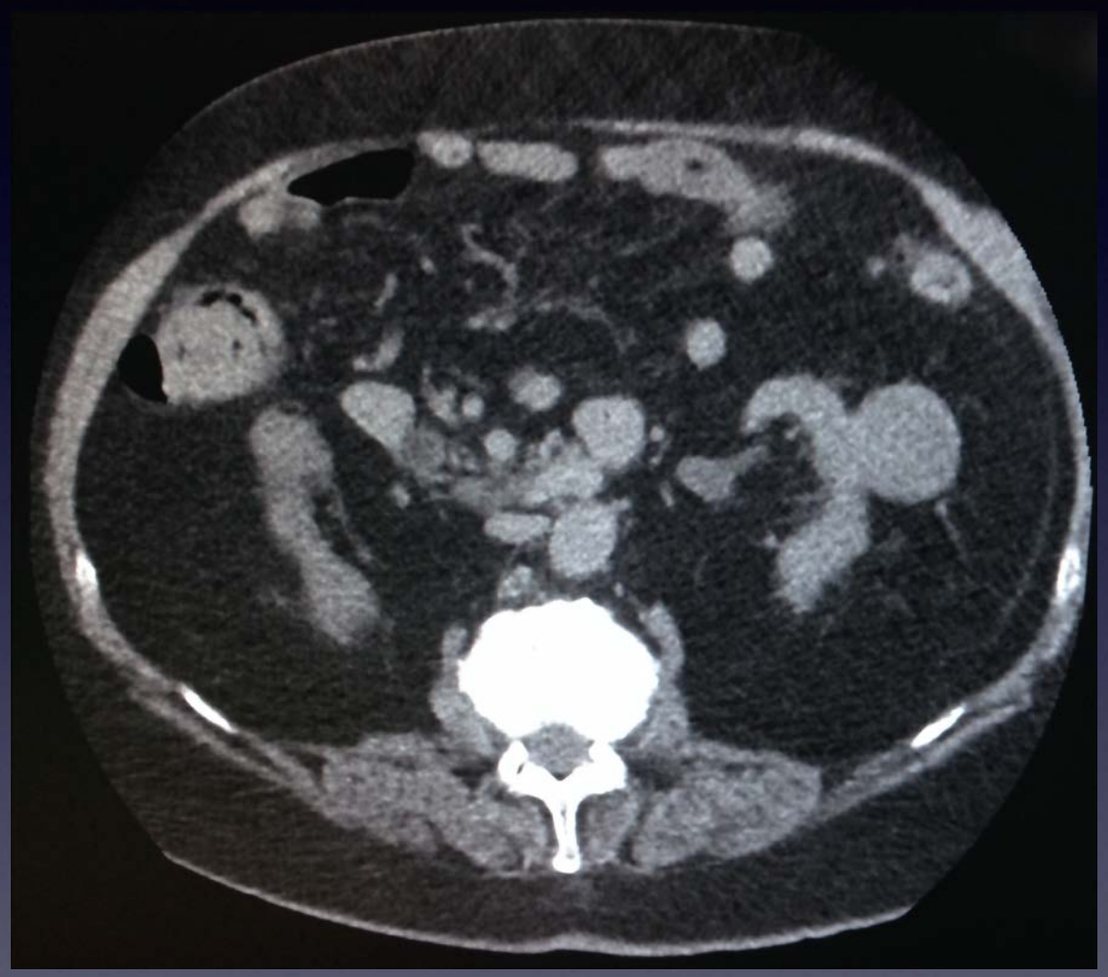
- For selected patients with T1a RCC
- Similar outcomes
- Less Renal Insufficiency
- Fewer complications

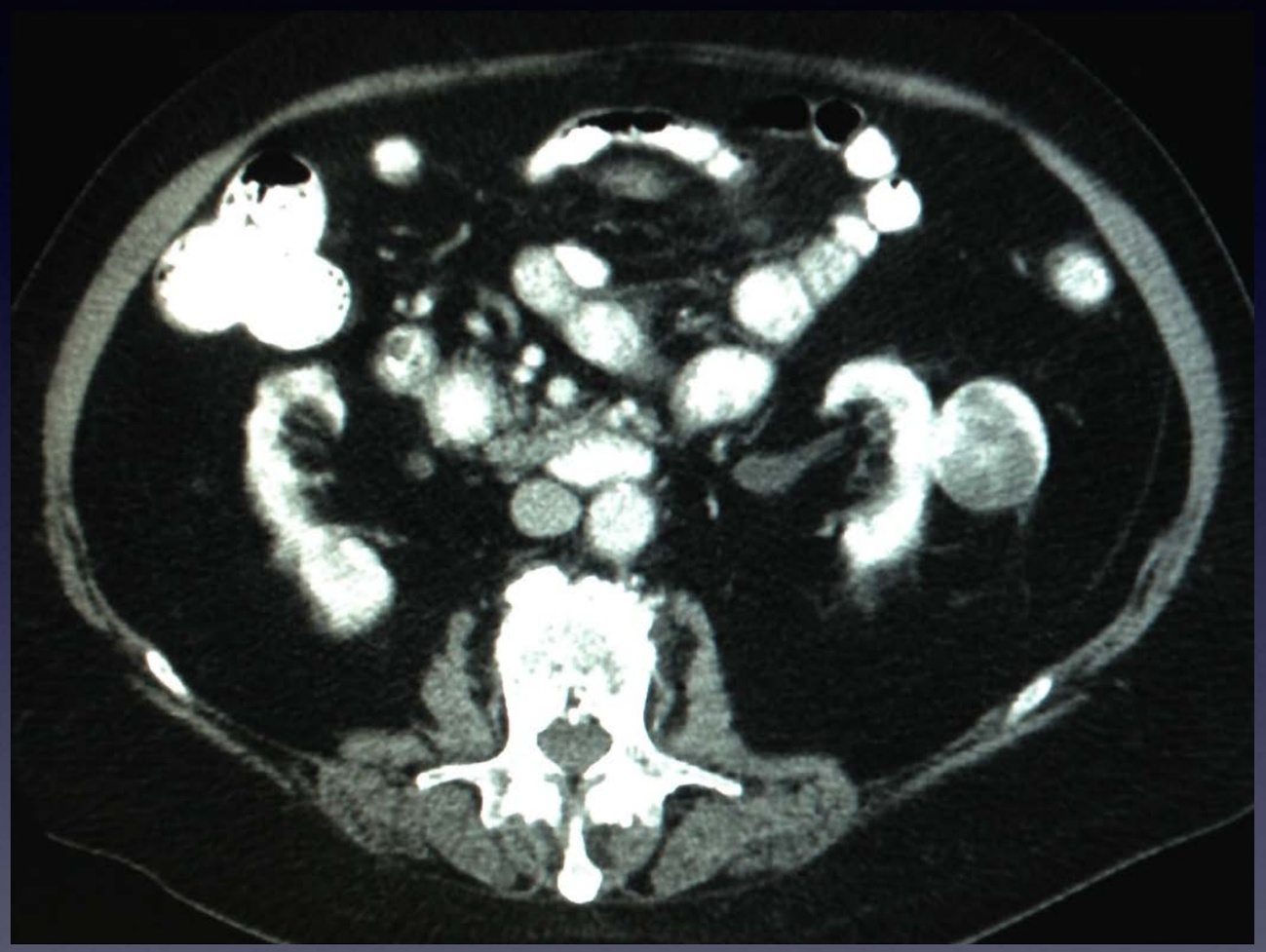


RFA

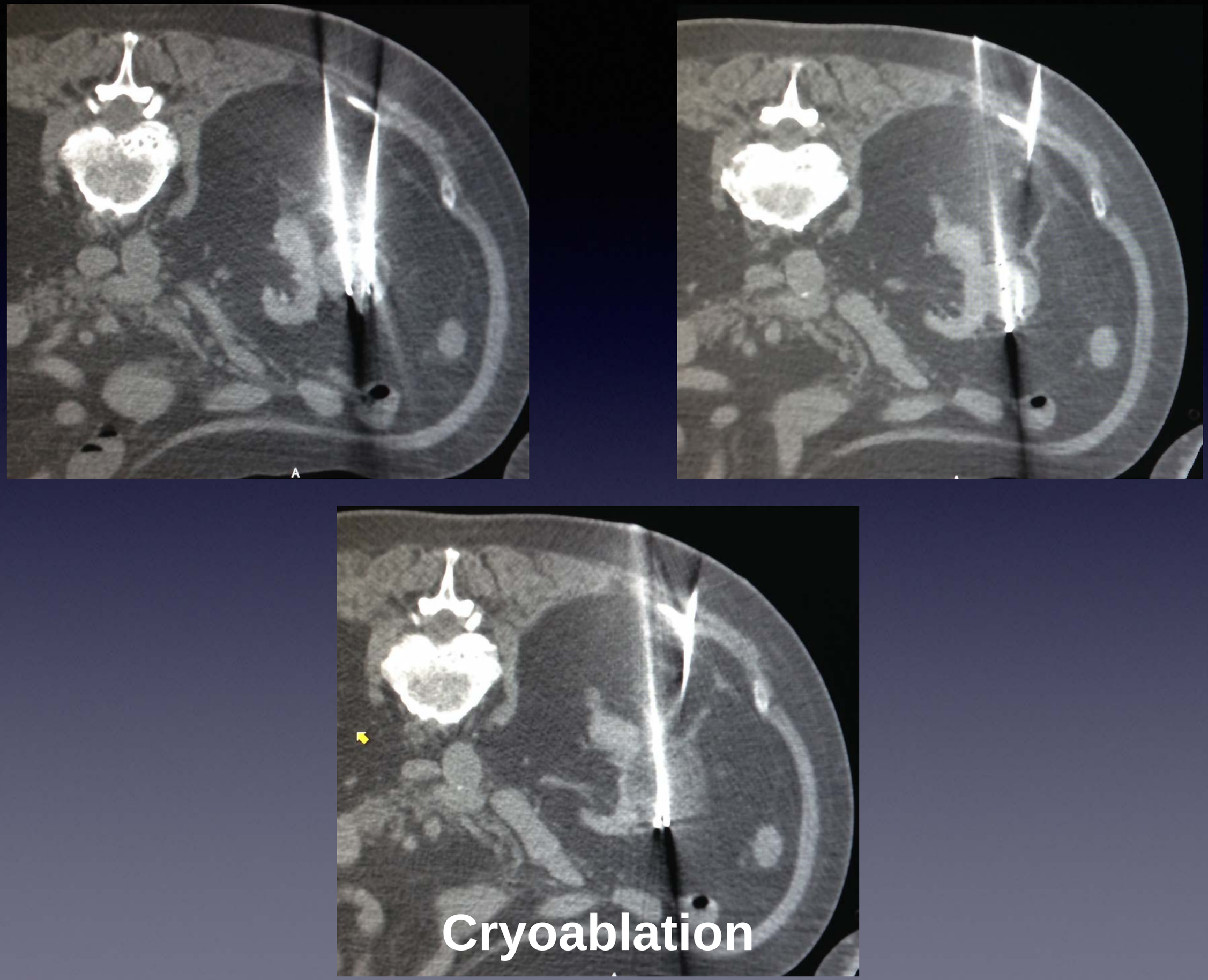
RFA

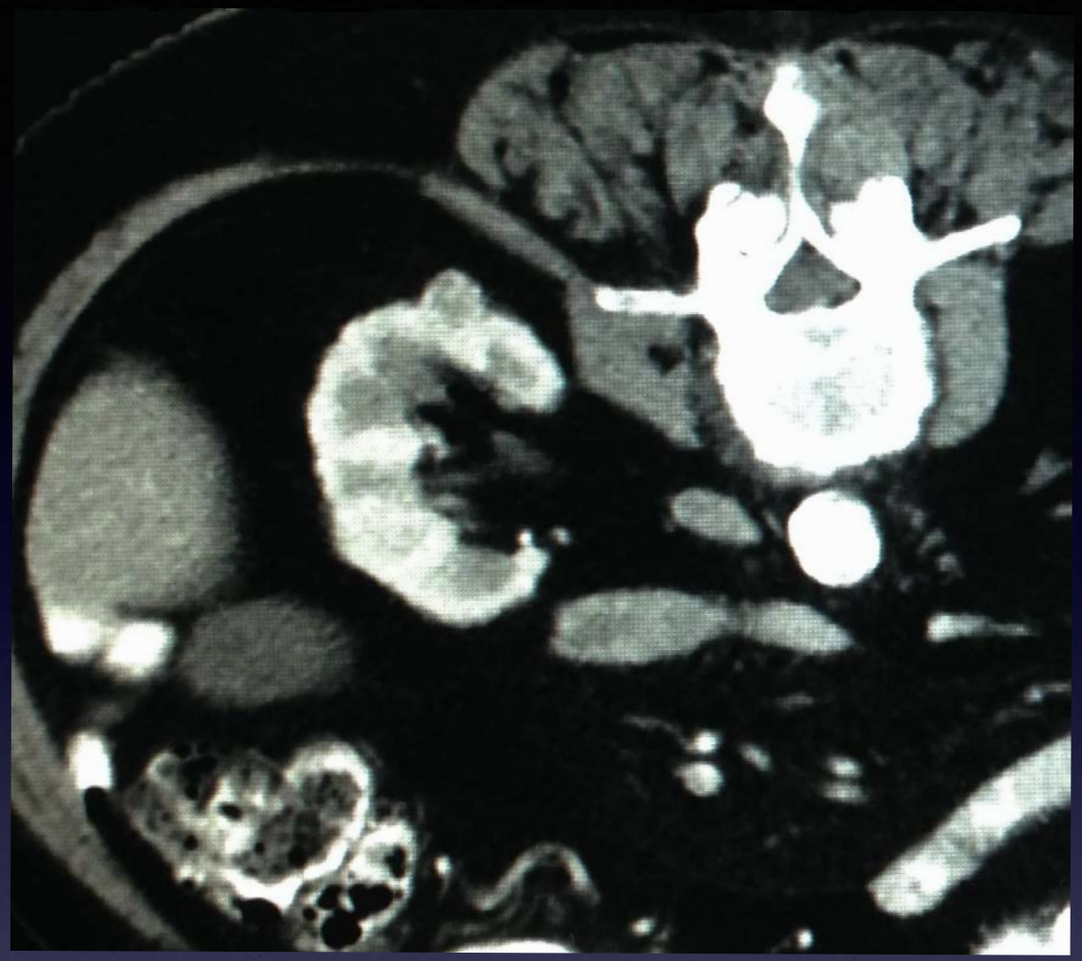
RFA





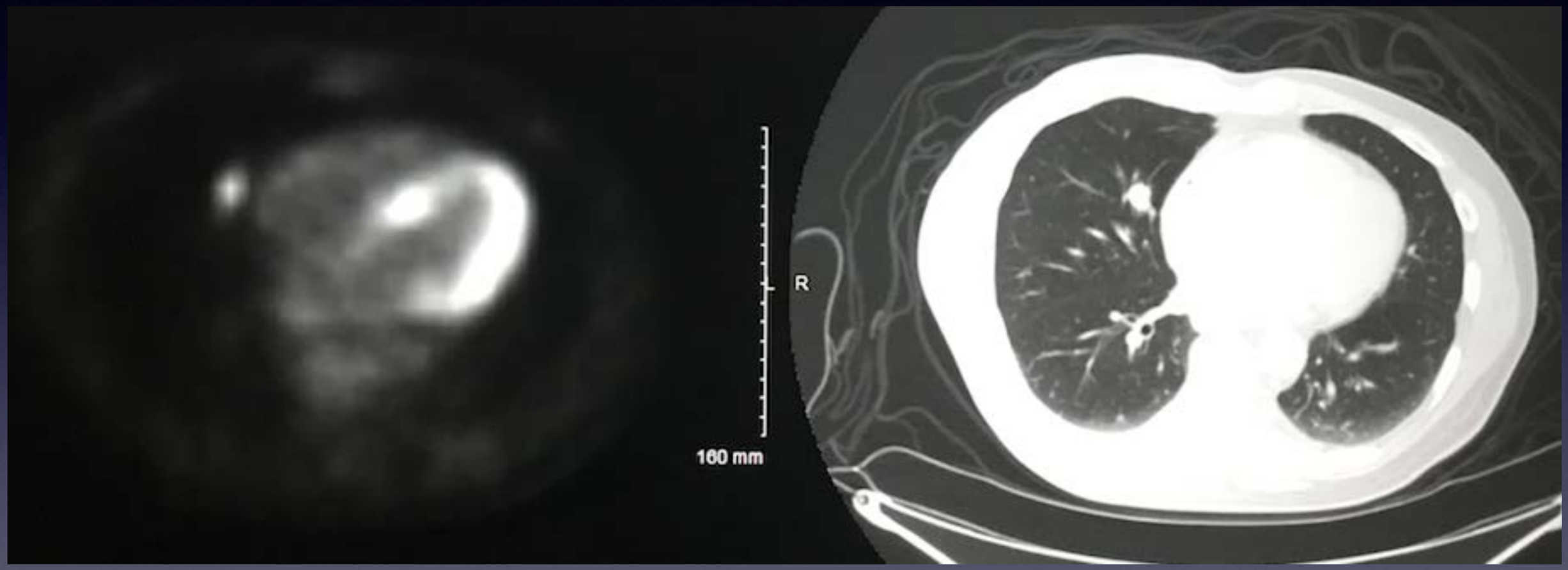
Cryoablation


A
Cryoablation



Cryoablation

70 yo M with a history of lung cancer s/p surgical resection, now with new FDG avid right lung lesion; Patient wishes to not undergo additional surgery nor radiation



Pre-procedure PET; 1.2 x 1.1 cm nodule

Parenchymal hemorrhage from 20G core biopsy x2 and antenna placement; Single
microwave antenna at 60W for 10 minutes

1 month post-ablation follow-up with no evidence of residual or recurrent disease

Lung Ablation

- Technical success 80% – 90%
- Best results lesions 2 – 3 cm
- 3,4,5 Year OS 97.7%, 72.9%, 55.7%

T. De Baere, et al, Percutaneous Thermal Ablation of Primary Lung Cancer, Diagnostic and Interventional Imaging (2016) 97, 1019 – 1024

What about lesions > 5 cm?

What about lesions > 5 cm?

Or patients with > 3 lesions?

Loco-regional Therapy

Percutaneous Ablation (Local)	Regional
Thermal	Transarterial Chemoembolization (TACE)
Non-Thermal	Transarterial Radioembolization (TARE)

Regional Therapy

- A region, such as a lobe or a segment of the liver, is targeted for drug delivery
  - Chemotherapy (TACE)
  - Radiation (TARE)

Conventional TransArterial ChemoEmbolization (TACE)

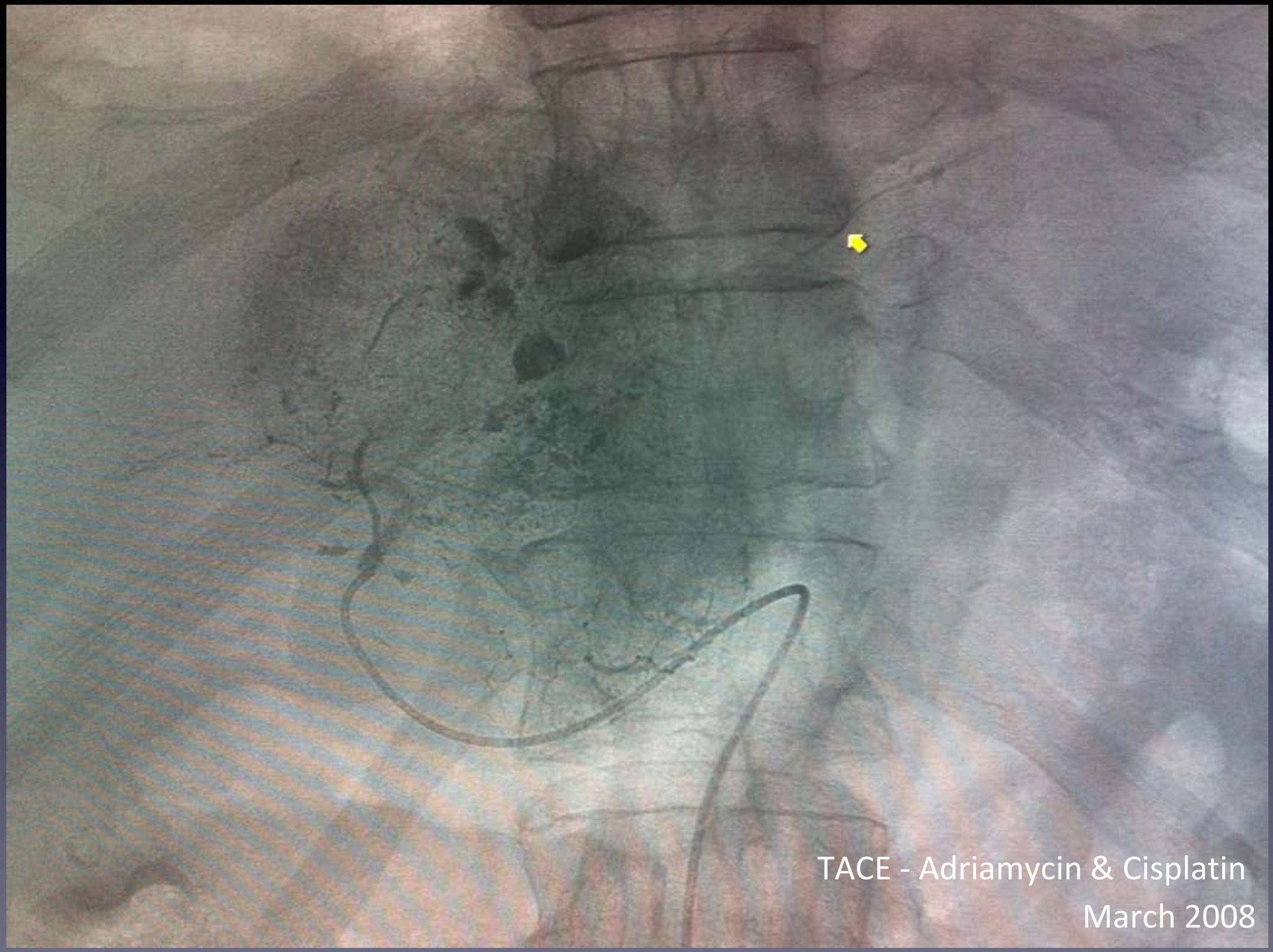
- Mixture of:
  - Chemotherapeutic Agents:
    - Doxorubicin
    - Cisplatin
- Lipiodol or Ethiodol

Conventional TransArterial ChemoEmbolization (TACE)

- Administered directly into the artery which supplies the tumor or the segment of liver which contains the tumor.


94 mm
L
R


TACE - Adriamycin & Cisplatin
March 2008


TACE - Adriamycin & Cisplatin
March 2008

March 2008

Conventional TransArterial ChemoEmbolization (TACE)

- Recommended 1st line therapy in intermediate stage disease without
- vascular invasion
- distant metastases

Conventional TransArterial ChemoEmbolization (TACE)

- Based on 2 landmark prospective randomized trials demonstrating:
  - Improved survival compared with best supportive care
  - preserved liver function
    - (Level IA evidence)

Lo, et al., “Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma,” Hepatology 2002; 35:1164-1171.

Overall Survival Rate:

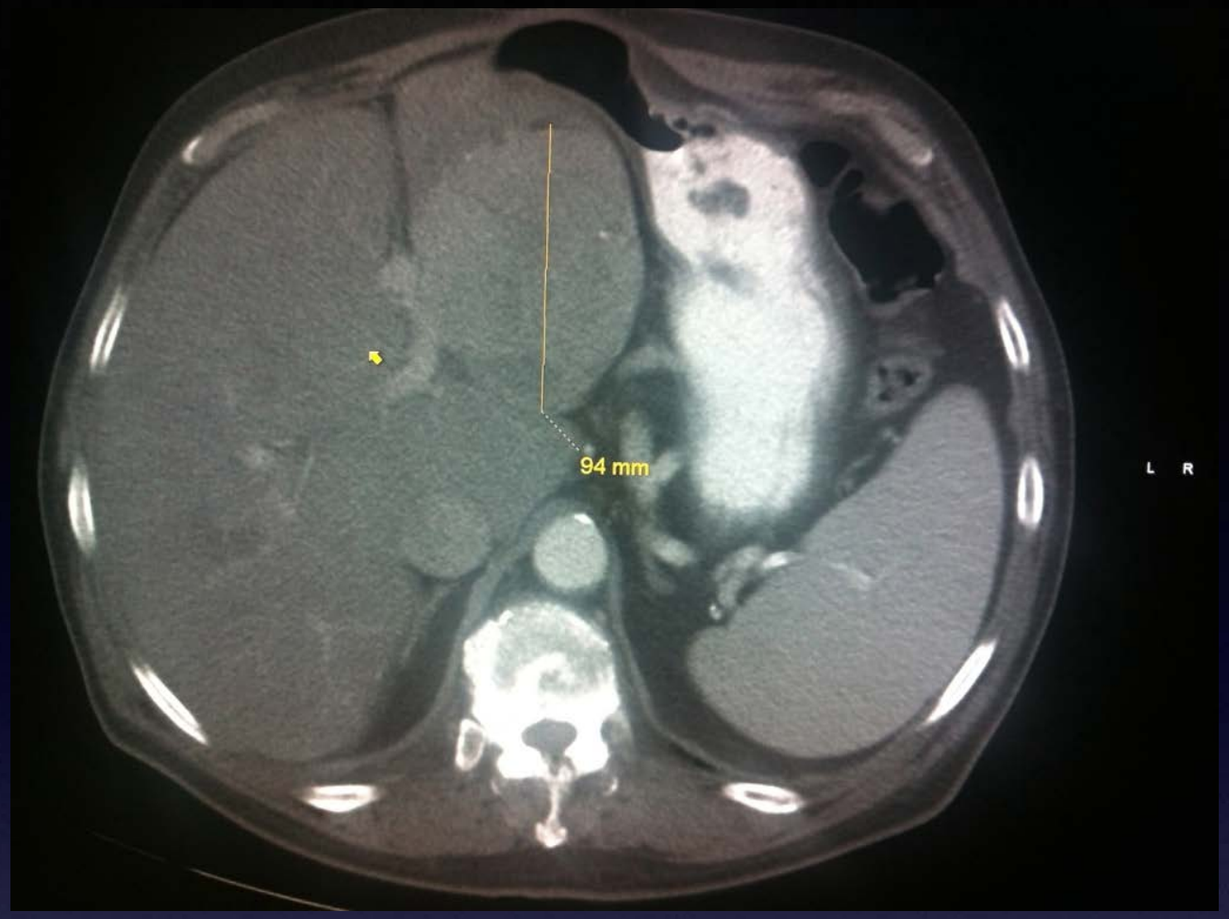
	1 Year	2 Year	3 Year
TACE	57%	31%	26%
BSC	32%	11%	3%

Llovet et al, “Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial.” Lancet 2002; 359:1734-1739.

Overall Survival Rate:

	1 Year	2 Year
TACE	75%	50%
BSC	63%	27%

Trial Stopped Early


94 mm
L R


R3:1
L R


58 mm

DEB-TACE

- Drug Eluding Bead
- Doxorubicin (HCC)
- Irinotecan (Colon Mets)

Doxyrubicin DEB-TACE

- Prospective, randomized trial, demonstrating:
  - Similar efficacy as Conventional TACE
  - Higher Doxorubicin Concentration
  - Reduced liver toxicity
  - Reduced doxorubicin-related side effects

Lammer, et al. “Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study.” Cadiovasc Intevent Radiol 210; 33:41-52.

Trans-Arterial Radioembolization (TARE)

TransArterial Radioembolization (TARE)

- Glass (Therasphere™) or Resin (SirSpheres™) microspheres
- Yttrium-90
- Embolized into the hepatic artery branch which supplies the lobe or segment with tumor

Yttrium-90

Uranium

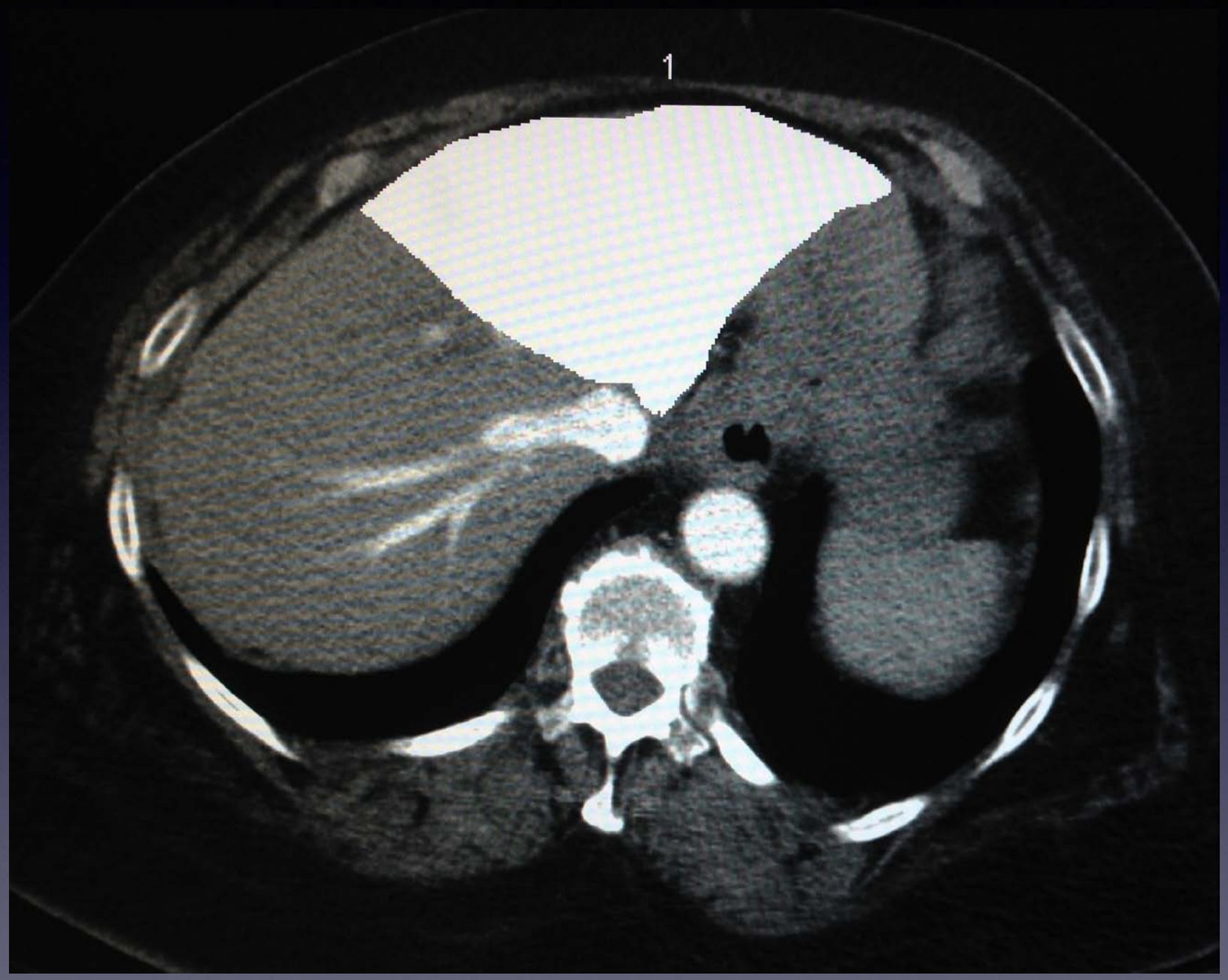
Strontium-90

Yttrium-90

- Beta decay to zirconium-90
- Half life 64 hours
- Average beta energy 0.9367 MeB
- Average tissue penetration 2.5mm
- Emitted electrons can interact with matter to cause Bremsstrahlung x-rays

Yttrium-90

- Low toxicity (well tolerated)
- Minimal PES (compared with TACE)
- Bridge to transplant
- Portal Vein Thrombosis
- Preserves liver vascularity



Calculate dose based on liver volume

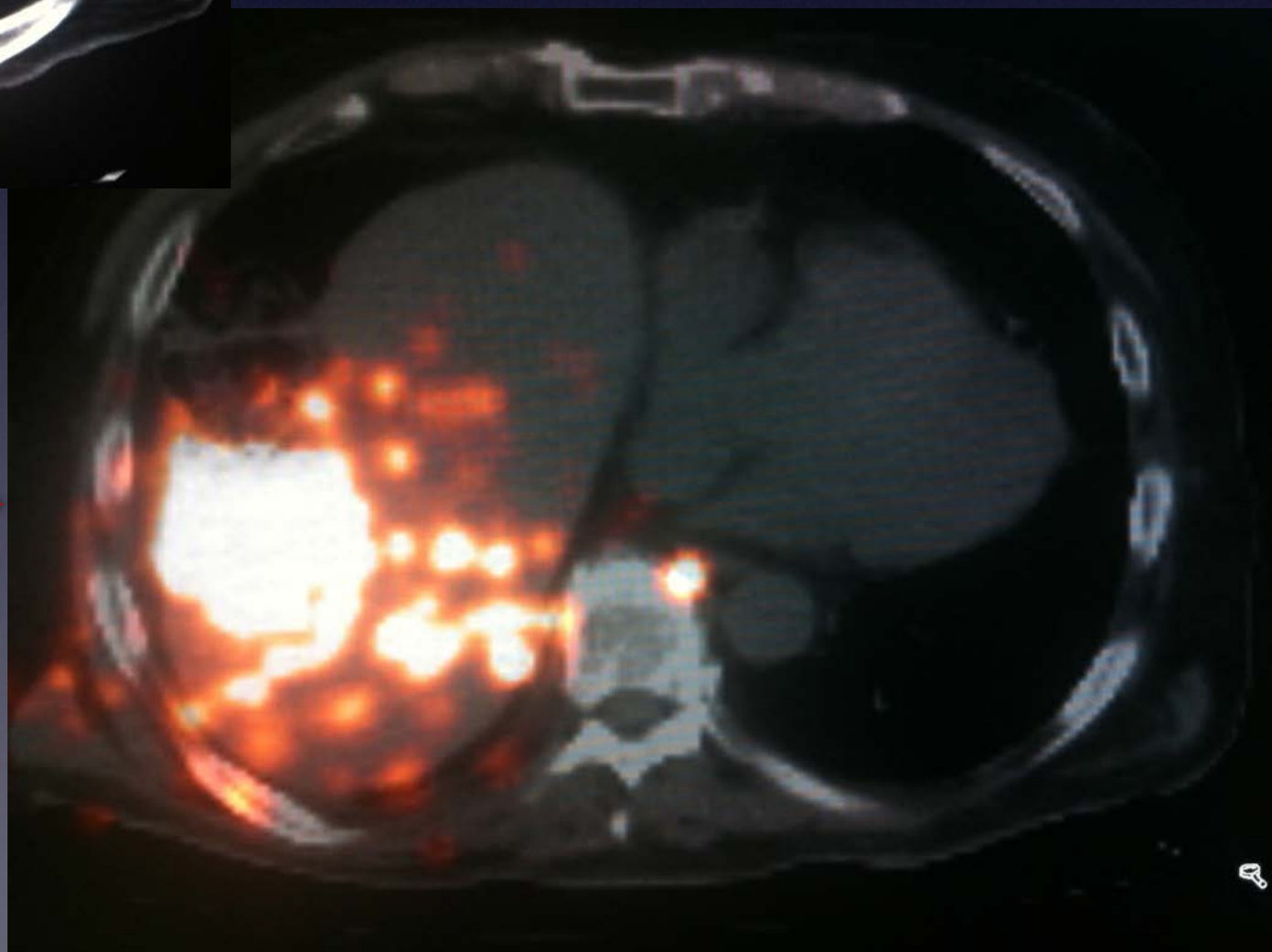
Angiogram with 99mTc MAA

MAA Scan
Evaluate Lung-Shunt fraction

Treat

Received
Y-90 TARE

Bremsstrahlung
Scan



TransArterial RadioEmbolization (TARE)

- Alternative to TACE
- Safe in Portal Vein invasion
- Similar survival data to conventional TACE
- Significantly reduced toxicity compared to TACE

Sorafenib

- Tyrosine Kinase Inhibitor
- Survival advantage for *advanced* metastatic HCC

Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP)

	Median OS	Median TTP
Sorafenib	10.7 months	5.5 months
Placebo	7.9 months	2.8 months

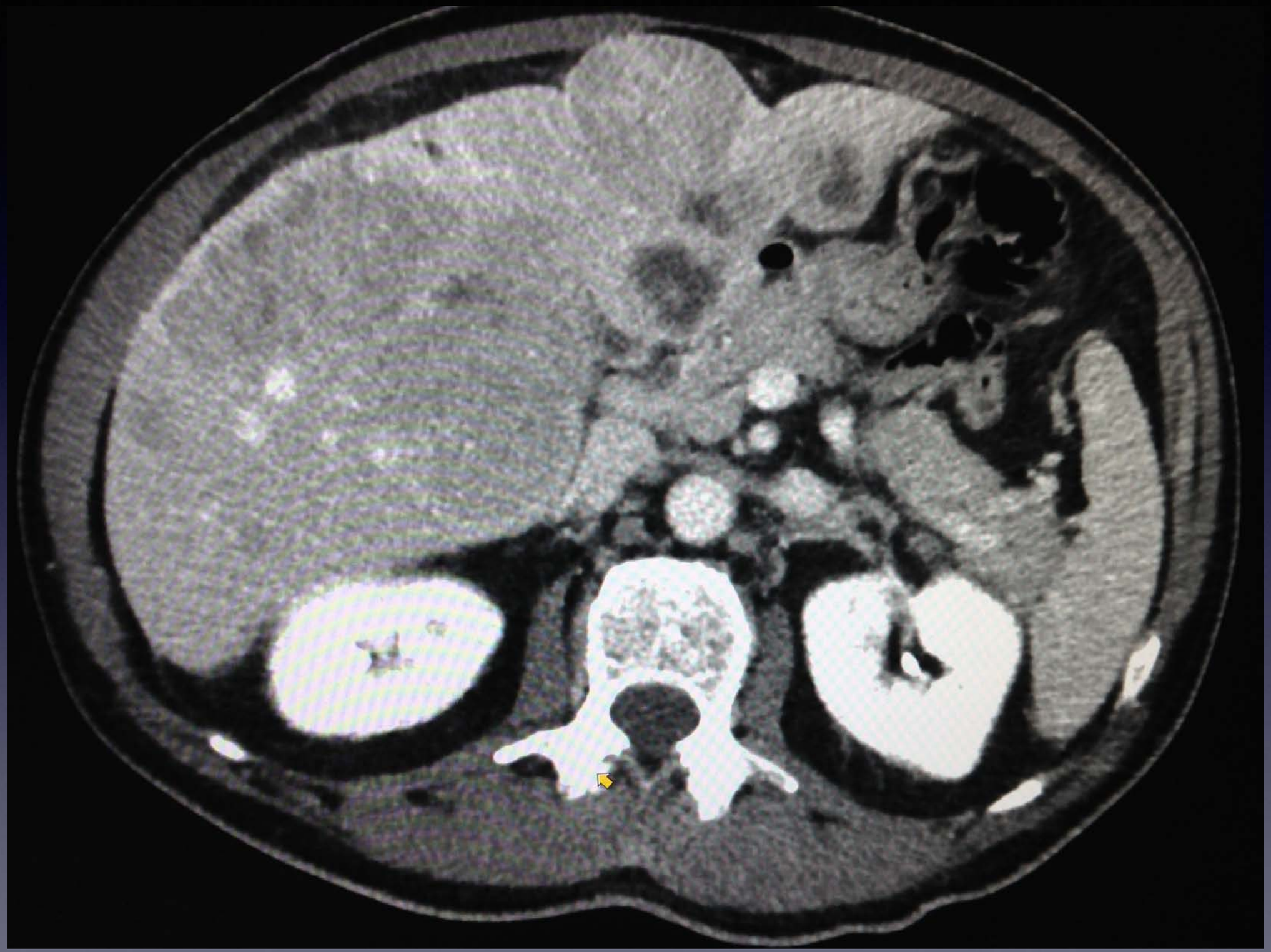
Sorafenib

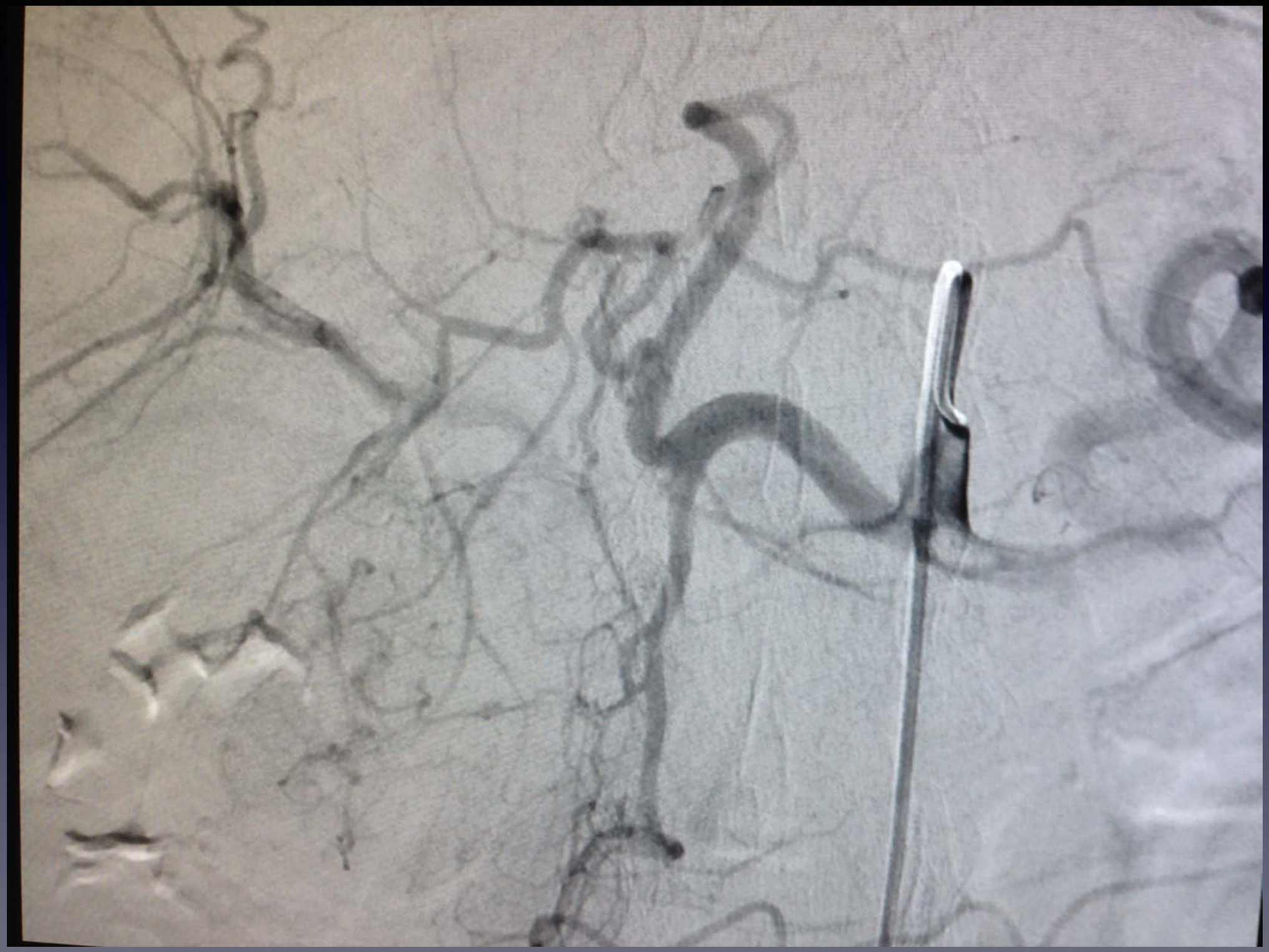
- Recommended for patients with:
  - Metastatic Disease
  - Not candidate for local or regional therapy
  - Progression following loco-regional therapy

(Level I evidence)

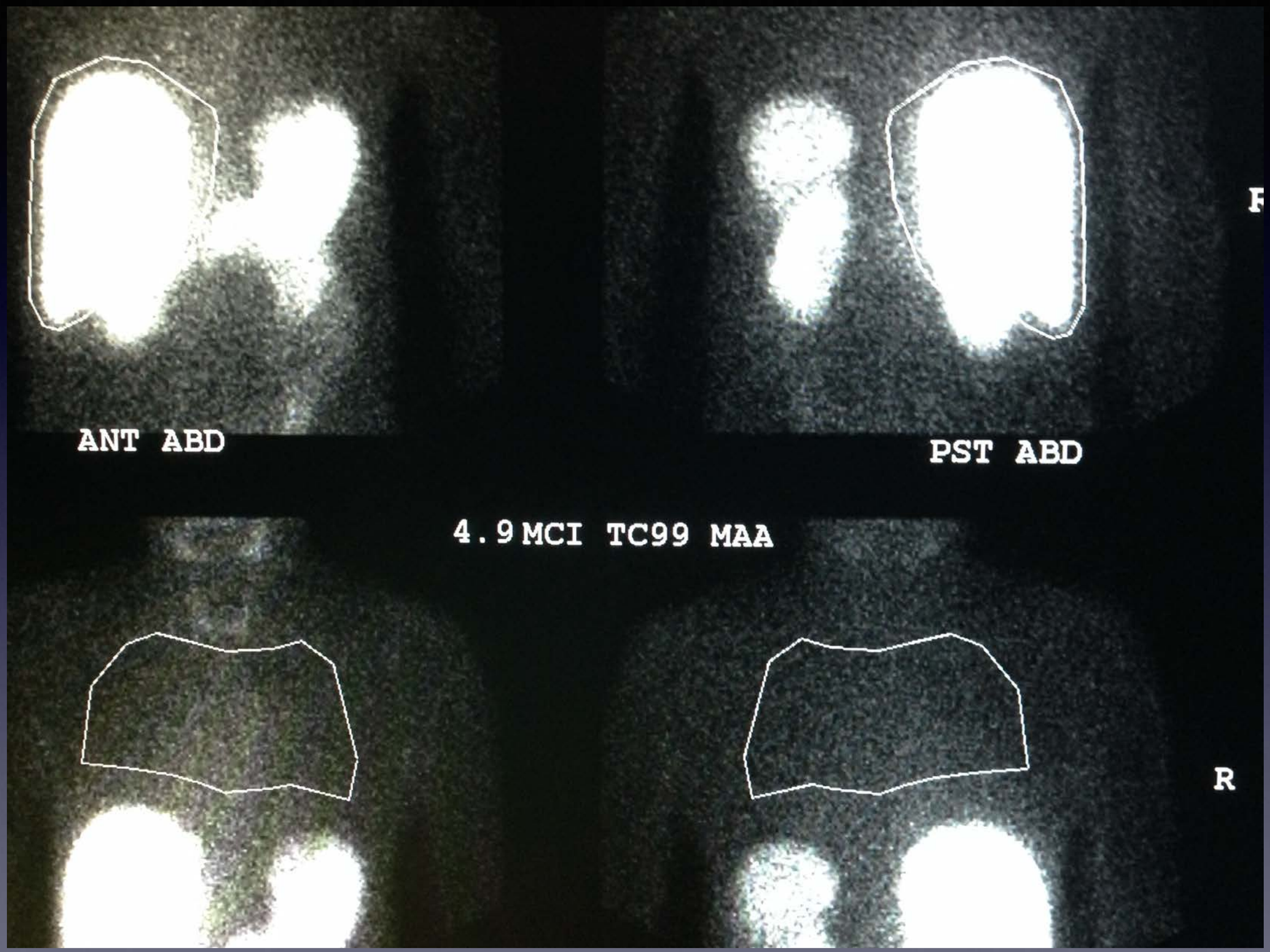
Neuroendocrine Tumor

- 60 years old man
- Metastatic Carcinoid Tumor
- Carcinoid Syndrome
- on monthly Sandostatin





MAA


ANT ABD
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4.9 MCI TC99 MAA
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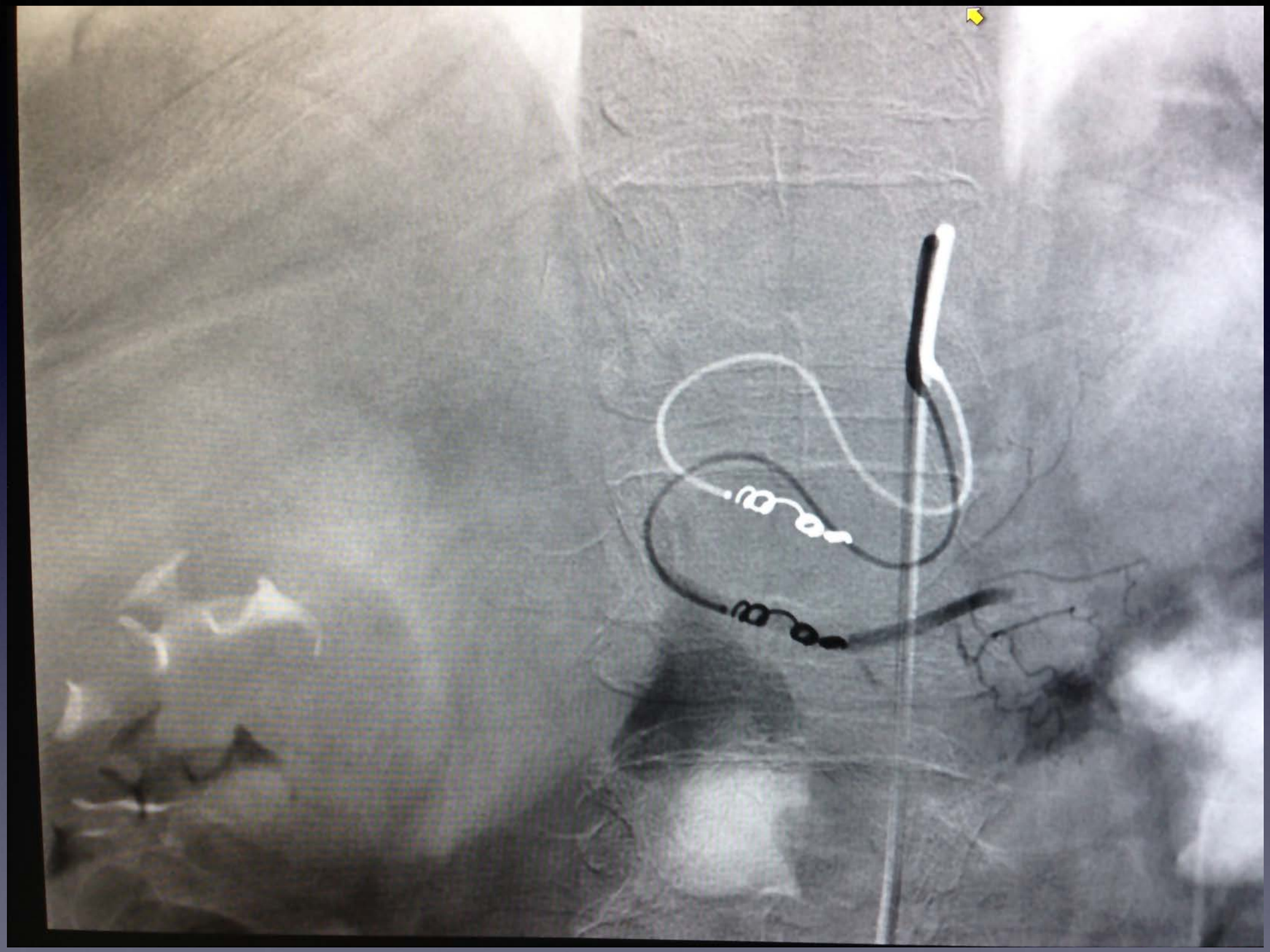

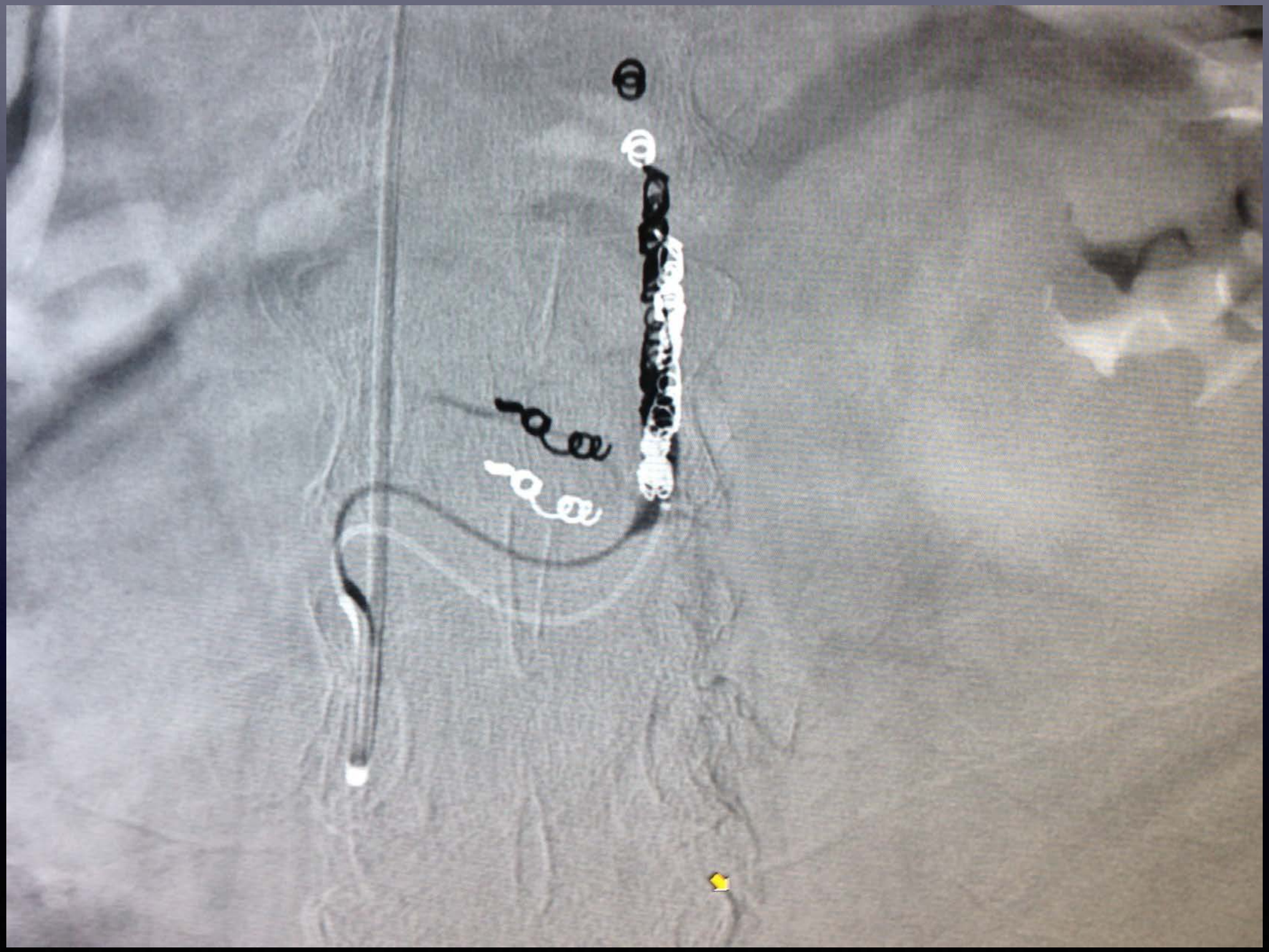

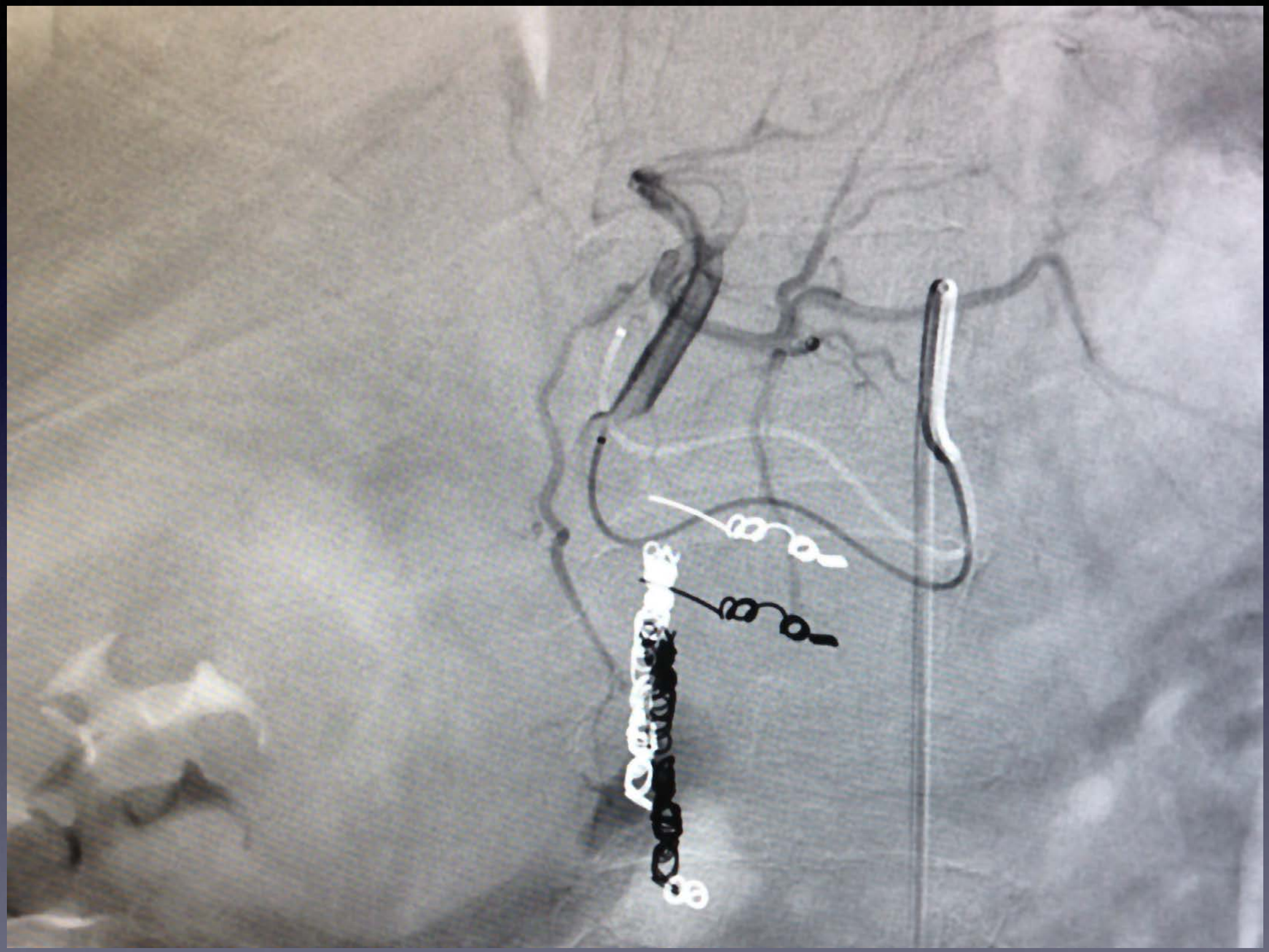

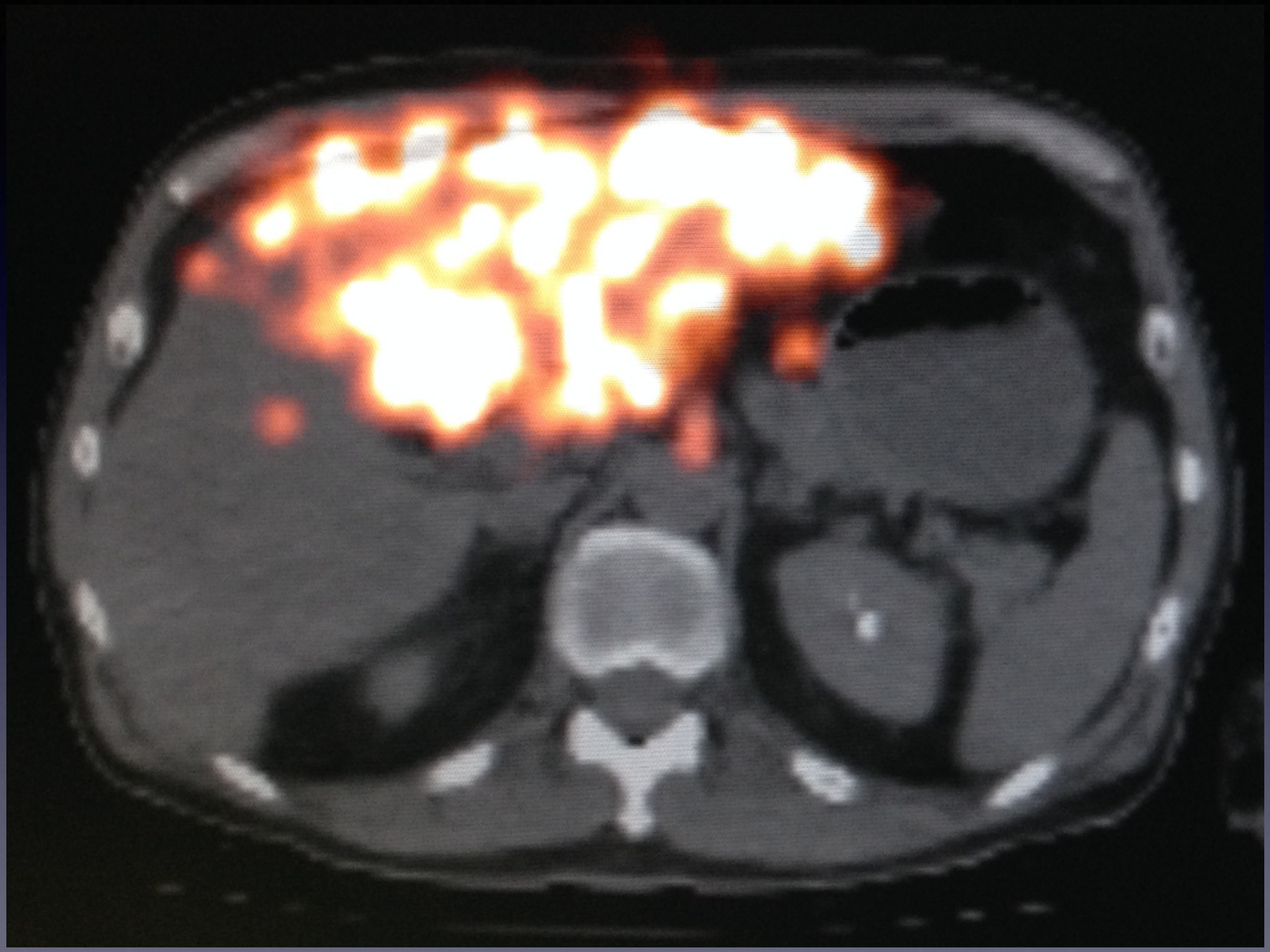

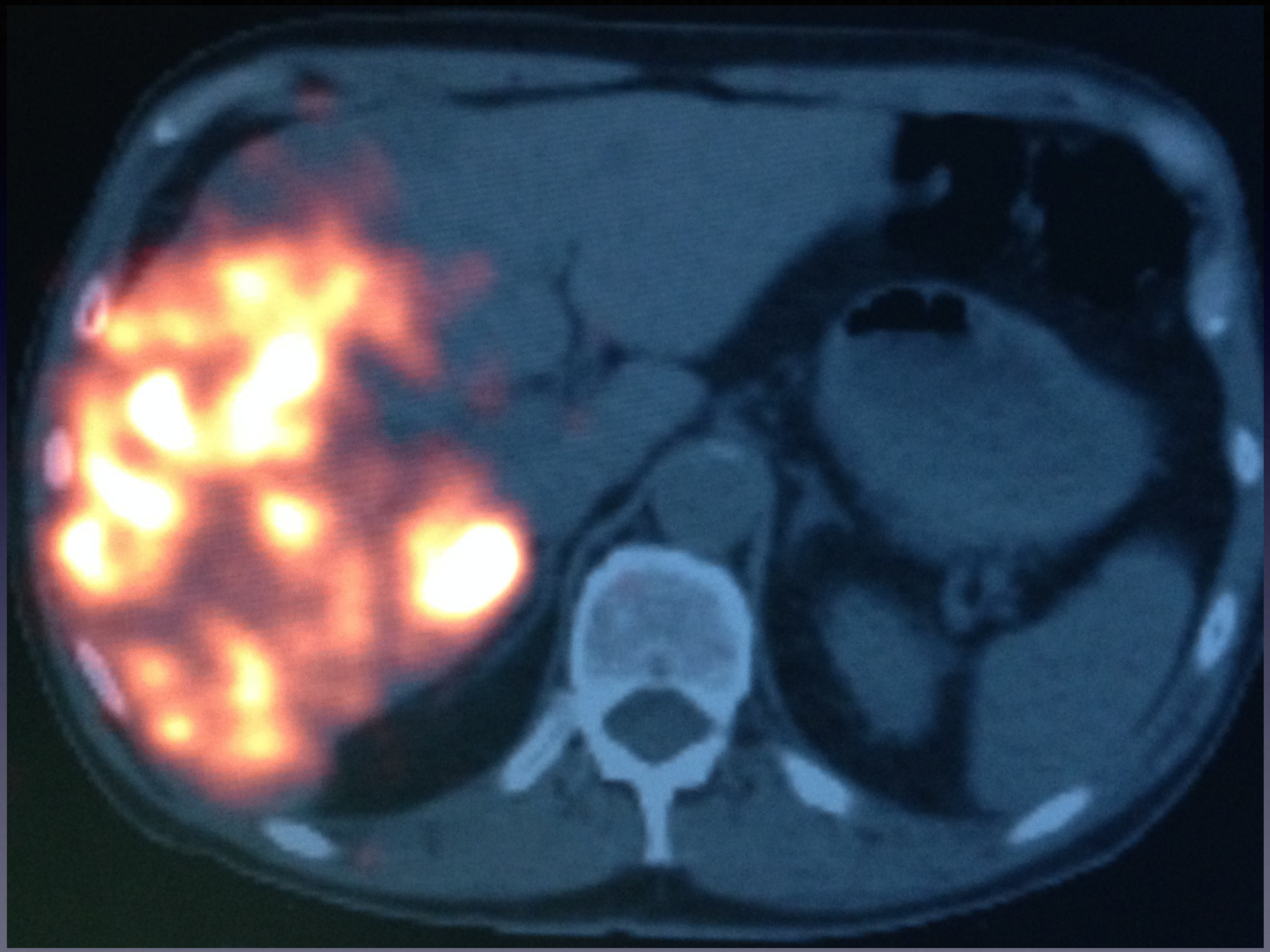

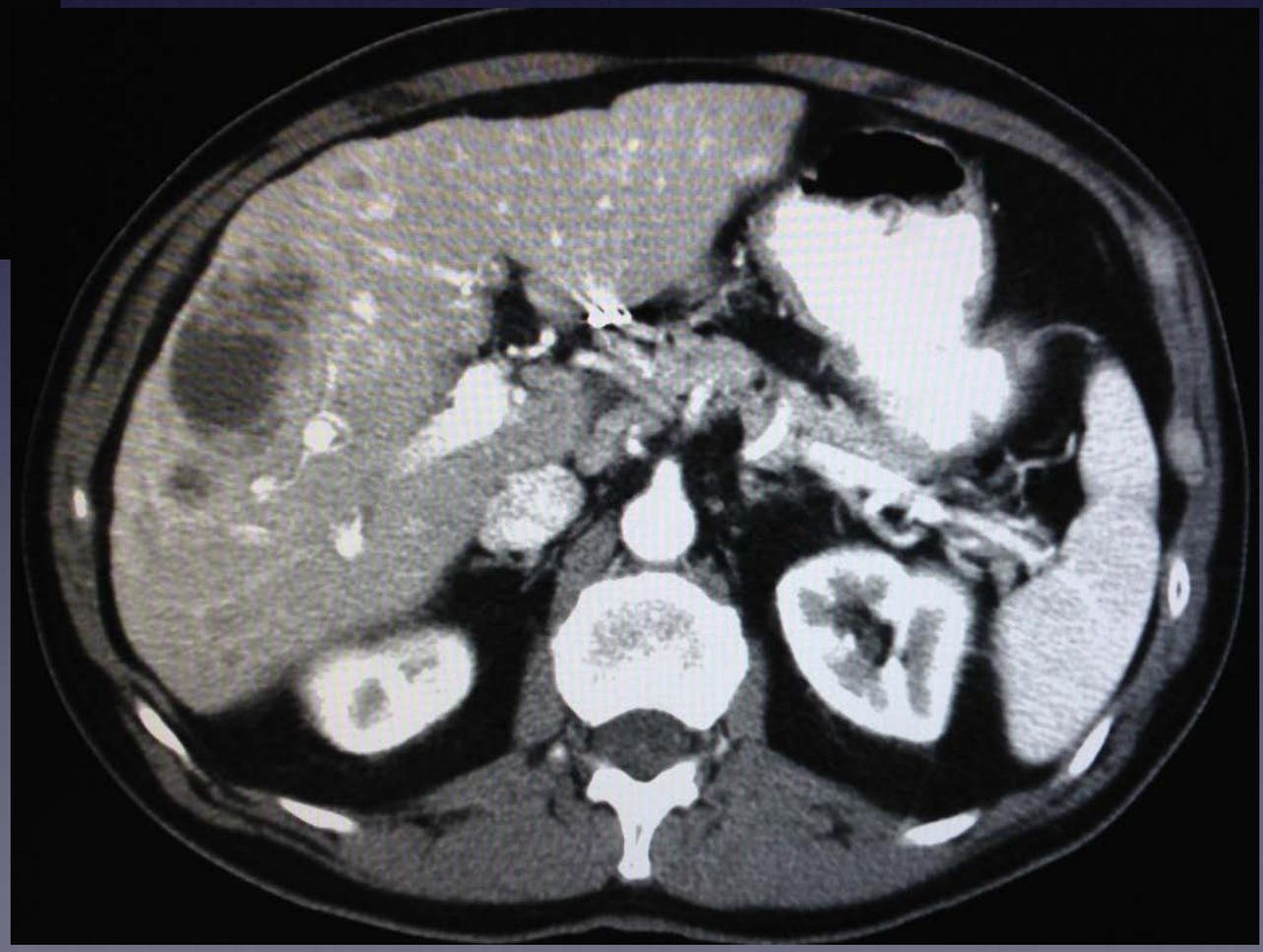

CRC Mets

CRC Mets

- Mainstay for *metastatic colon cancer* treatment is Systemic Therapy.

CRC Mets

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However . . .

CRC Mets

- Surgical Resection
  - Isolated hepatic metastases
    - Limited in Number
    - No major vascular involvement
    - Increase 5-year survival from 40% to 60%

CRC Mets

- Patient who are not surgical candidates
- 5-year survival rates following RFA approach surgical resection
  - Tumors < 4cm

CRC Mets

- RFA added to systemic chemotherapy for unresectable CRC mets

- increased median progression free survival by nearly 7 months (16.8 vs 9.9)

CRC Mets

- What about Regional Treatment for CRC Mets?
  - TACE/TARE?

Hepatic Intra-Arterial Injection of Drug-Eluting Bead, Irinotecan (DEBIRI) in Unresectable Colorectal Liver Mets Refractory to Systemic Chemotherapy: Results of Multi-Institutional Study

- Response rates of 66% at 6 months
- Overall survival 19 months
- Progression free survival 11 months

Robert C. et al., Annals of Surgical Oncology (2011) 18:192-198.

Hepatic Intra-Arterial Injection of Drug-Eluting Bead, Irinotecan (DEBIRI) in Unresectable Colorectal Liver Mets Refractory to Systemic Chemotherapy: Results of Multi-Institutional Study

- DEBIRI was safe and effective in treatment of metastatic colorectal cancer refractory to multiple lines of systemic therapy.

Robert C. et al., Annals of Surgical Oncology (2011) 18:192-198.

CRC Mets

- Randomized Phase III Trial of DEBIRI TACE v. FOLFIRI
- Prolonged OS (22 months v. 15 months)
- Progression Free Survival (7 months v. 4 months)
- Extrahepatic Progression (13 months vs. 9 months)

Giammaria et al., Intra-arterial Infusion of Irinotecan-loaded Drug-eluting Beads (DEBIRI) versus Intravenous Therapy (FOLFIRI) for Hepatic Metastases from Colorectal Cancer: Final Results of a Phase III Study

CRC Mets TARE?

- Addition of Y-90 TARE to 2nd and 3rd line Systemic Chemotherapy
    - significantly prolonged TTP
        - 15.9 months v. 9.7 months
    - longer median survival
        - 29.4 months v 12.8 months

First Line Y90 for CRC?

First-line selective radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicenter, randomized, phase 3 trials

Harpeet, et al…, Lancet Oncology, 2017 Sept; 18(9): 1159-1171

FoxFire Combined

- SIRFLOX
- FOXFIRE
- FOXFIRE - Global

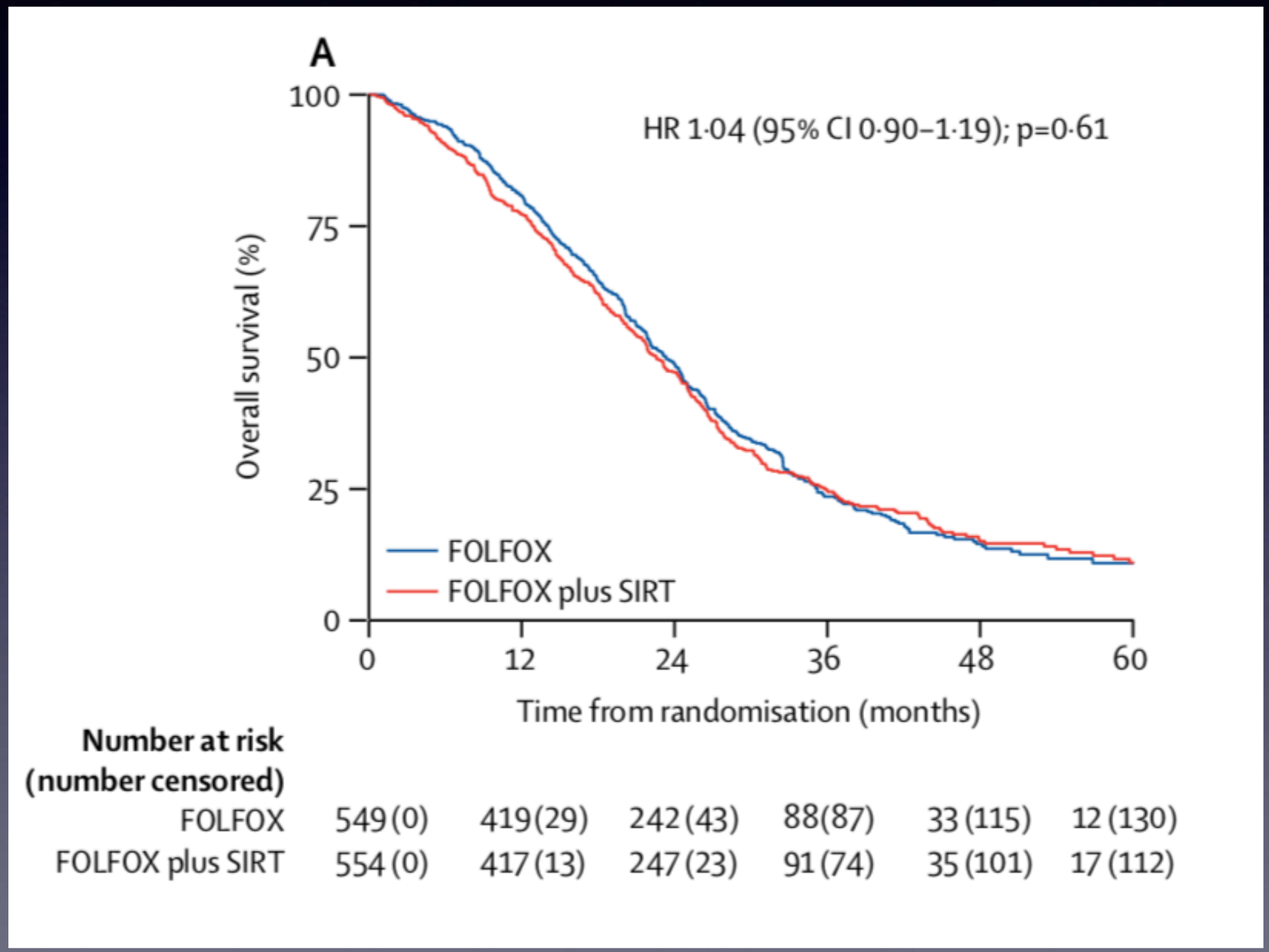
FoxFire Combined

- 1,103 Patients
- ITT
- Liver dominant +/- extrahepatic mets

FoxFire Combined

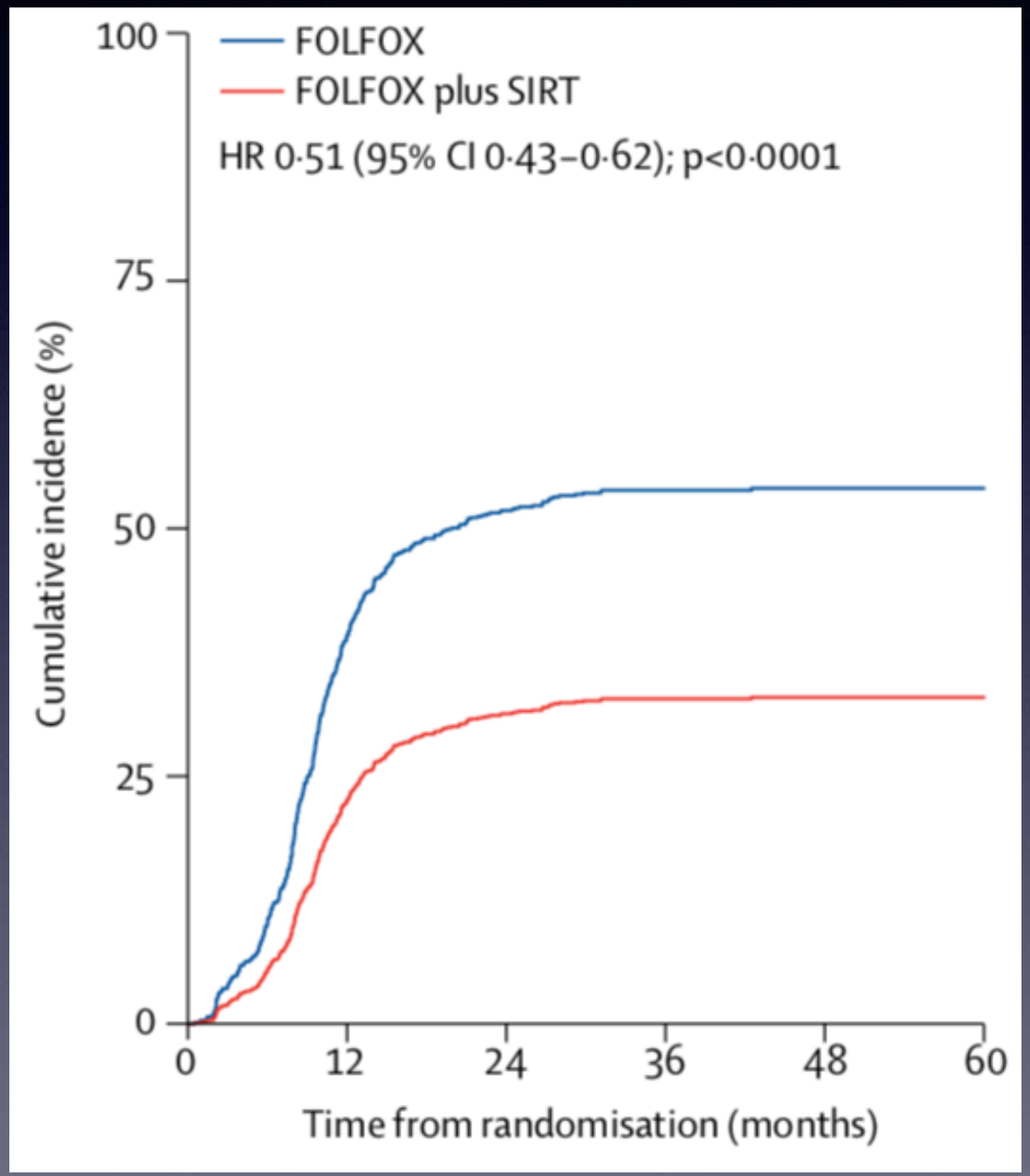
- mFOLFOX (+/- Bevacizumab)
- mFOLFOX (+/- Bevacizumab) + TARE

FoxFire Combined



Number at risk (number censored)						
FOLFOX	549 (0)	419 (29)	242 (43)	88 (87)	33 (115)	12 (130)
FOLFOX plus SIRT	554 (0)	417 (13)	247 (23)	91 (74)	35 (101)	17 (112)

FoxFire Combined



FoxFire Combined

- Objective (complete or partial) response
  - 400 / 554 (72%) – Folfox + SIRT
  - 346 / 529 (63%) – Folfox alone
    - P=0.001

FoxFire Combined

- Right sided primary Colon Cancer
  - FOLFOX + SIRT
    - Increased OS by 4.9 months
    - Decreased risk of death at any time point by 36%
      - P=0.007

CRC Mets to Liver

- Select patients can benefit
- Local Ablation
- Regional Treatment (TACE/TARE)

Conclusion

- Patient selection is key
- Interventional Radiologist has a lot to offer your oncology patients
- Make sure your IR is involved in MMC