Locoregional Therapy for Liver Malignancies

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Disclosures

- Consultant: Boston Scientific, TriSalus, AstraZeneca, Sirtex, ABK, Replimune, Guerbet

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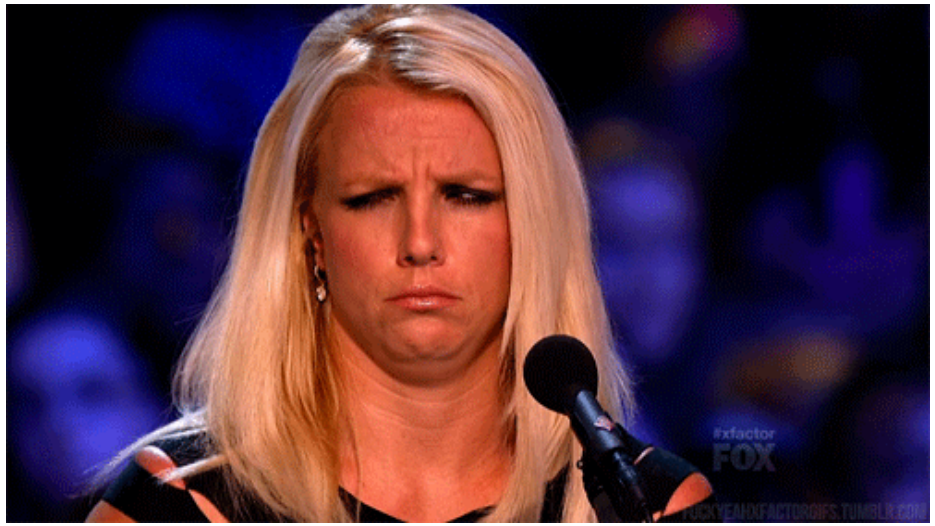
What can we treat? Just about anything!

The Key Concept is where IR fits

- Locoregional Treatment Options
  - Ablation
    - Fire and Ice
    - Newer tech
  - Intra-arterial options
    - Radioembolization
    - Chemoembolization/Bland Embolization
  - New Horizon Modalities
    - PEF
    - IRE
    - PHP
    - Histotripsy

The Key Concept is where IR fits

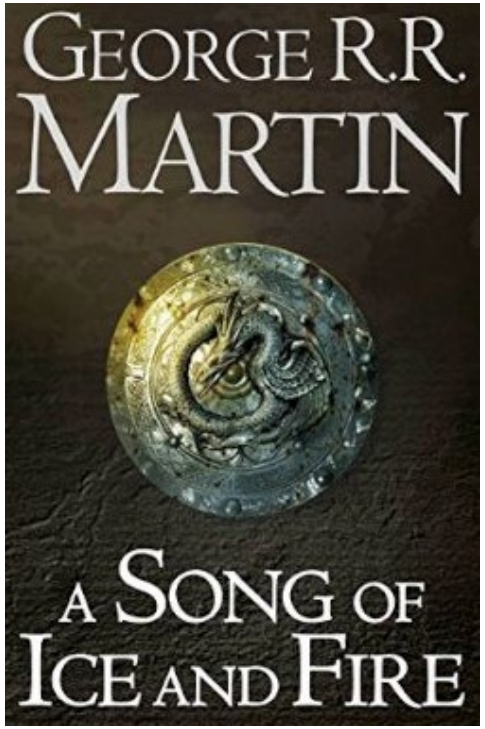
- Rationale for Therapy
  - Evidence for Ablation
    - HCC
    - mCRC
  - Evidence for Y90
    - HCC
    - mCRC
  - Evidence for TACE
    - mNET
  - Evidence for combination therapy
    - HCC
  - Case Examples



Thermal Ablation

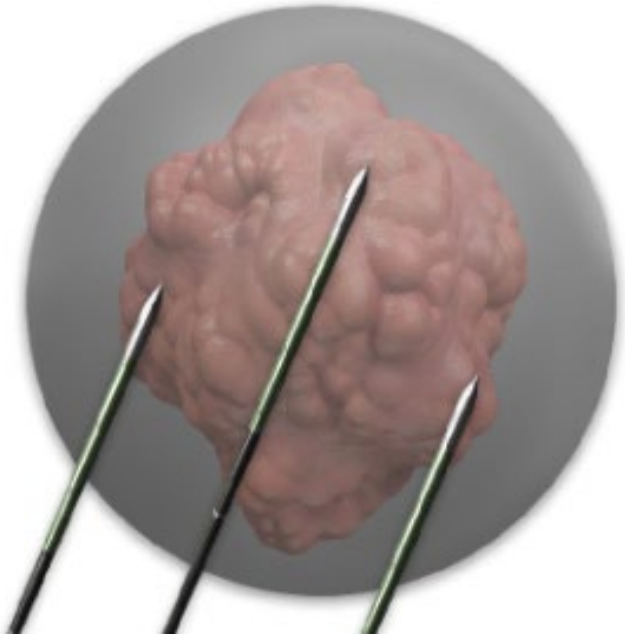
- Can be utilized for curative and bridging treatments in HCC or isolated metastatic disease to the liver

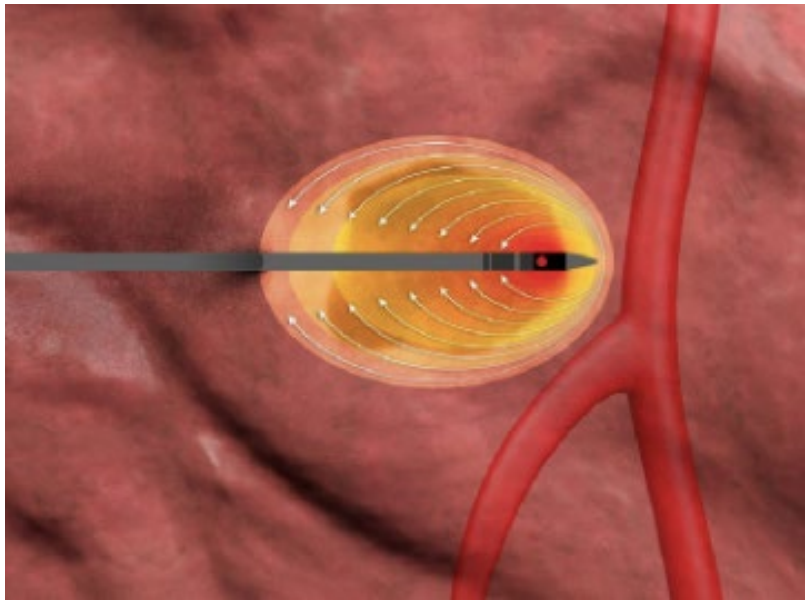
- Radiofrequency Ablation
- Microwave Ablation
- Cryoablation

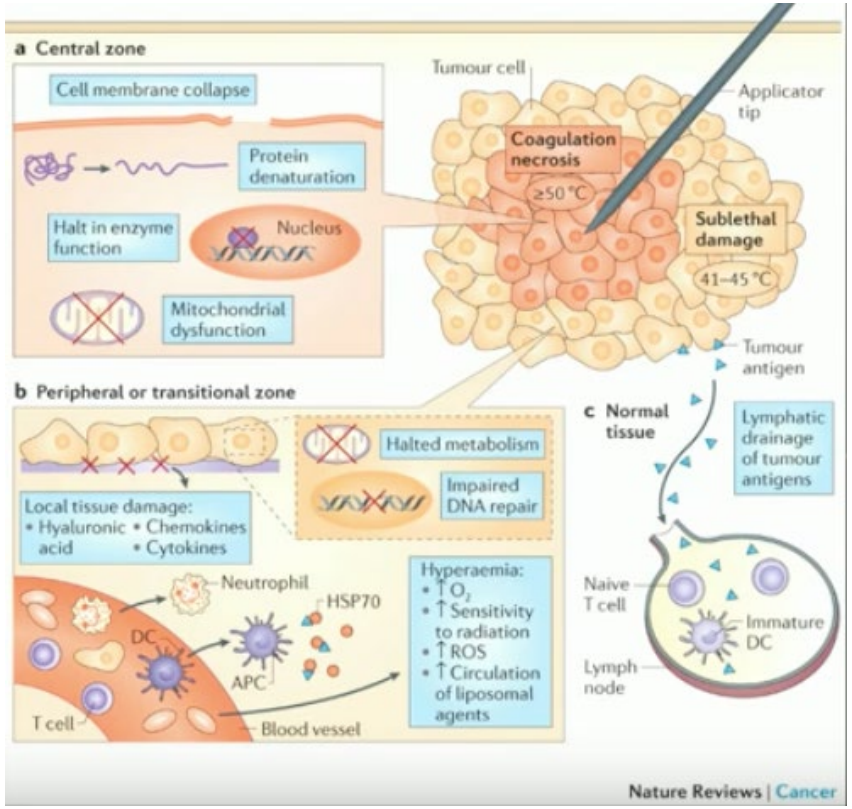


Thermal Ablation

- Microwave Ablation
  - Utilizes dielectric hysteresis (water molecules continuously realign with the electric field to produce heat)
  - Produces high temperatures (>60 degrees Celsius), resulting in coagulative necrosis.







Thermal Abla

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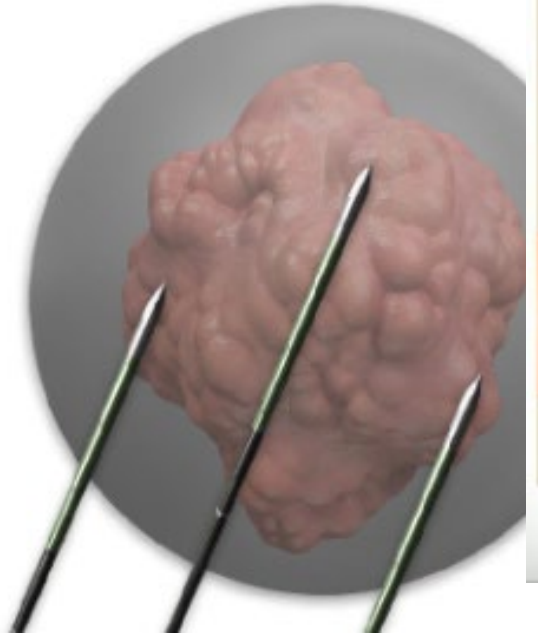
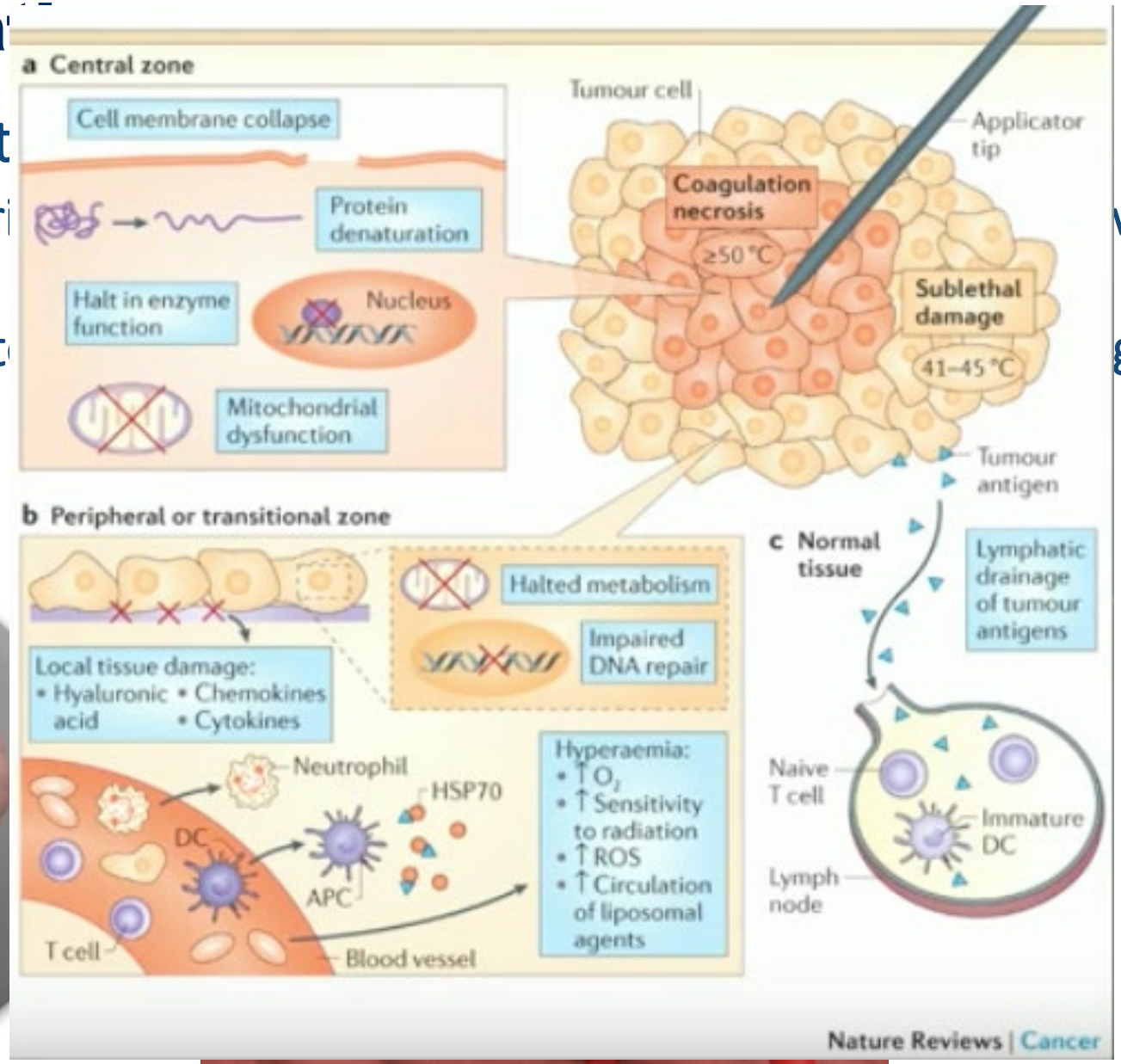
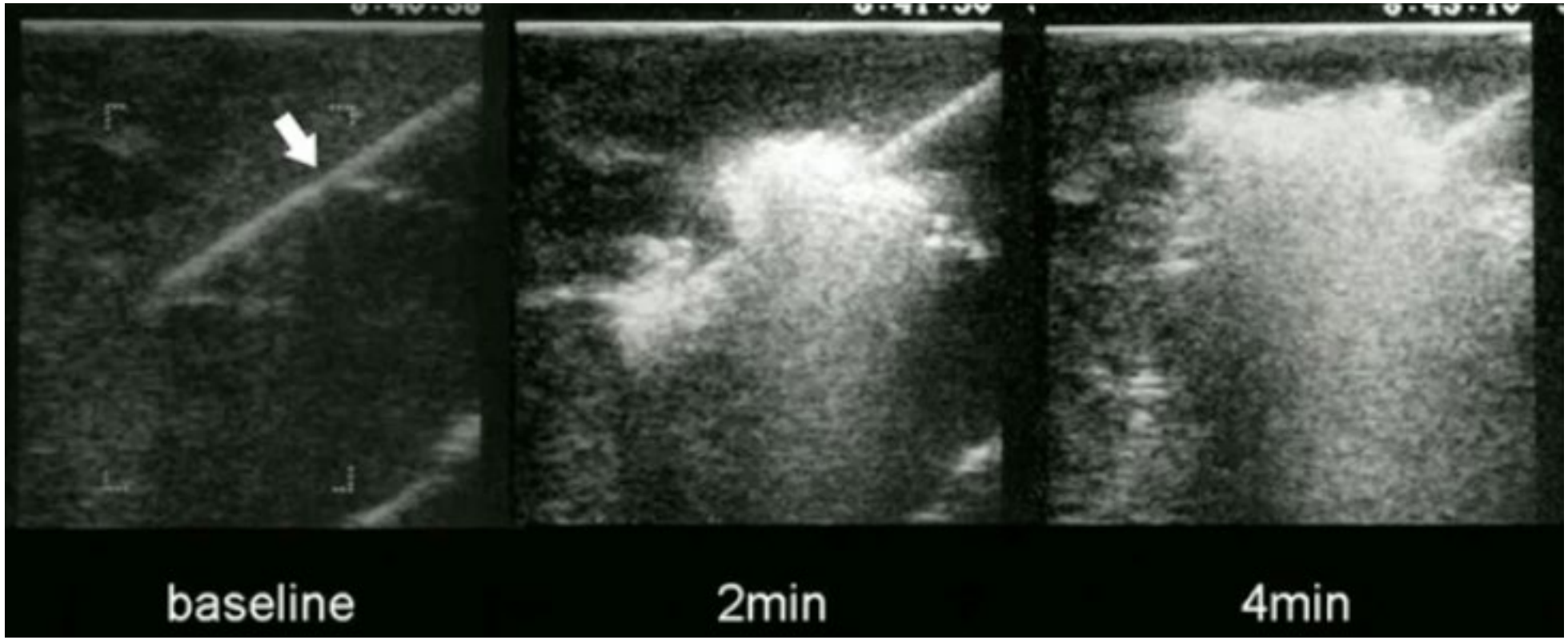




Thermal Ablation for HCC



Ablation vs Surgery

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ⩽3 cm. Results of a multicenter Italian survey

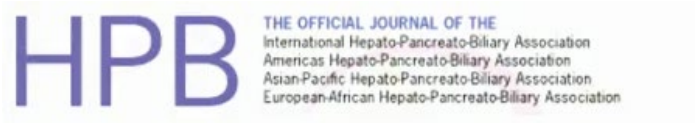
Maurizio Pompili[1,*], Antonio Saviano[1], Nicoletta de Matthaeis[1], Alessandro Cucchetti[2], Francesco Ardito[3], Bruno Federico[4], Franco Brunello[5], Antonio D. Pinna[2], Antonio Giorgio[6], Stefano M. Giulini[7], Ilario De Sio[8], Guido Torzilli[9], Fabio Fornari[10], Lorenzo Capussotti[11], Alfredo Guglielmi[12], Fabio Piscaglia[13], Luca Aldrighetti[14], Eugenio Caturelli[15], Fulvio Calise[16], Gennaro Nuzzo[3], Gian Ludovico Rapaccini[1], Felice Giuliante[3]

- 544 patients, HCC ≤3 cm, CP A
  - SR: 246
  - RFA: 298
- No difference in 4-yr OS (74.4% and 66.2%, p=0.353)
- No difference in cumulative HCC recurrence (56% vs 57.1%, p=0.765)
- Conclusion: Despite a higher rate of local tumor progression with RFA, RFA provides long-term outcomes similar to surgical resection.

2 more studies supporting ablation vs surgery

Radiofrequency ablation compared to resection in early-stage hepatocellular carcinoma

Samer Tohme[1], David A. Geller[1], Jon S. Cardinal[1], Hui-Wei Chen[1], Vignesh Packiam[1], Srinevas Reddy[1], Jennifer Steel[1,2], James W. Marsh[1] & Allan Tsung[1]



- Conclusion: RFA is comparable to surgical resection in terms of OS and DFS with shorter LOS and fewer post-operative complications.

Radiofrequency Ablation versus Hepatic Resection for the Treatment of Hepatocellular Carcinomas 2 cm or Smaller: A Retrospective Comparative Study

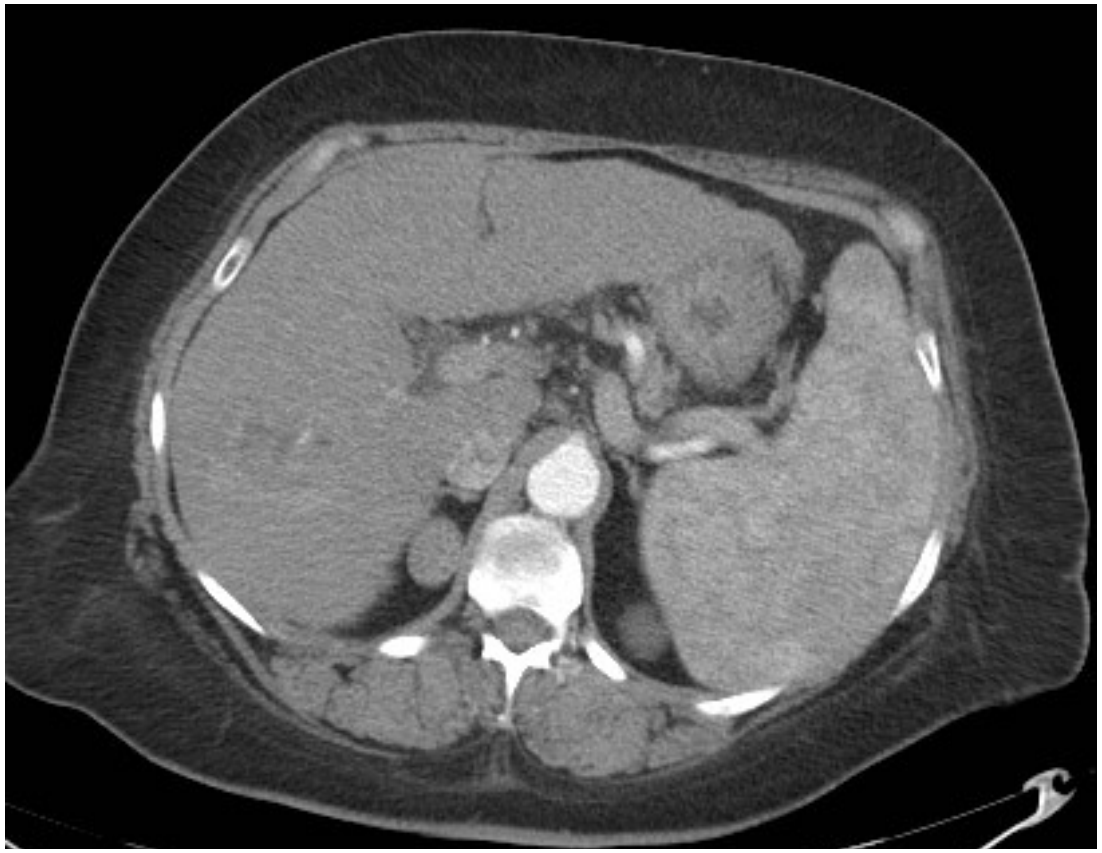
Zhen-Wei Peng, MD, Xiao-Jun Lin, MD, Yao-Jun Zhang, MD, Hui-Hong Liang, MD, Rong-Ping Guo, MD, Ming Shi, MD, and Min-Shan Chen, MD, PhD

- Conclusion: RFA provides better OS and RFS than surgical resection, with fewer major complications, compared to surgical resection, particularly for central tumors.

Ablation Case Example

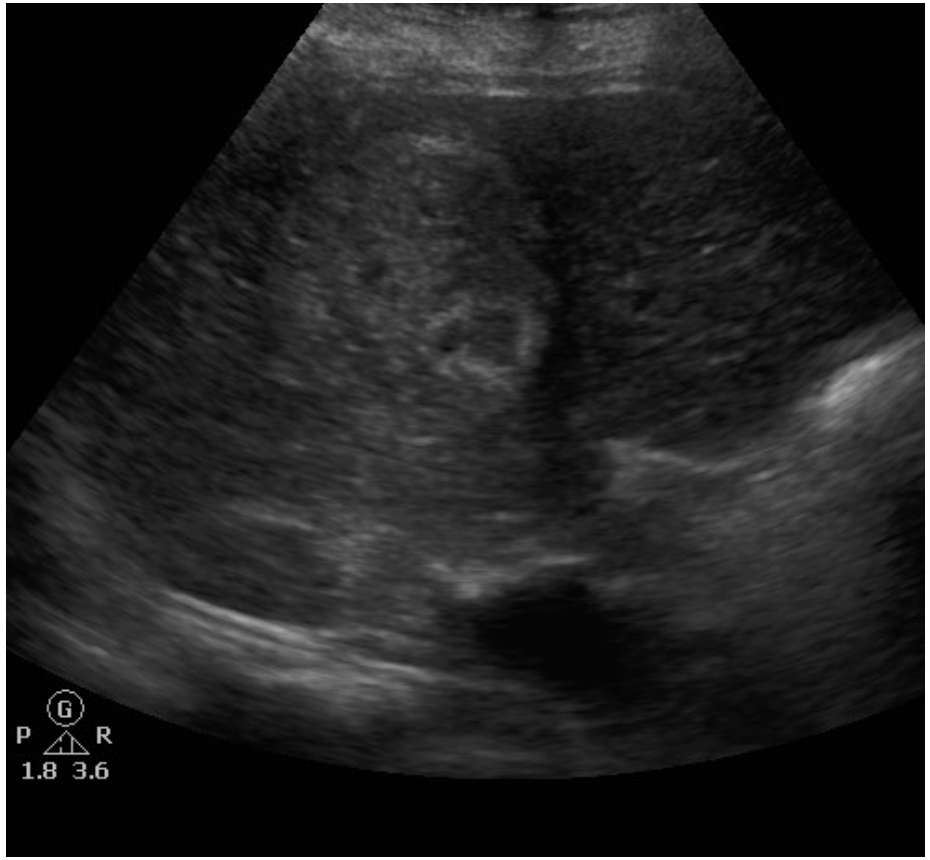
- 54 year old female with history of HCV and a 7 cm HCC diagnosed by imaging.

- CP- A, MELD - 8, ECOG- 0, tbili – 1.2, AFP – 4000, remaining labs WNL

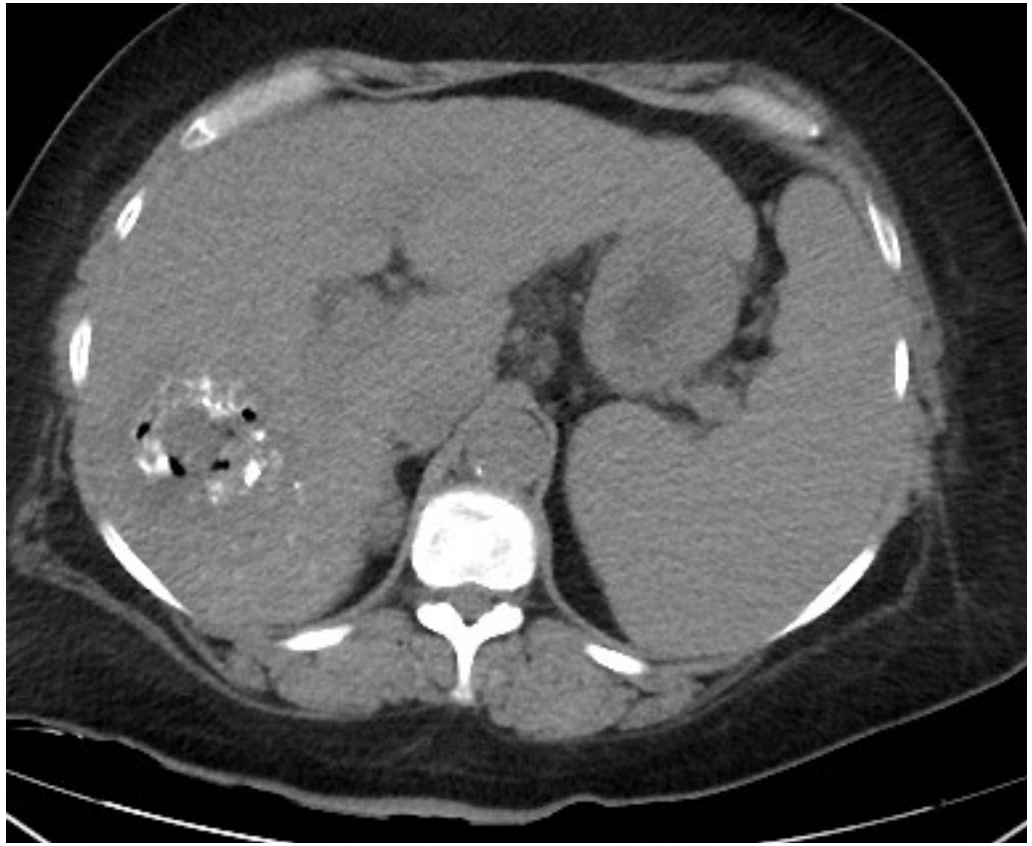


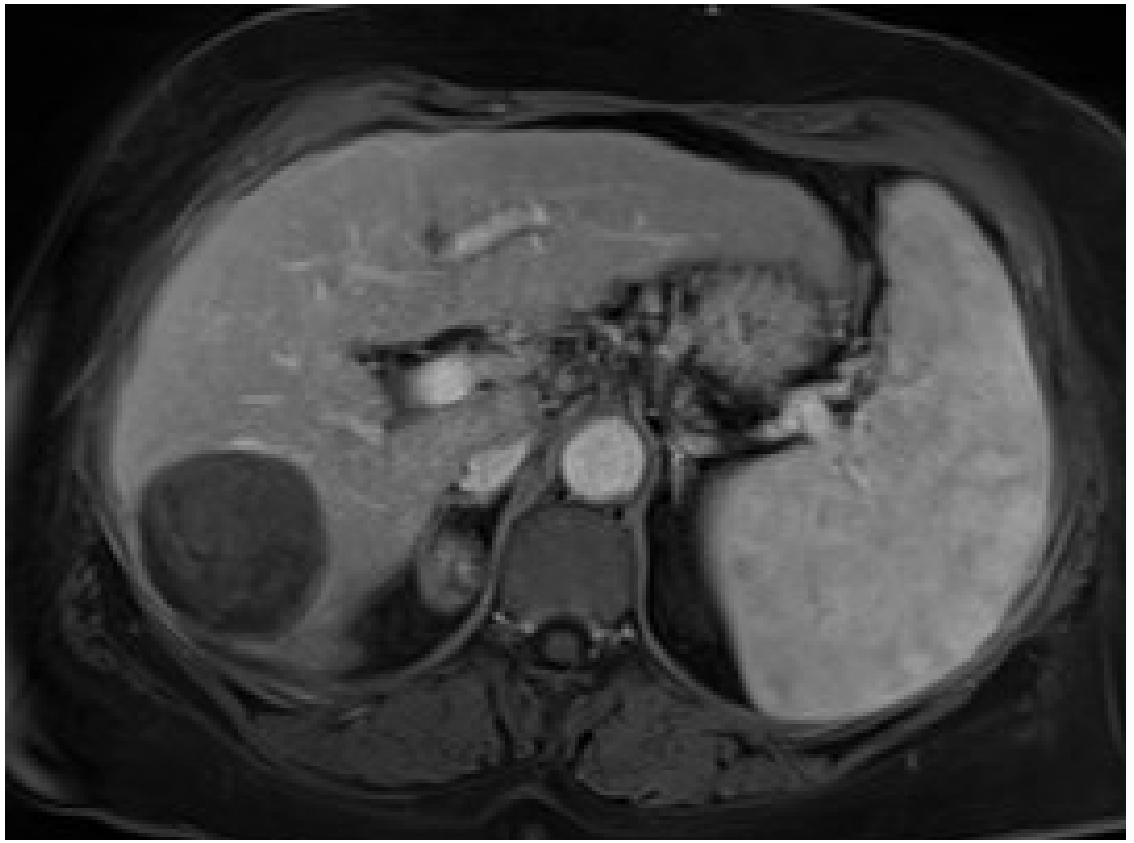
Patient initially treated with TAE with LUMI Beads

Pre- Ablation Images



Immediate Post- Ablation CT with gas deposition within lesion on left and 3 month MRI on right





Patient Follow – Up

- This patient was initially considered for right hepatectomy however due to splenic size as well as underlying cirrhosis, referred for locoregional therapy first.

- TAE/Ablate strategy resulted in good radiographic response with AFP dropping from 4000 to 9.

Ablation for unresectable mCRC CLOCC Trial

- Randomized Phase II Trial
  - Systemic therapy plus aggressive local therapy with ablation +/- surgery vs systemic therapy alone
  - 119 patients from 22 hospitals from 2002-2007
  - Similar OS at 3 years
    - 61.7% vs 57.6%
  - Median OS
    - 45.3 months in combination arm vs 40.5 months for systemic (p=0.22)
  - PFS at 3 years
    - 27.6% in combination arm vs 10.6% in systemic arm (p=0.025)

- But things get interesting if you keep looking…

Ann Oncol. 2012 Oct;23(10):2619-2626.

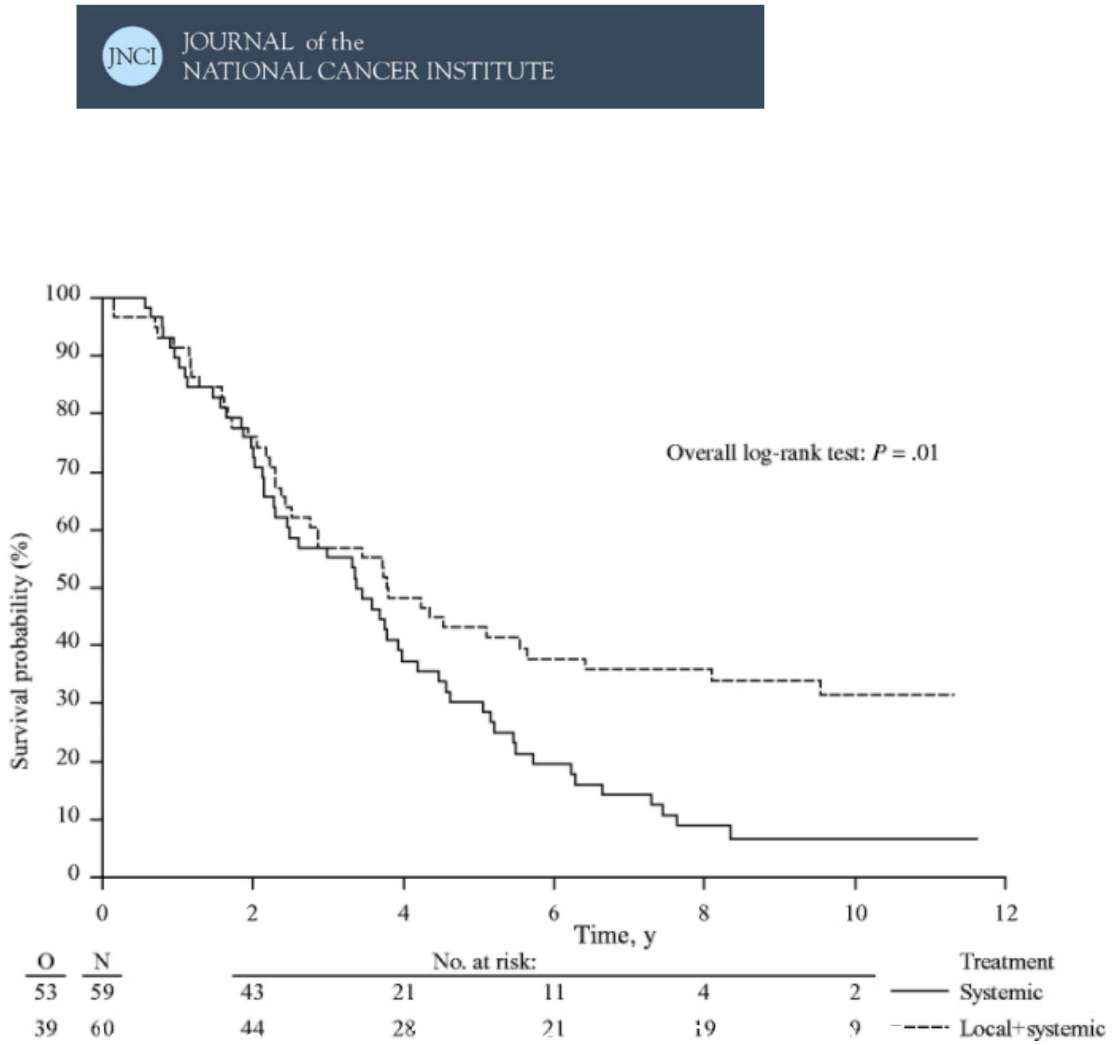
CLOCC Trial

J Natl Cancer Inst. 2017 Mar 17;109(9):djx015. doi: 10.1093/jnci/djx015

Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial

Theo Ruers [1,✉], Frits Van Coevorden [1], Cornelis J A Punt [1], Jean-Pierre E N Pierie [1], Inne Borel-Rinkes [1], Jonathan A Ledermann [1], Graeme Poston [1], Wolf Bechstein [1], Marie-Ange Lentz [1], Murielle Mauer [1], Gunnar Folprecht [1], Eric Van Cutsem [1], Michel Ducreux [1], Bernard Nordlinger [1]; for the European Organisation for Research and Treatment of Cancer (EORTC)[1]; Gastro-Intestinal Tract Cancer Group[1]; Arbeitsgruppe Lebermetastasen und tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO)[1]; and the National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG)[1]

- Median follow-up of 9.7 years, 35% of patients in the combination arm still alive vs 10.2% in the systemic only arm (p=0.01)
- Key Takeaway: Aggressive local treatment can prolong OS in patients with unresectable mCRC.



Ablation for unresectable mCRC COLLISION Trial

Thermal ablation versus surgical resection of small-size colorectal liver metastases (COLLISION): an international, randomised, controlled, phase 3 non-inferiority trial

Susan van der Lei, MD [a,e,v,*] · Robbert S Puijk, MD PhD [a,e,f,*] · Madelon Dijkstra, MD PhD [a,e] · Hannah H Schulz, MD [a,e] · Danielle J W Vos, MD [a,e] · Jan J J De Vries, MD [f] · et al. Show more

THE LANCET Oncology

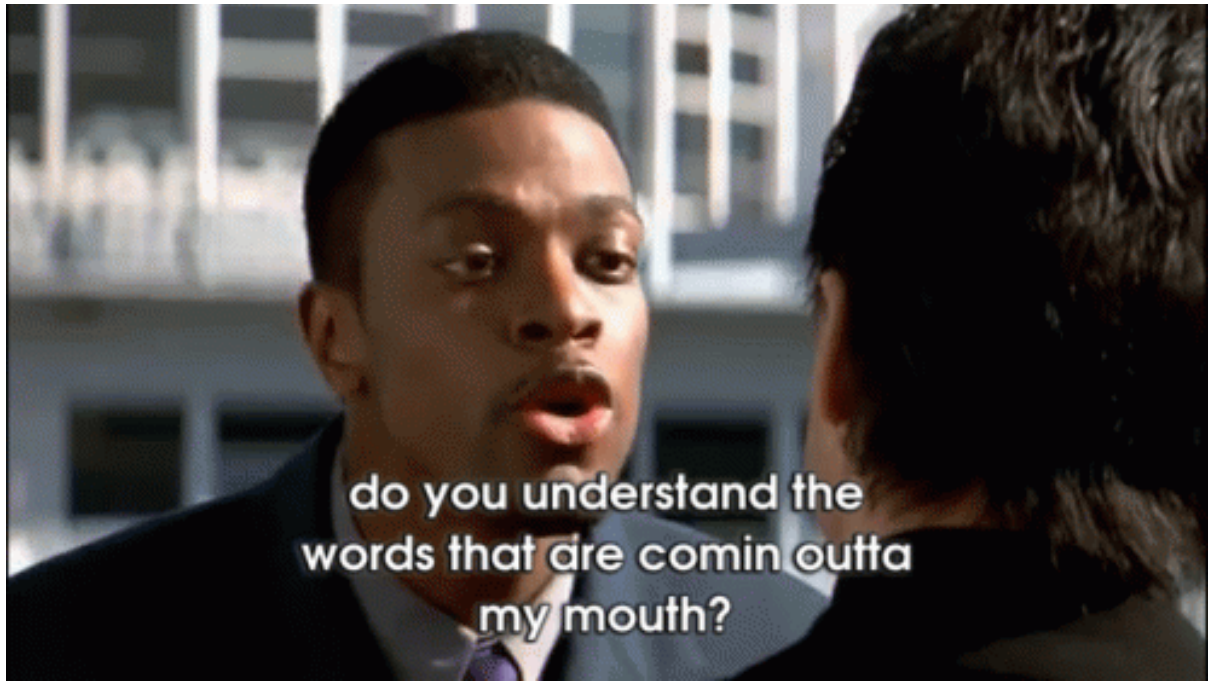
- Phase 3, international, randomized, controlled non-inferiority study
- ≤ 10 resectable liver metastases (≤ 3cm), no extrahepatic disease
- Patients randomized to thermal ablation or surgical resection
- Primary Endpoint: Overall Survival
  - Trial stopped early after interim analysis (met non-inferiority and safety criteria)

mCRC COLLISION Trial Key Findings

- Median OS not reached in either group
- Non-inferiority: Thermal ablation vs resection (HR 1.05; 95% CI 0.69-1.58; p=0.83)
- Local control: Non-inferior
- Adverse Events:
  - Thermal ablation: 19%
  - Resection: 46%
- Serious AEs:
  - Thermal ablation: 7%
  - Resection: 20%
- Hospital stay: shorter with ablation
- Procedure-related morbidity: lower with ablation

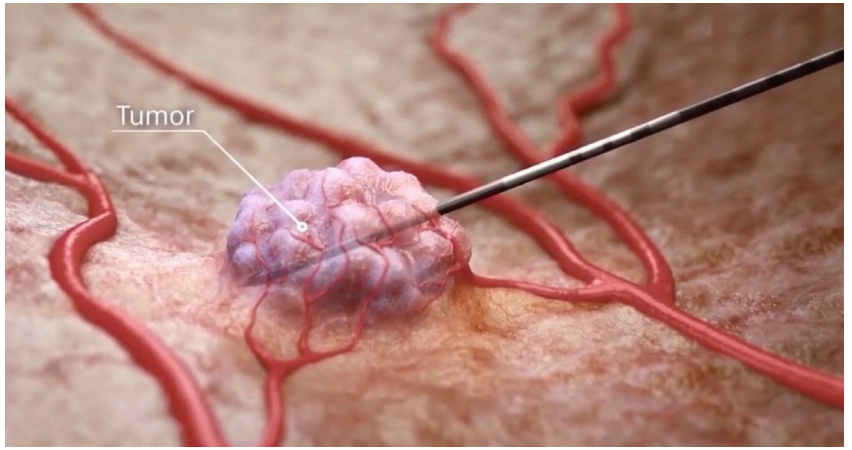
mCRC COLLISION Clinical Implications

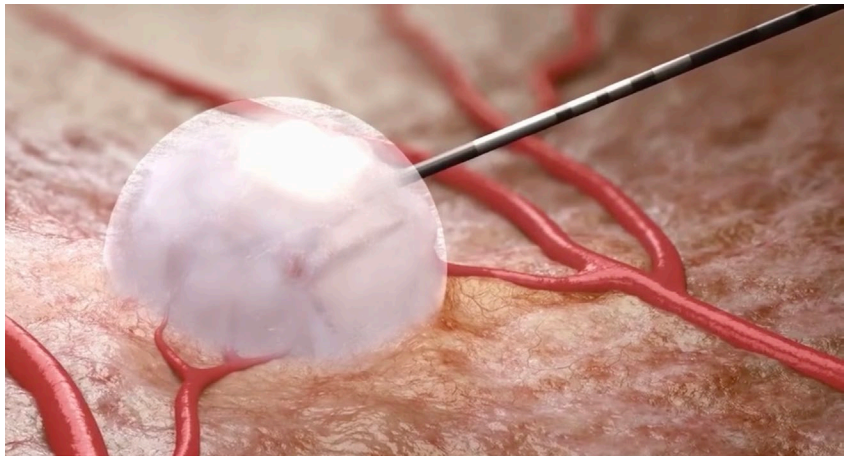
- Thermal ablation: valid, less invasive alternative to resection for small-size mCRC
- Oncologic outcomes: Comparable survival and local control
- Safety: Improved profile with fewer complications and shorter recovery



Cryoablation

- Like MWA, minimally invasive ablative modality
- Utilizes the Joule-Thompson effect to create rapid freeze/thaw cycles that cause cellular damage and vascular stasis
- Results in targeted cell death while preserving health surrounding tissue





Cryoablation vs MWA

Multicenter randomized controlled trial of percutaneous cryoablation versus radiofrequency ablation in hepatocellular carcinoma

Randomized Controlled Trial > Hepatology. 2015 May;61(5):1579-90. doi: 10.1002/hep.27548. Epub 2015 Mar 20.

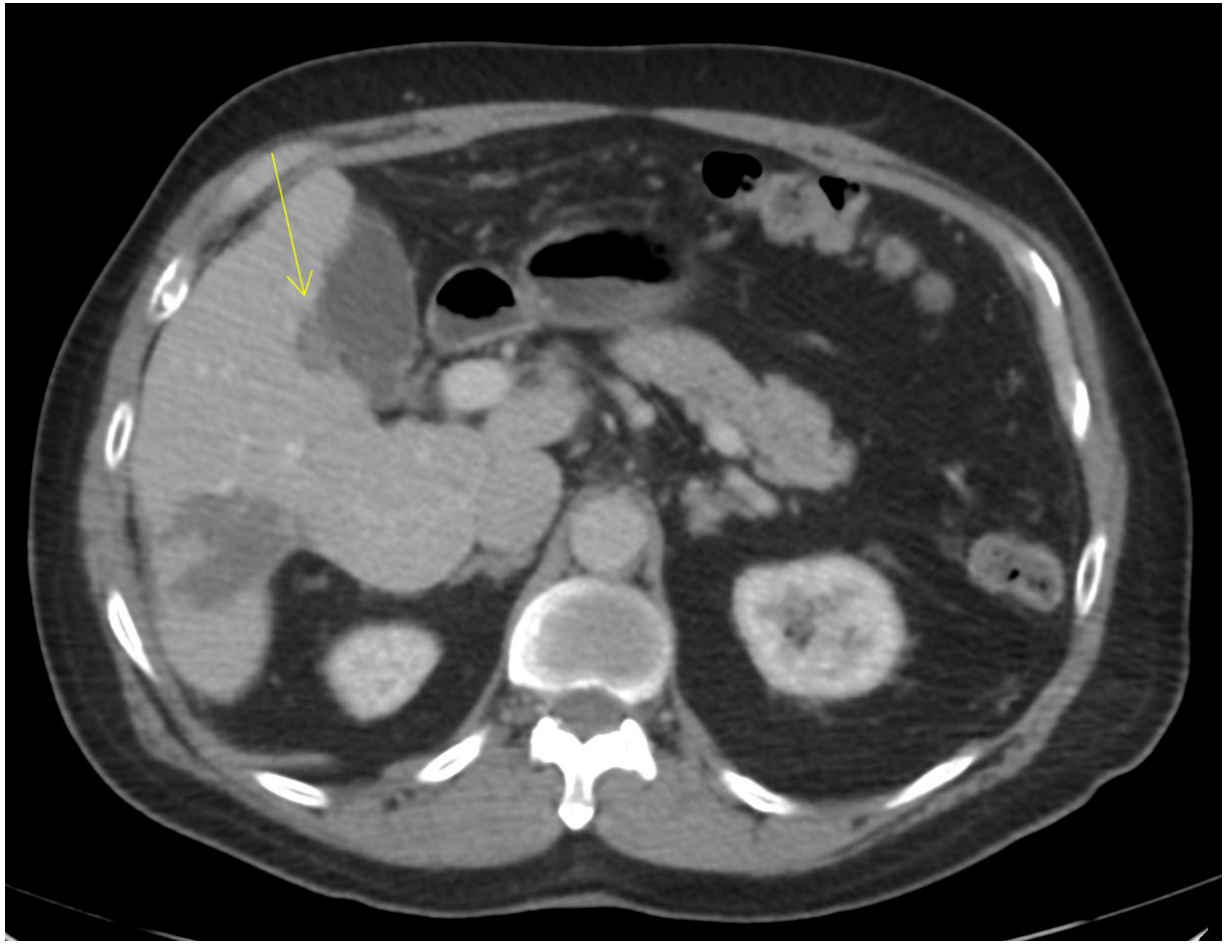
Chunping Wang [1], Huaming Wang, Wuwei Yang, Kaiwen Hu, Hui Xie, Ke-Qin Hu, Wenlin Bai, Zheng Dong, Yinying Lu, Zhen Zeng, Min Lou, Hong Wang, Xudong Gao, Xiujuan Chang, Linjing An, Jianhui Qu, Jin Li, Yongping Yang

- Multicenter RCT
- 360 patients, CP-A and CP-B, tumors up to 4cm
- Similar safety and efficacy with no difference in 5-yr OS
- Cryoablation resulted in significantly lower local tumor progression compared to RFA
  - LTP at 1, 2, and 3 yrs: 3%, 7%, and 7% for cryoablation vs 9%, 11%, and 11% for RFA (p=0.043)
  - Tumors >3cm: LTP significantly lower for cryoablation (7.7% vs 18.2%, p=0.041)

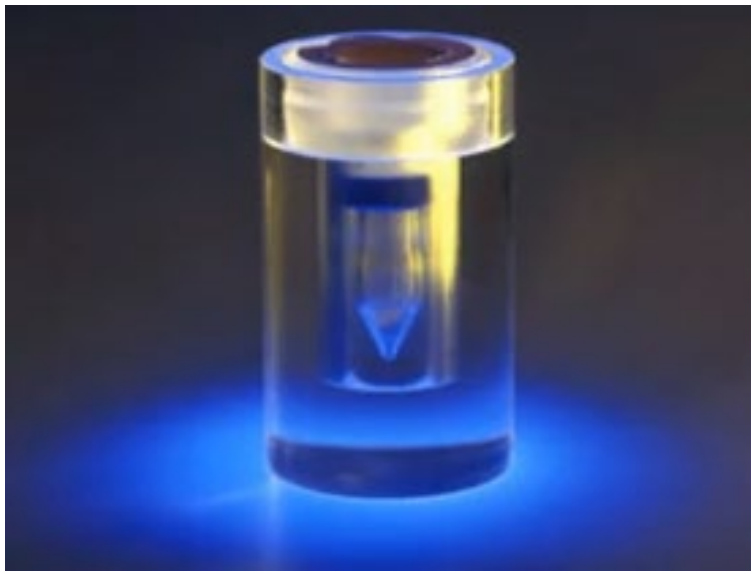
Cryoablation Case Example

- 67 yo male with HBV-cirrhosis with previously treated seg 6 tumor
- Unable to treat tumor on the gallbladder

Cryoablation Case Example



Does that make sense?

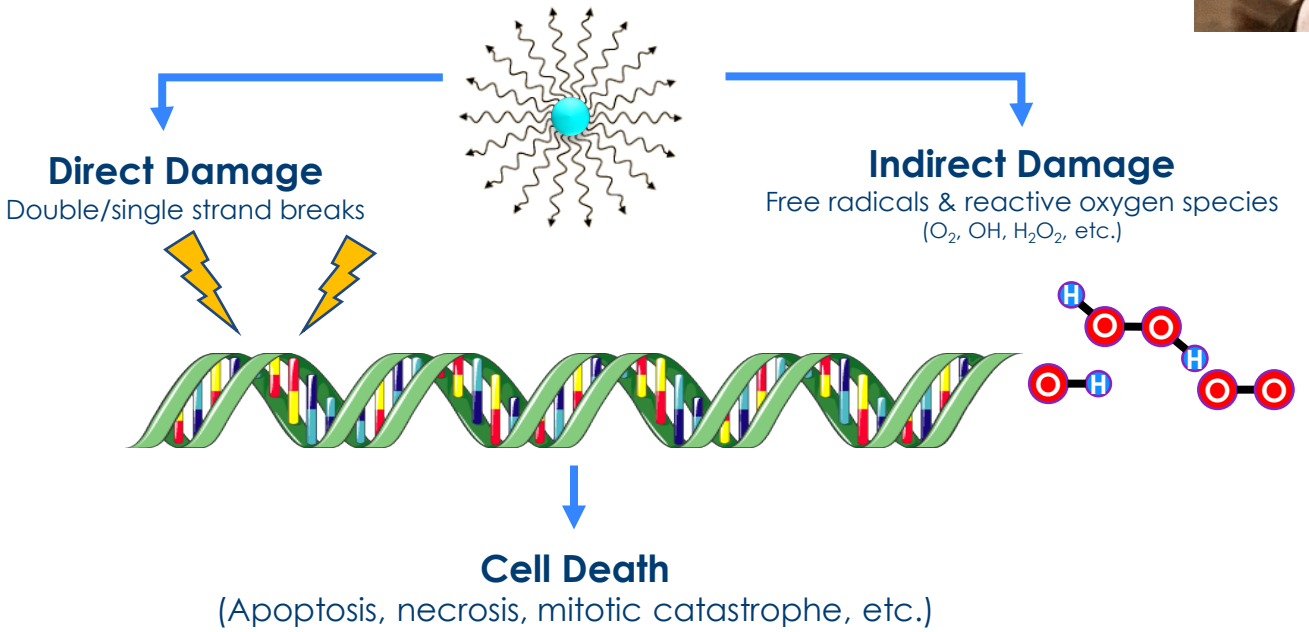


Y90 Radioembolization

- Theraspheres and Sir-spheres FDA approved for use in primary liver cancer
- Sir-spheres FDA approved for use in mCRC
- Beta emitter
  - 64.1 hr half-life
- Tissue penetration
  - Mean 2-4mm
  - Max 11mm (synergistic effect)
- 1 GBq in 1 kg tissue = ~50 Gy

Y90 Energy and Tumor Concepts

- Tumorcidal effects 2/2 near-pure emission of Beta particles
  - Average energy of 933.7 keV (~2.5mm distance traveled)
    - Bq implies the number of decays per second
      - "The pew-pews"
    - Need double-stranded DNA breaks to kill tumor cells
      - Majority of radiation produces single-stranded breaks



^{90}Y for HCC – Dosing Rationale

$$Dose_{(Gy)} = \frac{Activity_{(GBq)} x\ 50\ _{(J/GBq)}}{Mass_{(Kg)}}$$

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^{90}Y for HCC – Dosing Rationale

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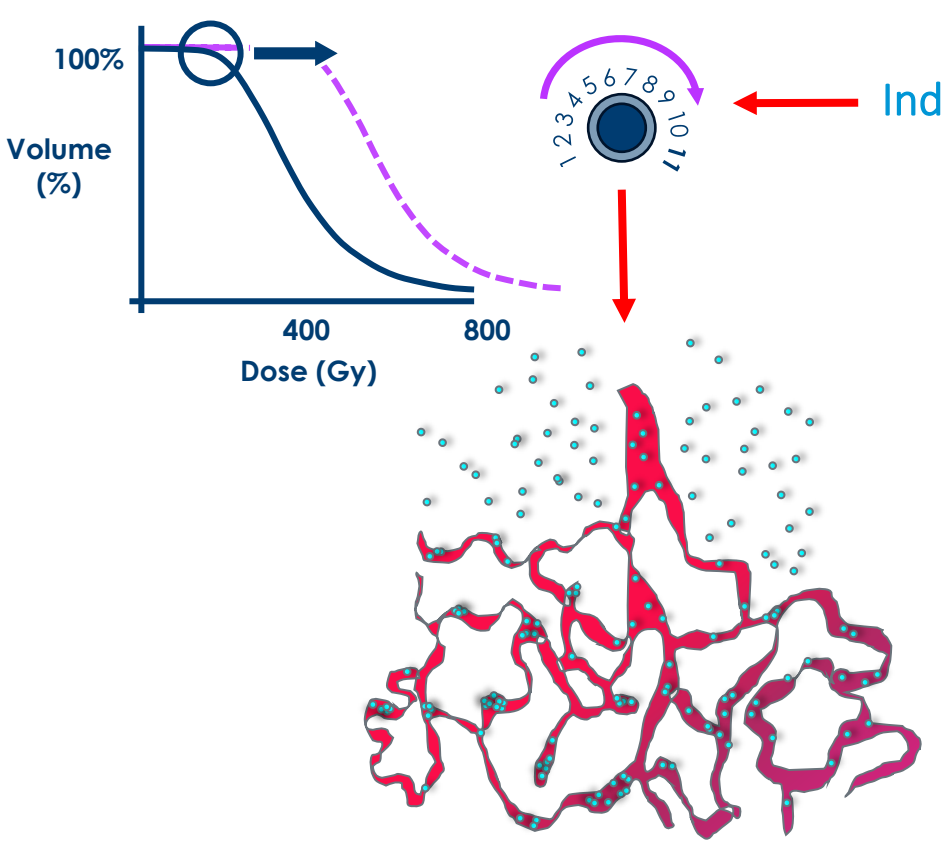
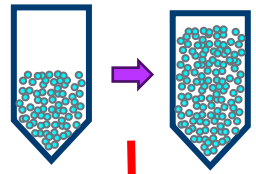
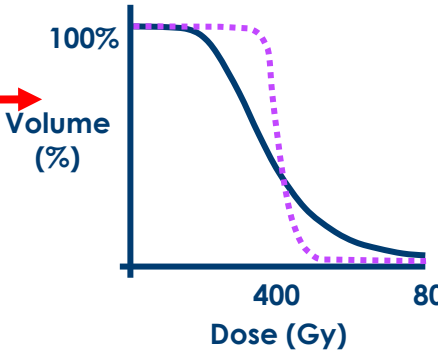
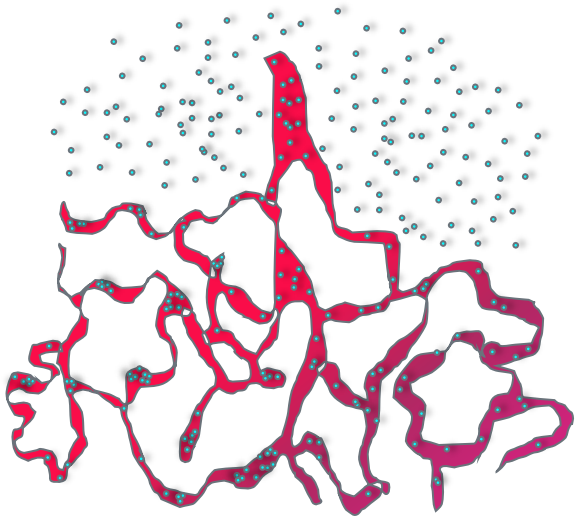


Individual sphere activity x # of spheres







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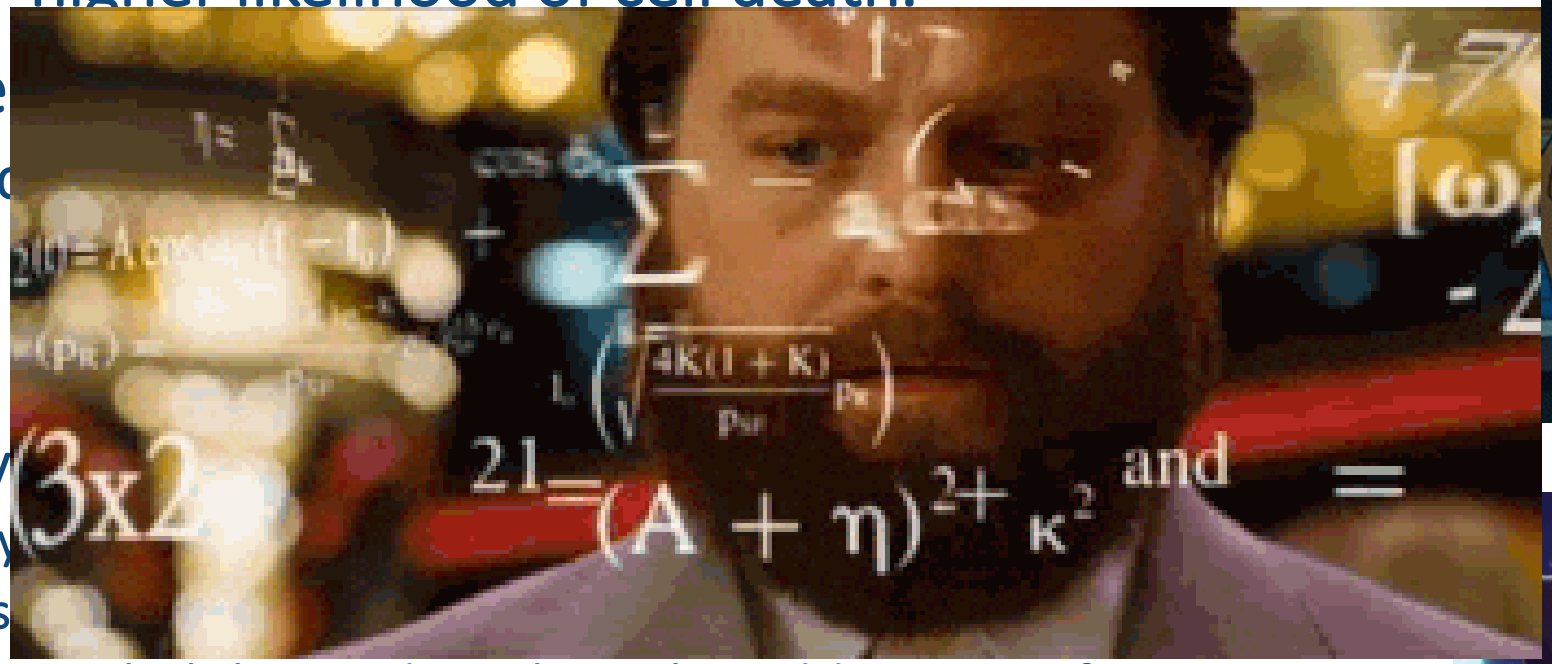
Radiation-induced Cell Death

- The goal is to accumulate “microbullet hits” in a tumor cell.
- More “hits” = higher likelihood of cell death.
- Need expone
  - Delivered ac
- Key Points:
  - More decay
    - These guy
    - Need lots
  - Y90 is about probability and stacking the odds in your favor.

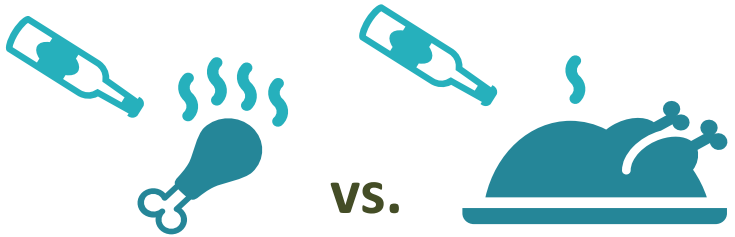


What We Know: Dose drives CPN…

- More Dose = Higher Rate of CPN
  - <190 Gy = 25% rate of CPN
  - >190 Gy = 67% rate of CPN
  - >400 Gy = 100% rate of CPN

- What drives dose?
  - Mass
  - Activity
    - More microbullets!

$$\textbf{Absorbed Dose}\ (Gy) = \frac{\textit{Activity}\ (GBq) \cdot 50}{\textit{Tissue Mass}\ (kg)}$$



Vouche et al. Hepatology. 2014 Jul;60(1):192-201.

Gabr et al. EJNMMI. 2021. 48(2): 580-583.

^{90}Y for HCC – Data

Trials

- **PREMIERE** – Y90 significantly prolongs TTP compared to cTACE
- **LEGACY** – Threshold dosimetry radiation segmentectomy has high rate of durable imaging response
- **DOSISPHERE-01** – Personalized dosimetry improves imaging response and downstaging to surgery for prolonged OS
- **TARGET** – Real-world study confirms tumor absorbed dose drives imaging response & OS
- **RASER** – Prospective study confirms imaging and pathologic response after Radiation Segmentectomy
- **TRACE** – Y90 offers superior tumor control and survival compared to DEB-TACE

Guidelines

Contemporary dosing recommendations from an international multidisciplinary group help to guide reproducible results for **5** HCC clinical scenarios:

Radiation Segmentectomy | Radiation Lobectomy | Multifocal Unilobar w/o PVT | Multifocal Bilobar w/o PVT | Macrovascular Invasion

International Guidelines

^{90}Y added to international guidelines and recommendations on the strength of pivotal trials

BCLC Barcelona Clinic Liver Cancer | NCCN | AASLD | ESMO

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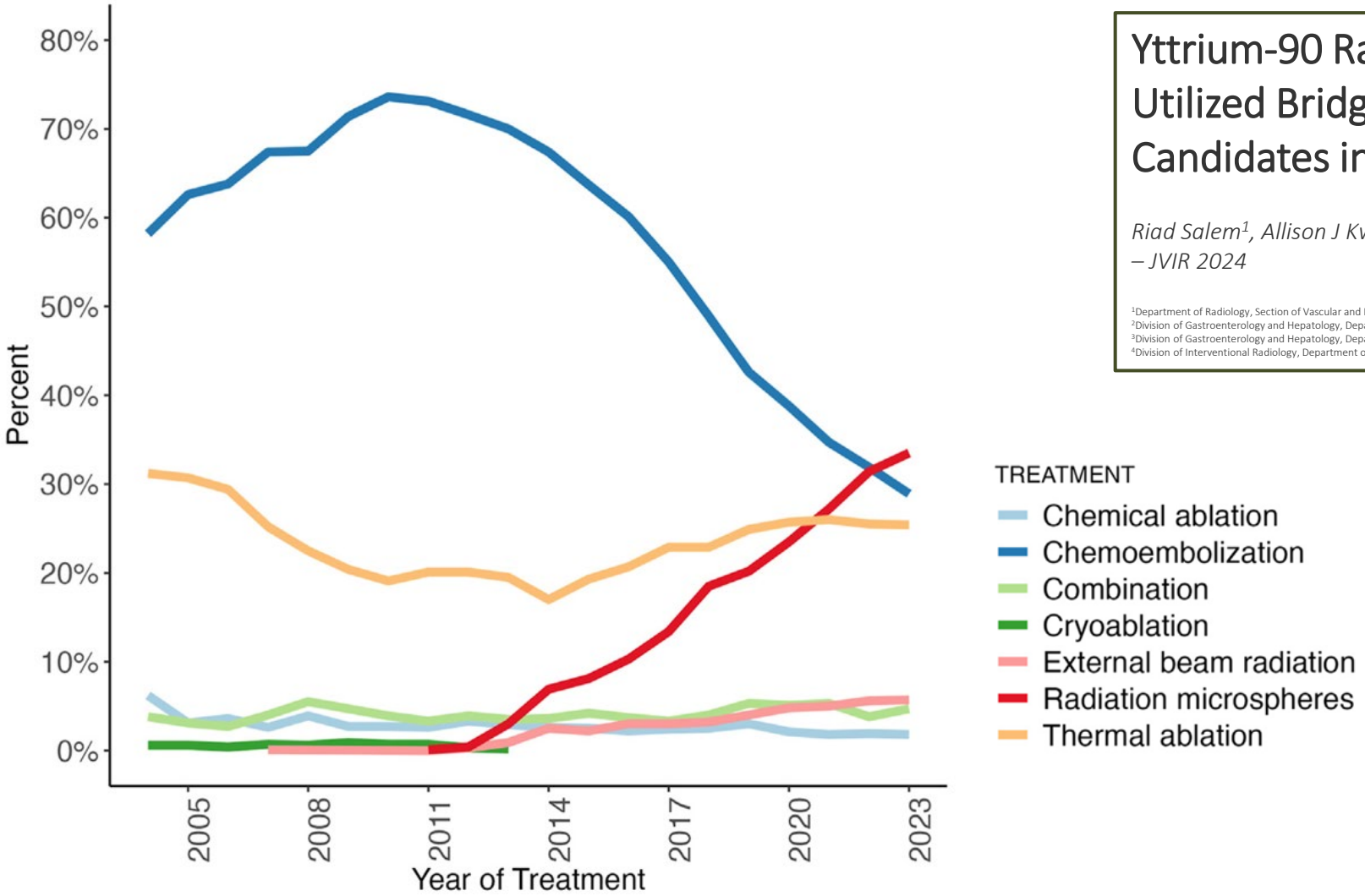
^{90}Y Timeline



Yttrium-90 Radioembolization Has Become the Most Utilized Bridging Treatment for Liver Transplant Candidates in the United States

Riad Salem[1], Allison J Kwong[2], Nathan Kim[3], Daniel Y Sze[4], Neil Mehta[3]
– JVIR 2024

[1]Department of Radiology, Section of Vascular and Interventional Radiology, Northwestern University, 676 N. St. Clair, Suite 800, Chicago, IL 60611
[2]Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University, Medicine, Stanford, CA
[3]Division of Gastroenterology and Hepatology, Department of Medicine, University of California at San Francisco, San Francisco, CA
[4]Division of Interventional Radiology, Department of Radiology, Stanford University, Stanford, CA

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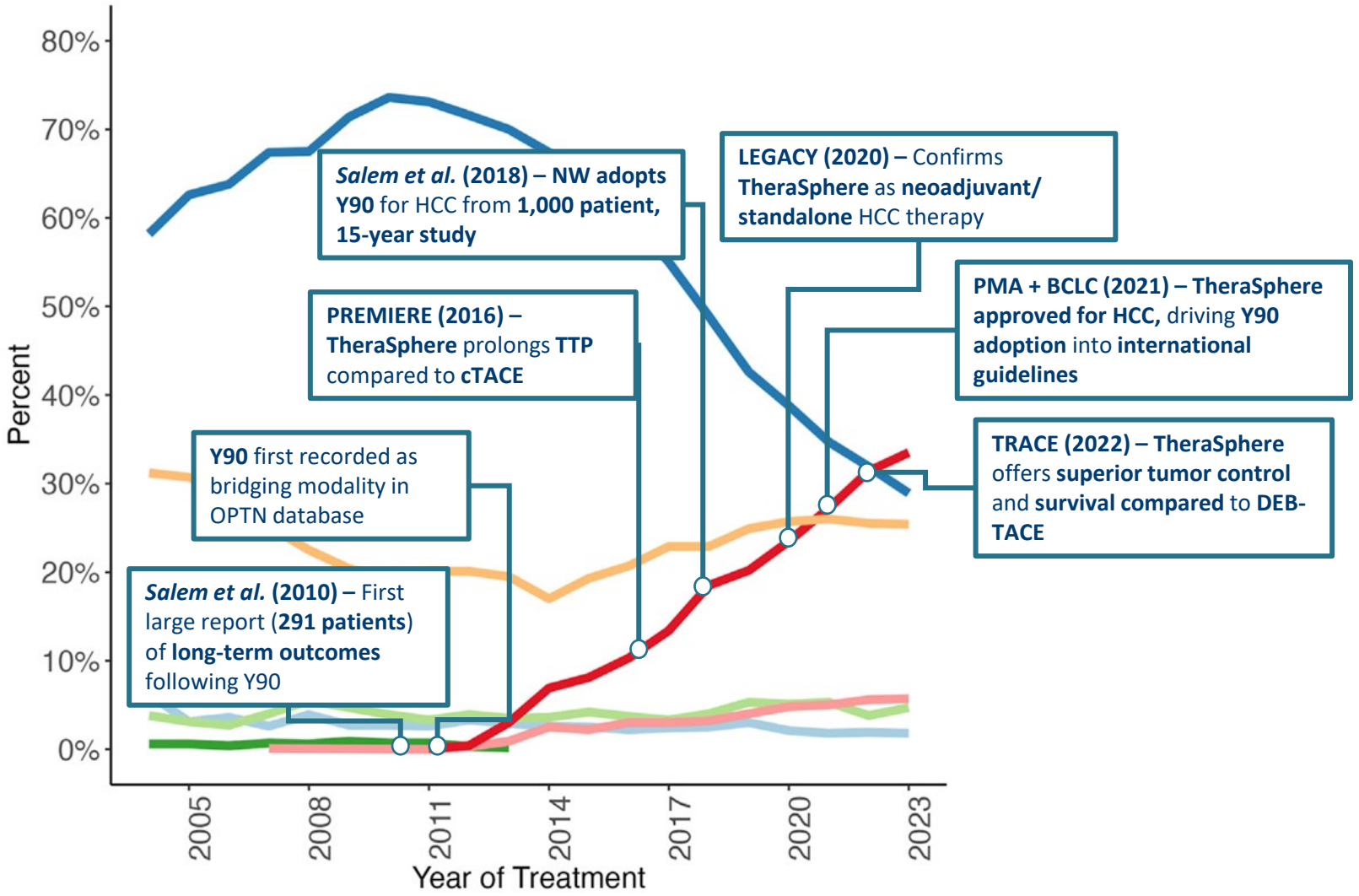
^{90}Y Timeline



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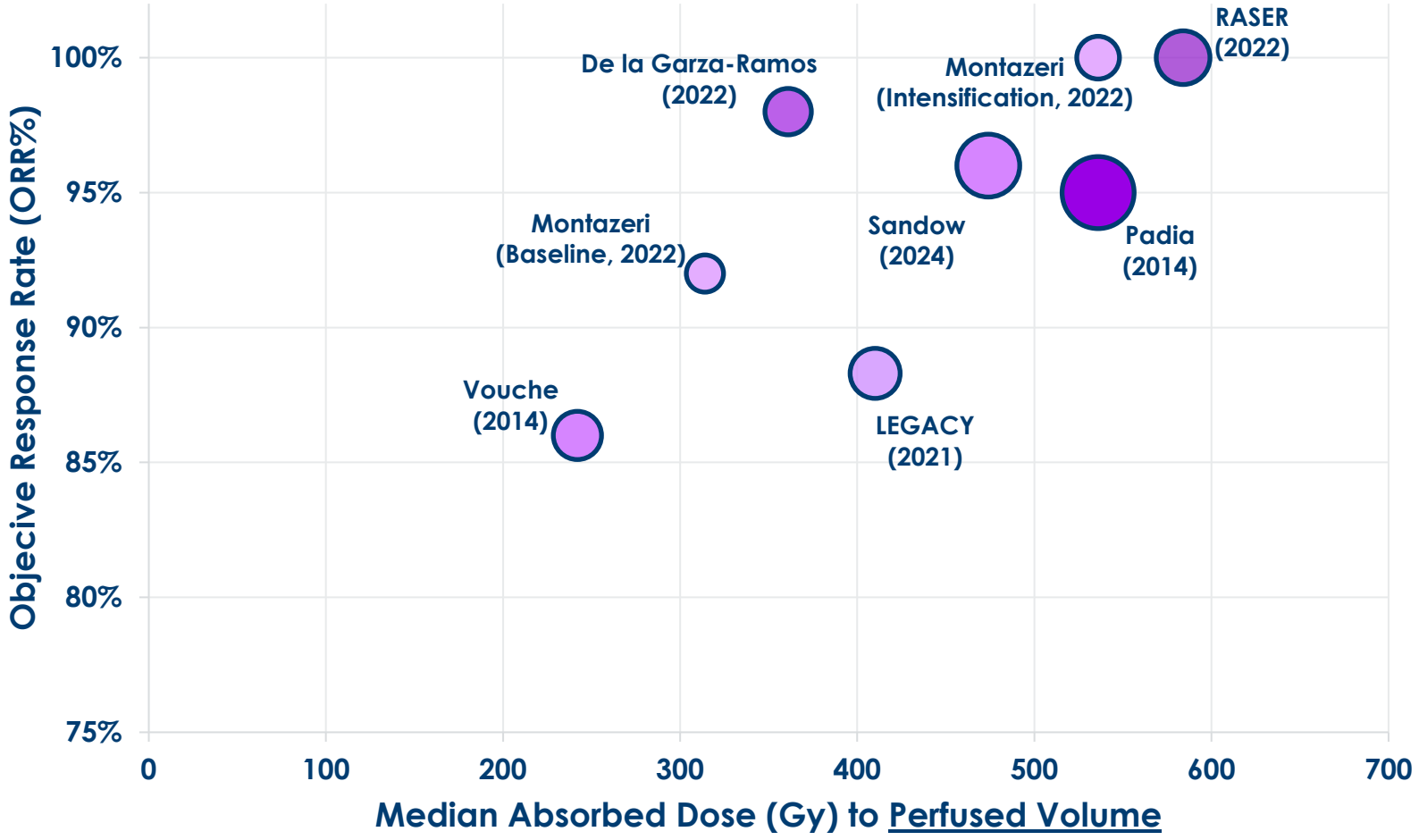
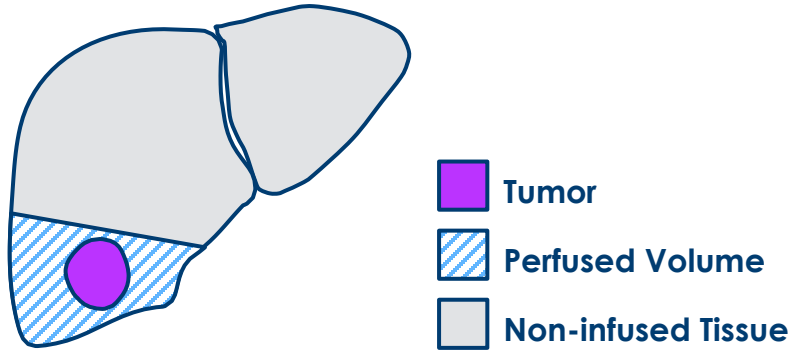
^{90}Y for HCC – Data

Absorbed Dose-Response Relationship with TheraSphere™



Radiation Segmentectomy

Higher doses drive **higher rates** of **response**



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^{90}Y for HCC – Data

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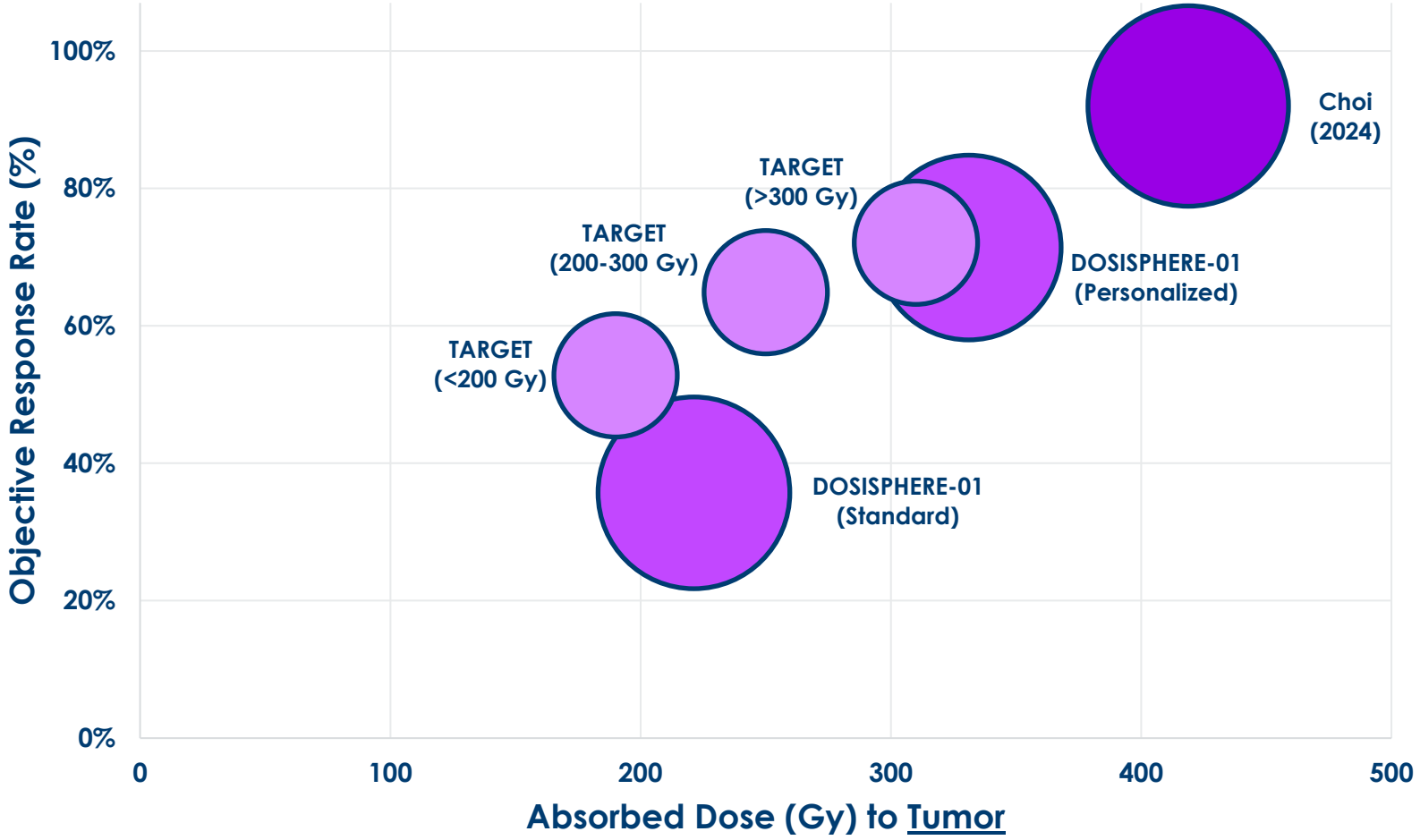
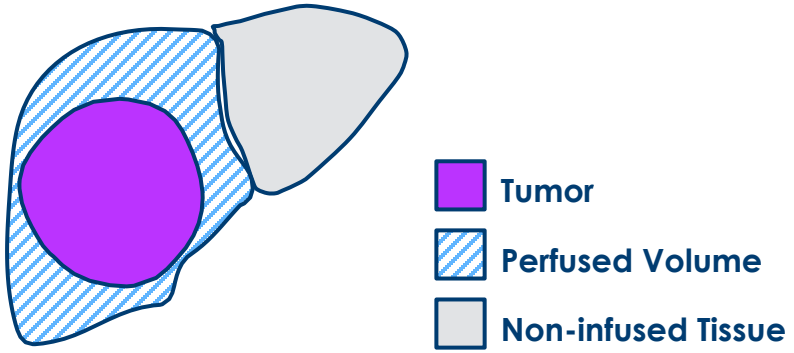


Large Tumors (≥5 cm)

Again… higher doses drive **higher rates** of **response**



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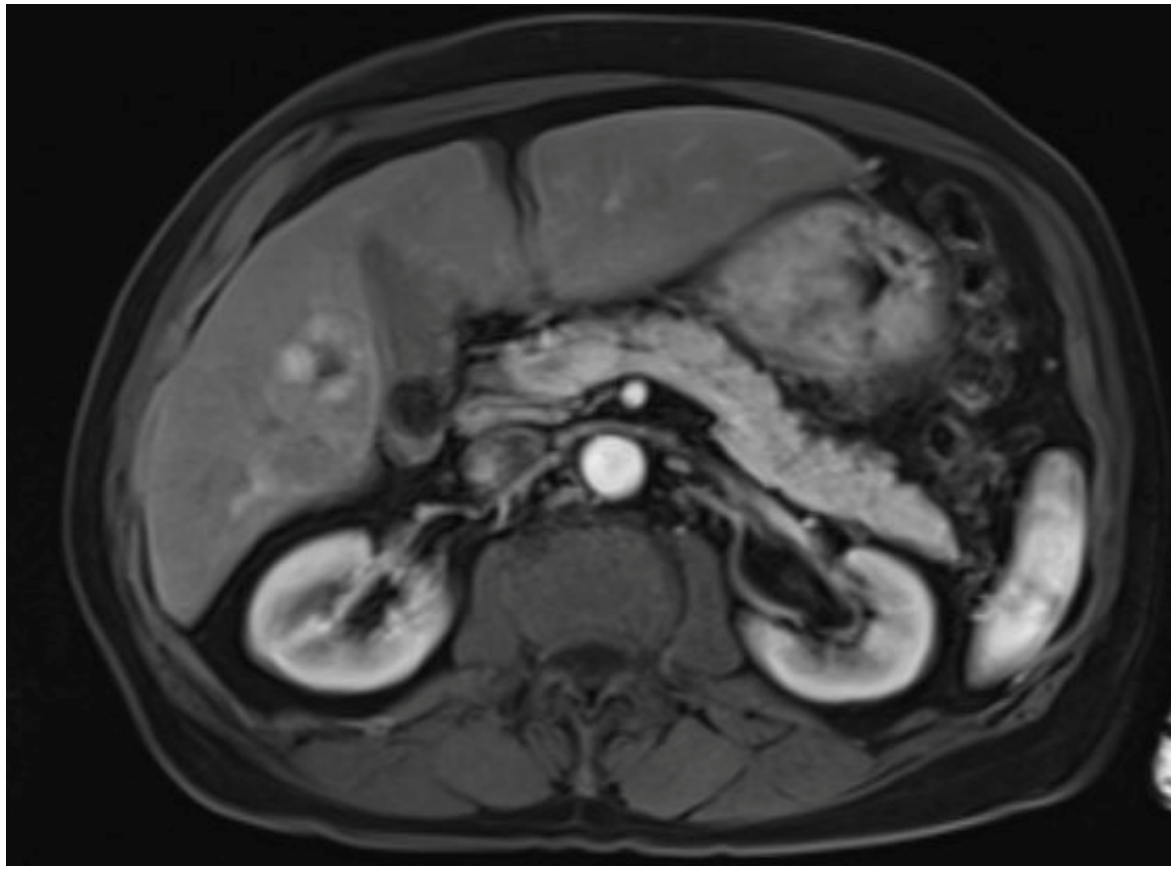
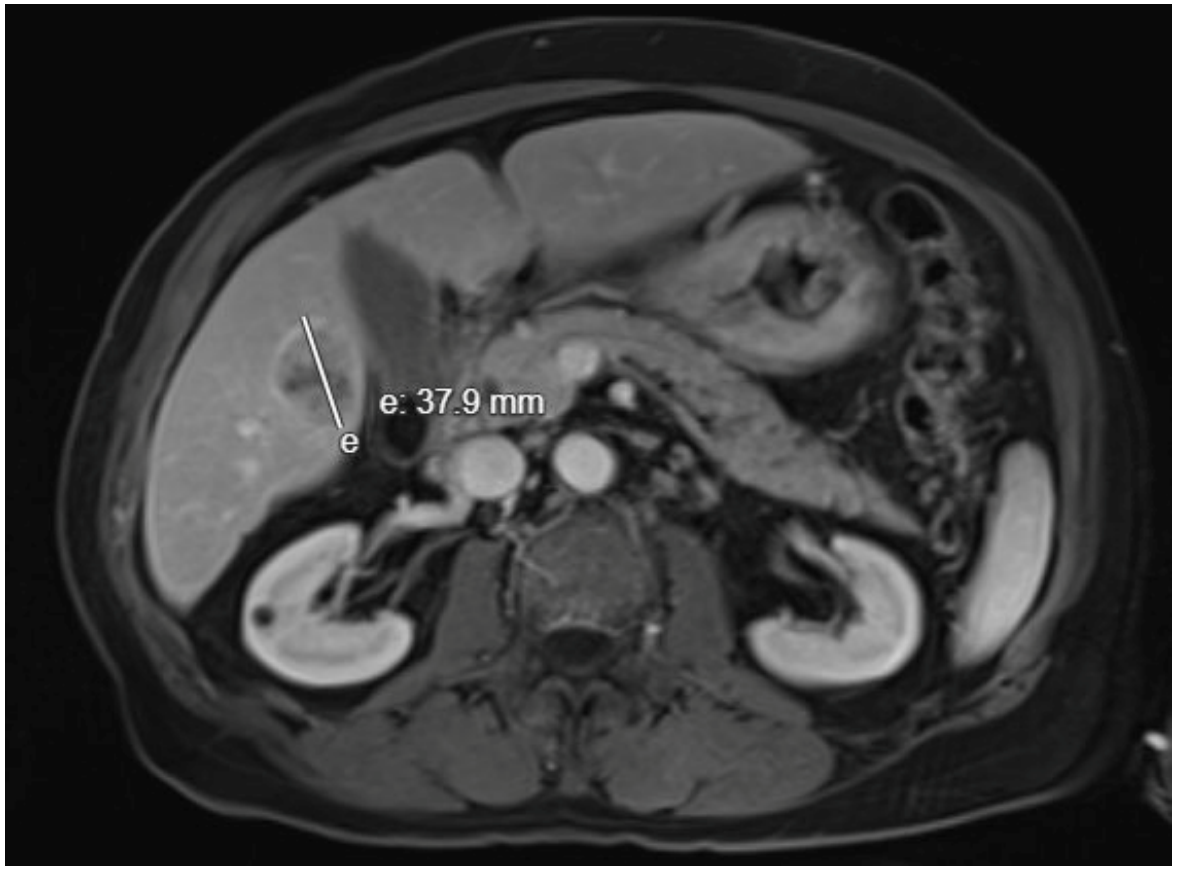
Y90 Case Example

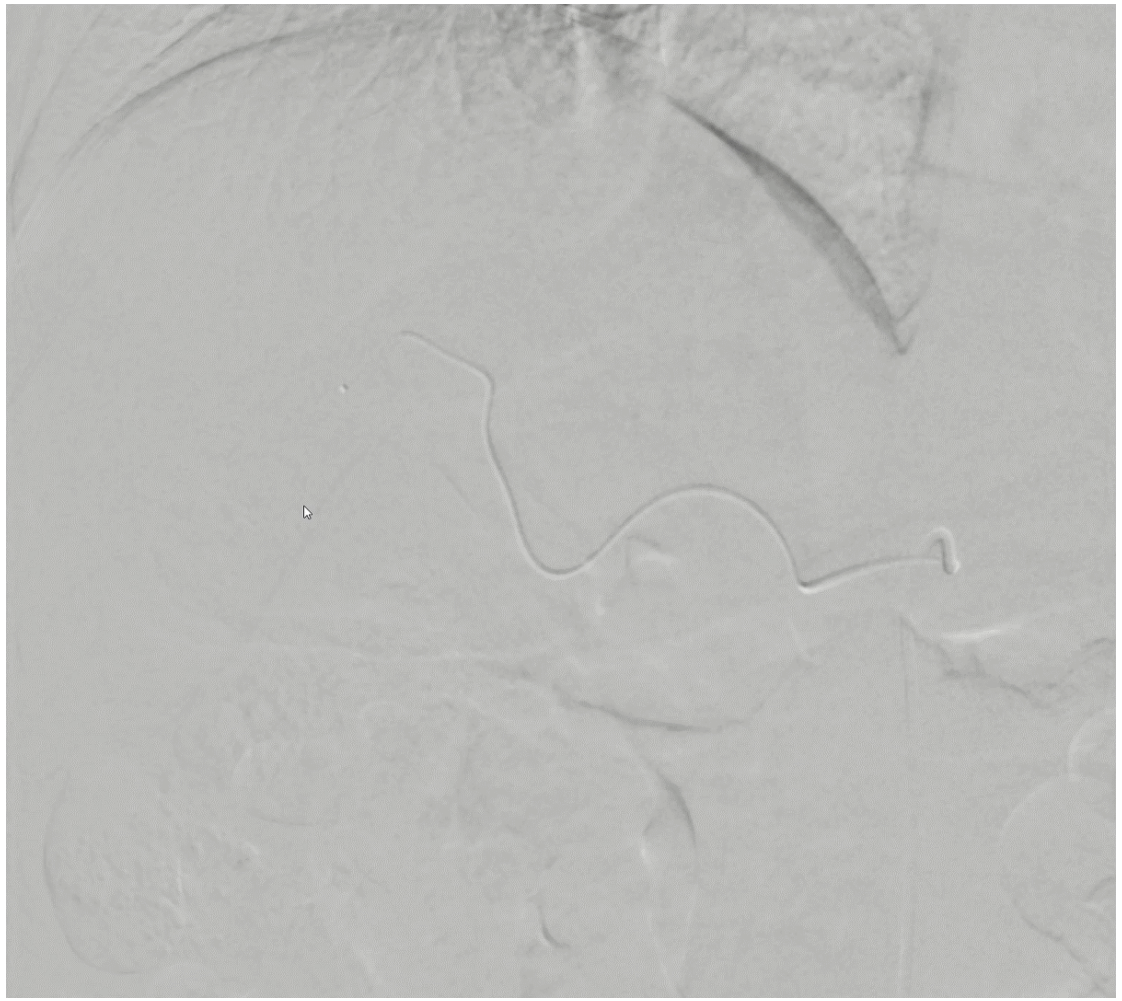
- 63 yo M with HCV cirrhosis found to have a 3.8cm mass in seg V
- MELD-Na 7
- Total Bilirubin 0,5, Albumin 3.2
- AFP 1.2

Imaging





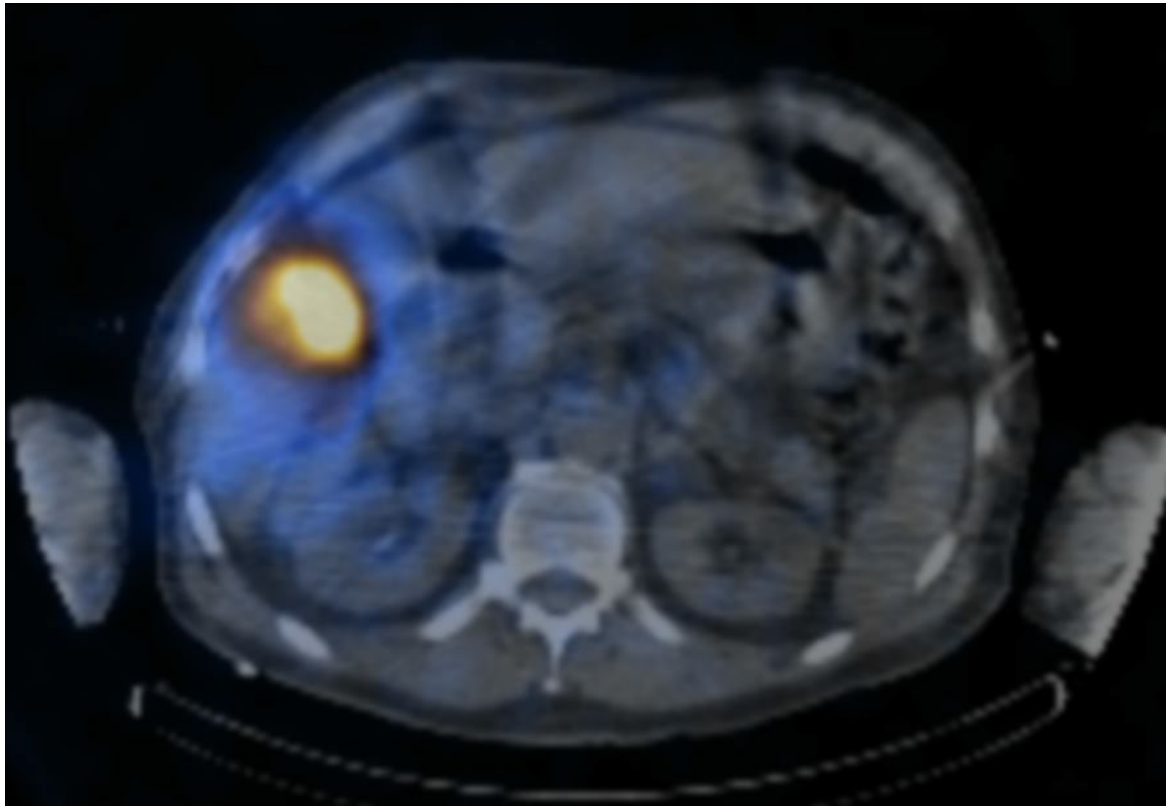
Mapping

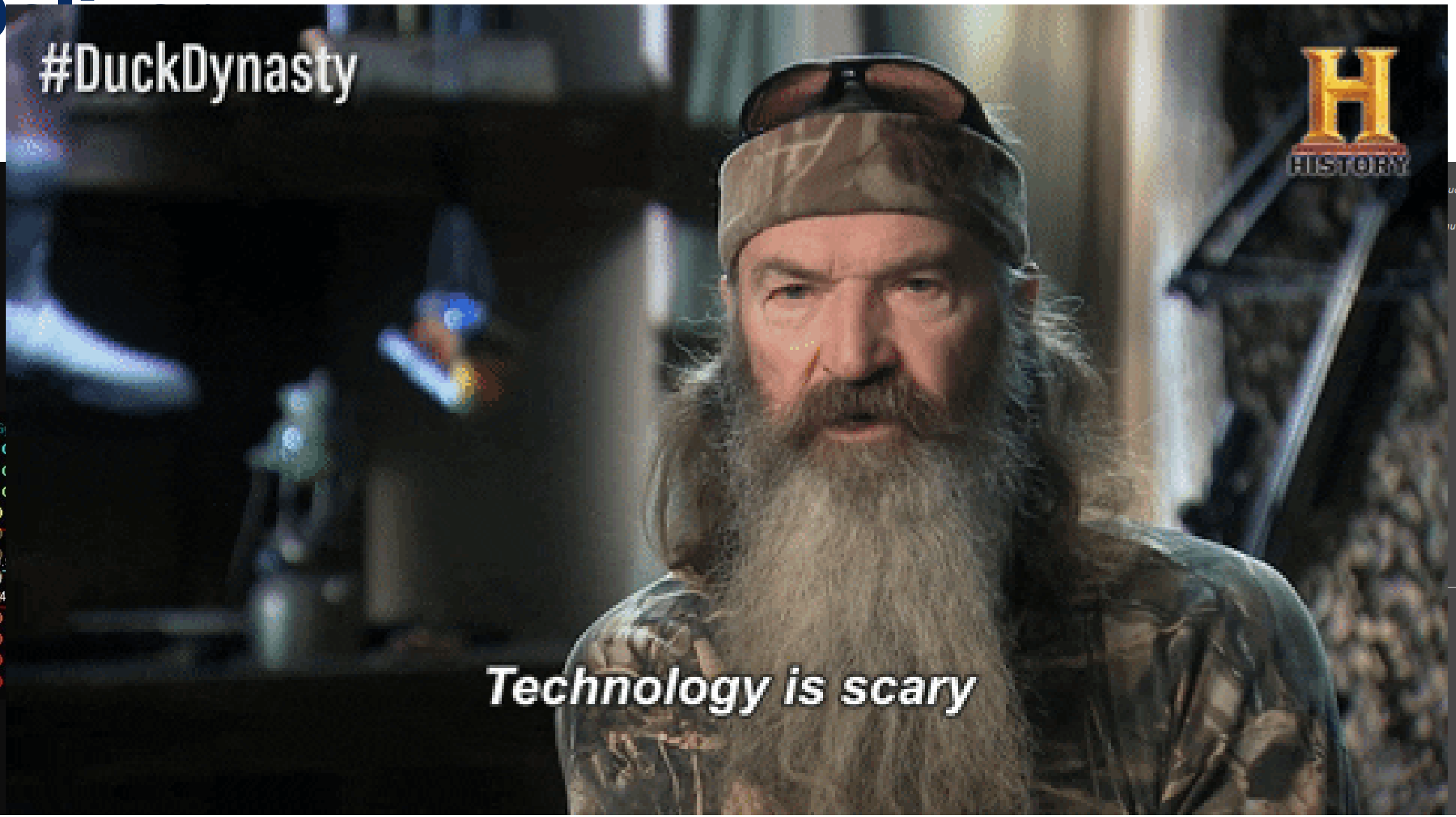


Delivery

- Perfused volume: 95mL
- LSF: 5.2%
- Target Dose: 691Gy

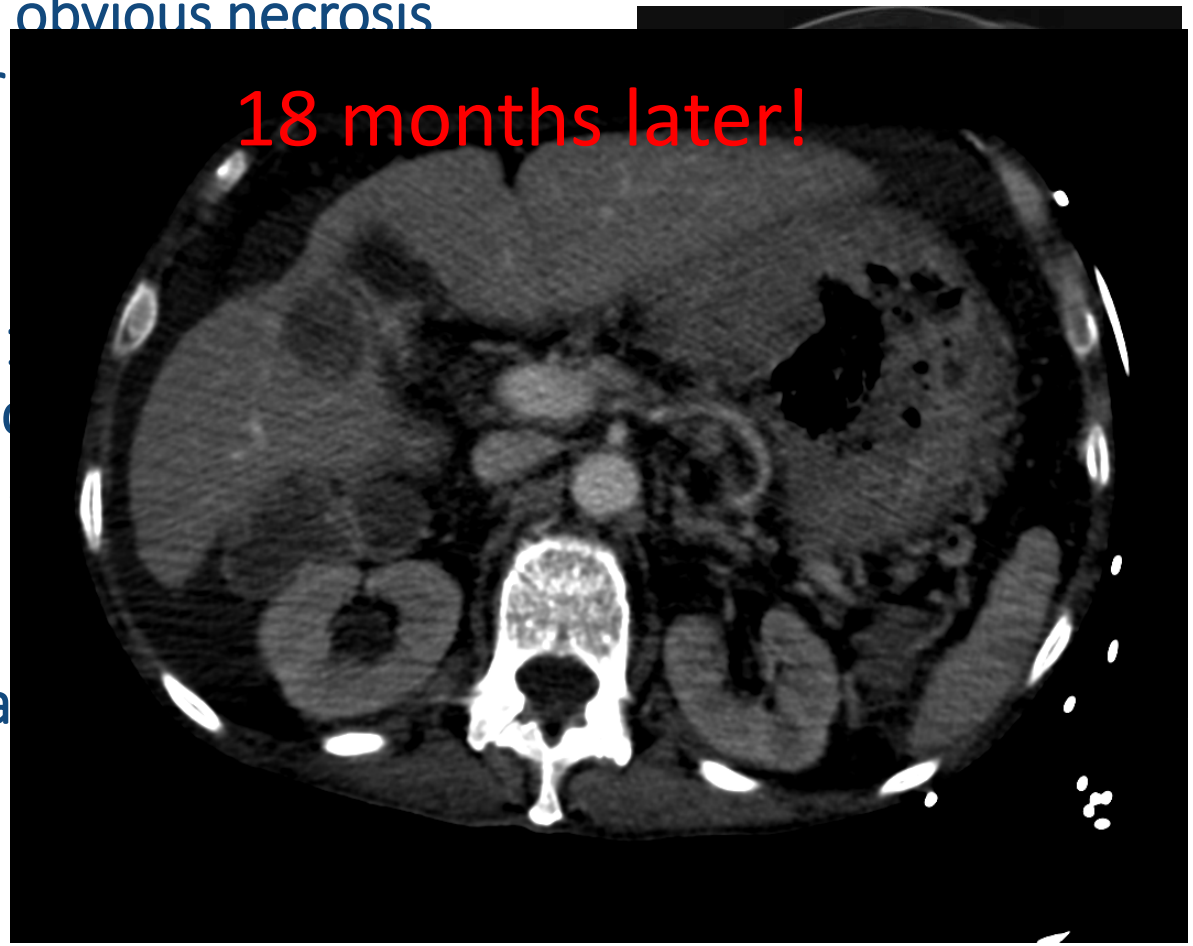
- We selected a 4GBq vial (W1 Thurs) to be delivered to a subsegmental branch of segment V

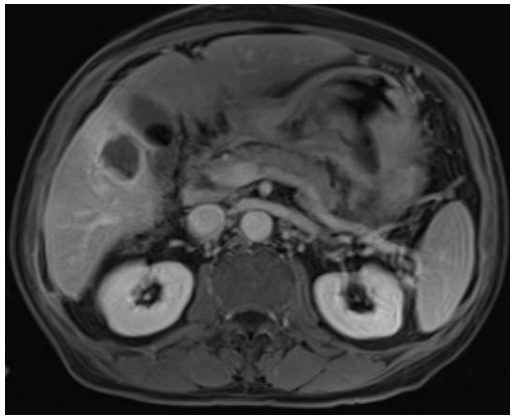



#DuckDynasty
HISTORY
Technology is scary

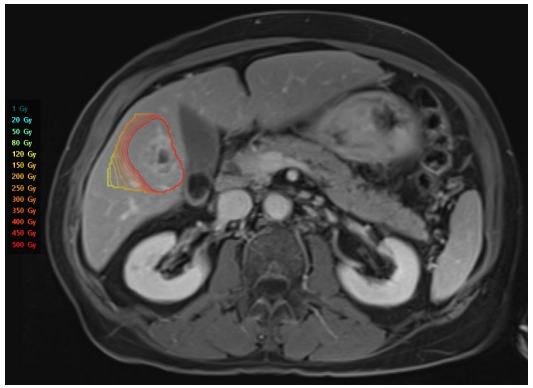
Follow-up Imaging and Discussion

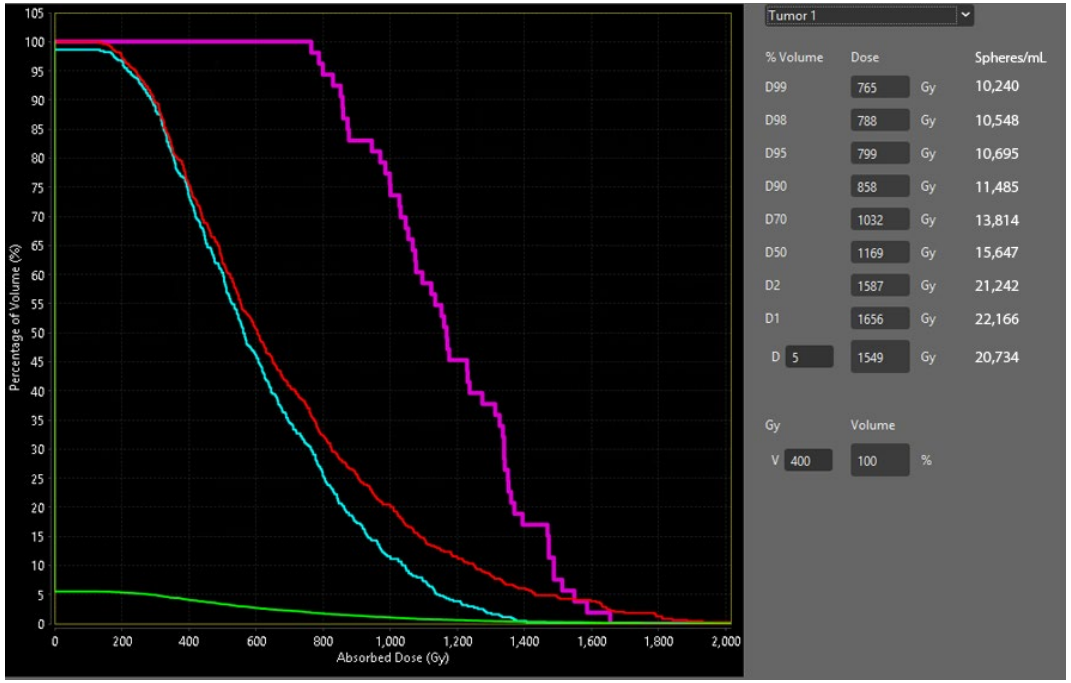
- 6 month MRI: CR with obvious necrosis throughout the tumor or recurrence.
- Using absorbed dose, spheres were delivered
  - Accounted for 22% of spheres/mL
- 614Gy to 83mL norma
  - 8,213 spheres/mL





Exploring the Case a Little More…





- Heterogeneous sphere distribution
  - Hot areas that receive more dose
    - D_5 = 1549Gy (20,734 spheres/mL)
  - Relatively colder areas that receive less dose
    - D_{95} = 799Gy (10,695 spheres/mL)
  - V_{400} = 100%
- Planned target dose: 691Gy
  - D_{95} = 799Gy
- Tumor volume: ~30mL
  - Perfused volume: 95mL

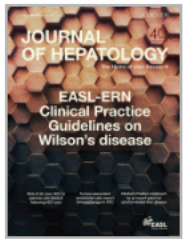
Radiation Segmentectomy is Curative for Early HCC!

ELSEVIER

Journal of Hepatology

Available online 22 January 2025

In Press, Journal Pre-proof ? What's this?



Expert Opinion

Radiation Segmentectomy for Early Hepatocellular Carcinoma is Curative

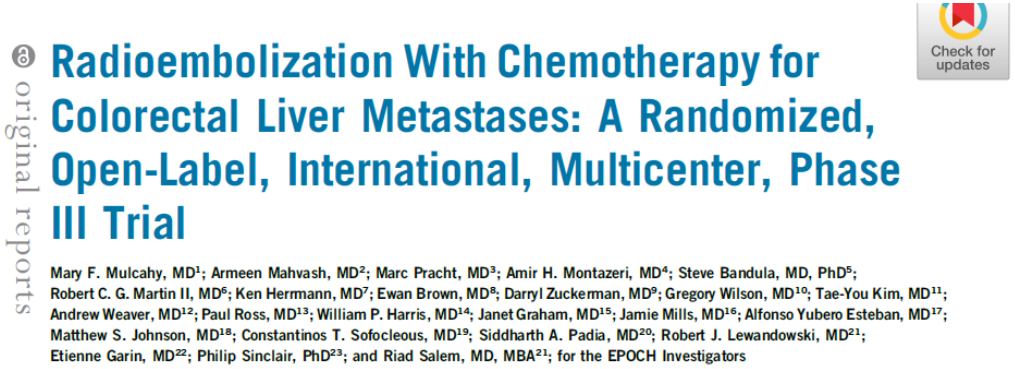
Riad Salem [1], Siddharth A. Padia [2], Beau B. Toskich [3], Jon D. Callahan [4], Kirk D. Fowers [5], Brian S. Geller [6], Guy E. Johnson [7], Laura Kulik [8], Tushar C. Patel [9], Robert J. Lewandowski [10], Edward Kim [11]

Radiation Segmentectomy is Curative for Early HCC

- CPN and no local progressions when applying threshold dosimetry of 400 Gy (glass) as demonstrated in the LEGACY study
- Neoadjuvant as a bridge to transplant or resection
  - Tumor response rates exceeding 90% by mRECIST
  - Time-to-progression of 2.4 years
  - Median overall survival of 6.7 years in selected patients
- Overall Survival at 1, 3 and 5 years of 100%, 82% and 75% in patients with baseline tumor size ≤3 cm.

Y90 for mCRC EPOCH

- Prospective, RCT of 428 patients at 95 sites worldwide
- Adding Y90 to standard of care 2nd line chemotherapy
- Results
  - Increased PFS 8 months vs 7.2 months (p=0.001)
  - Increased hPFS 9.1 months vs 7.2 months (p<0.001)
  - No significant difference in OS
  - Chemotherapy-related adverse events were comparable between the groups
  - Y-90 did not compromise ability to receive additional chemotherapy


original reports

Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial

Mary F. Mulcahy, MD[1]; Armeen Mahvash, MD[2]; Marc Pracht, MD[3]; Amir H. Montazeri, MD[4]; Steve Bandula, MD, PhD[5]; Robert C. G. Martin II, MD[6]; Ken Herrmann, MD[7]; Ewan Brown, MD[8]; Darryl Zuckerman, MD[9]; Gregory Wilson, MD[10]; Tae-You Kim, MD[11]; Andrew Weaver, MD[12]; Paul Ross, MD[13]; William P. Harris, MD[14]; Janet Graham, MD[15]; Jamie Mills, MD[16]; Alfonso Yubero Esteban, MD[17]; Matthew S. Johnson, MD[18]; Constantinos T. Sofocleous, MD[19]; Siddharth A. Padia, MD[20]; Robert J. Lewandowski, MD[21]; Etienne Garin, MD[22]; Philip Sinclair, PhD[23]; and Riad Salem, MD, MBA[21]; for the EPOCH Investigators

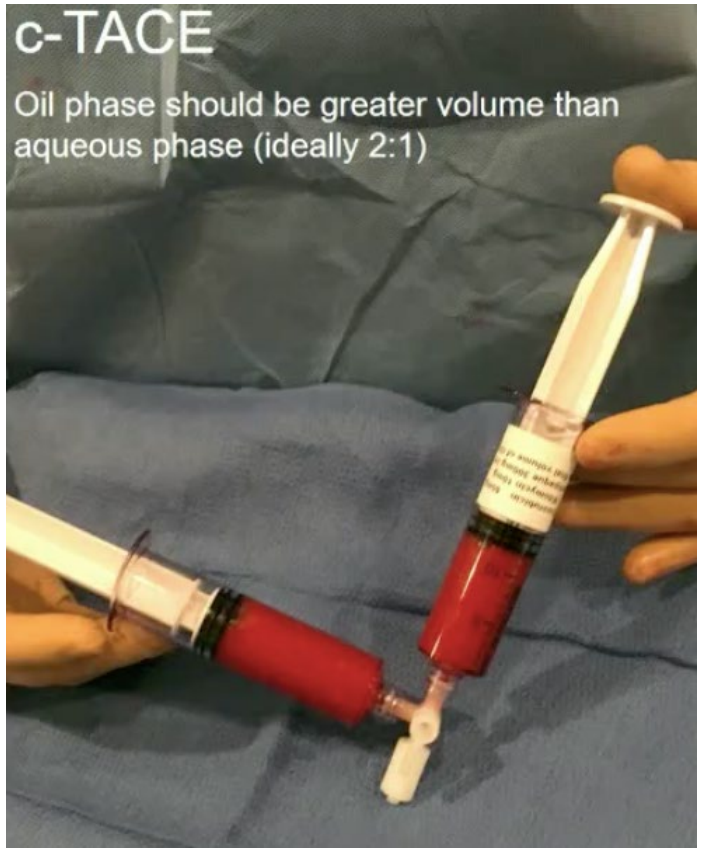
Mulcahy et al., 2021. *J Clin Oncol*.

A Brief History Lesson: Interventional Oncology's Toddler Years

- "You can't really know where you are going until you know where you have been."
  - Maya Angelou

TACE

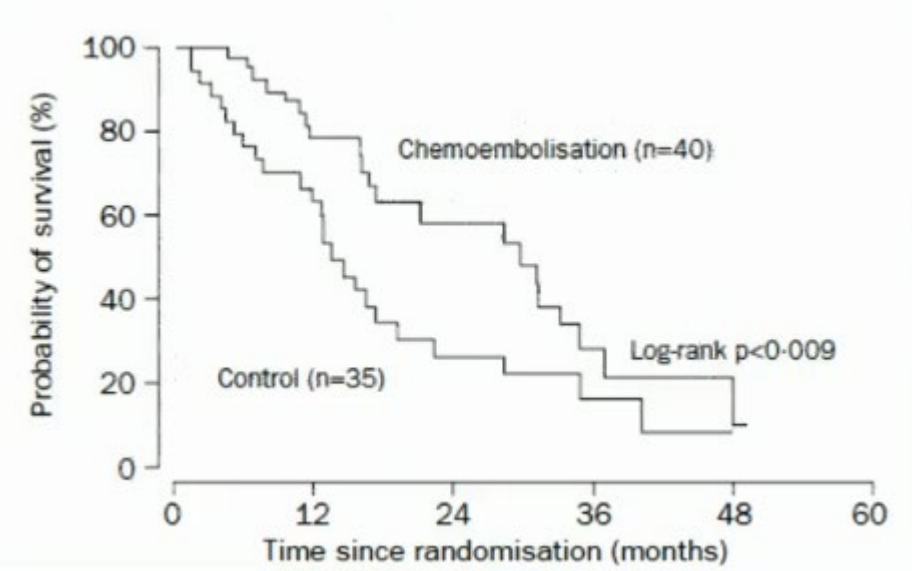
- Generate tumor necrosis by:
  - Therapeutic agent delivery
  - Tissue devascularization
- Types
  - cTACE
  - DEB-TACE
- Chemo agents
  - Doxorubicin
  - Cisplatin
  - Mitomycin



Intra-arterial Therapy (Chemoembolization)

Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial

*Josep M Llovet, Maria Isabel Real, Xavier Montaña, Ramon Planas, Susana Coll, John Aponte, Carmen Ayuso, Margarita Sala, Jordi Muchart, Ricard Solà, Joan Rodés, Jordi Bruix, for the Barcelona Clínic Liver Cancer Group**

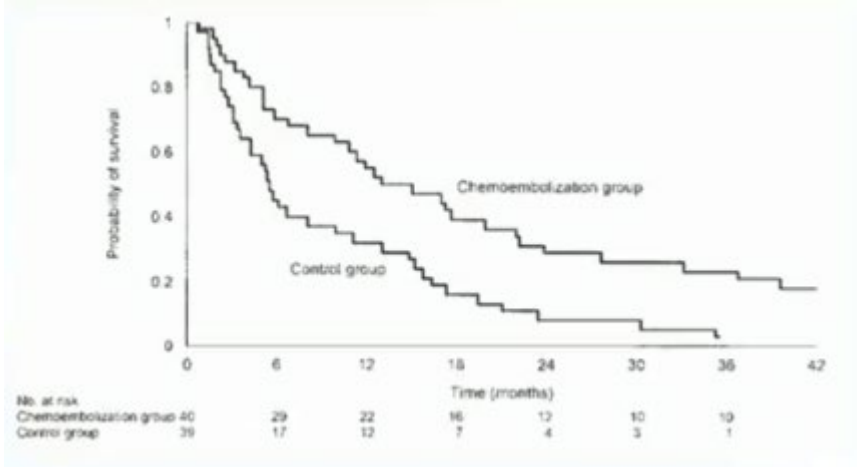


Survival	1-yr	2-yr
TACE	75%	50%
BSC	63%	27%

Intra-arterial Therapy (Chemoembolization)

Randomized Controlled Trial of Transarterial Lipiodol Chemoembolization for Unresectable Hepatocellular Carcinoma

Chung-Mau Lo, Henry Ngan, Wai-Kuen Tso, Chi-Leung Liu, Chi-Ming Lam, Ronnie Tung-Ping Poon, Sheung-Tat Fan, and John Wong



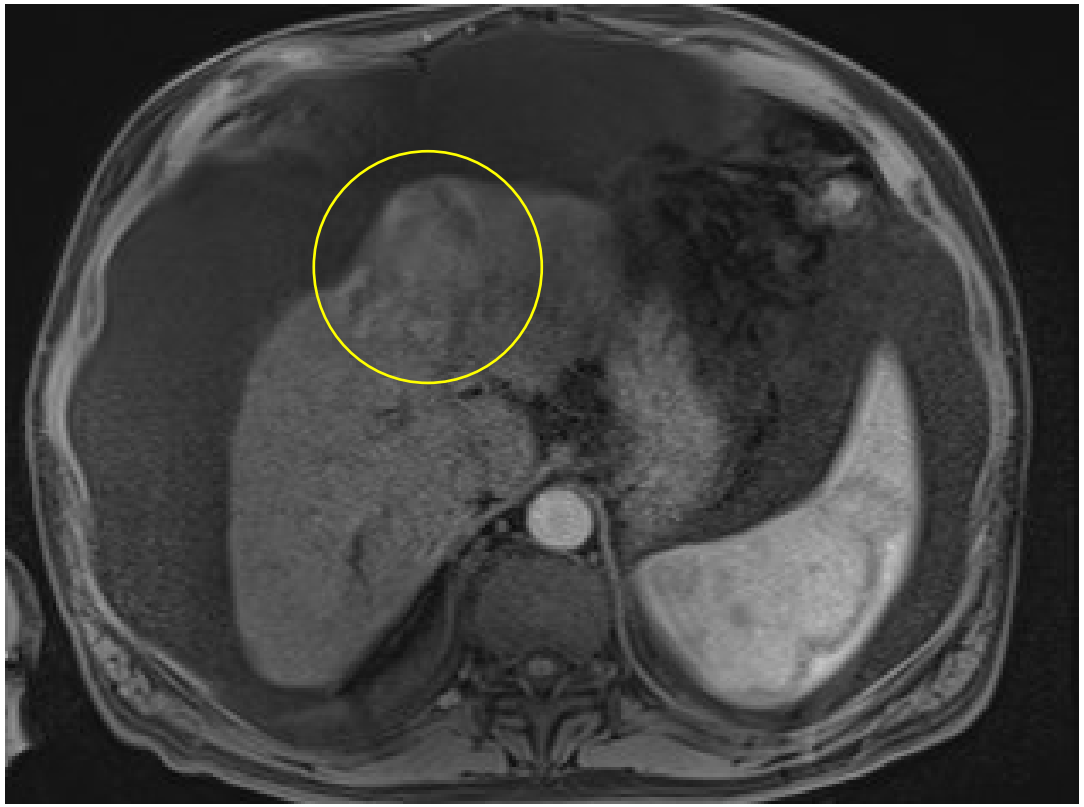
Survival	1-yr	2-yr	3-yr
TACE	57%	31%	26%
BSC	32%	11%	3%

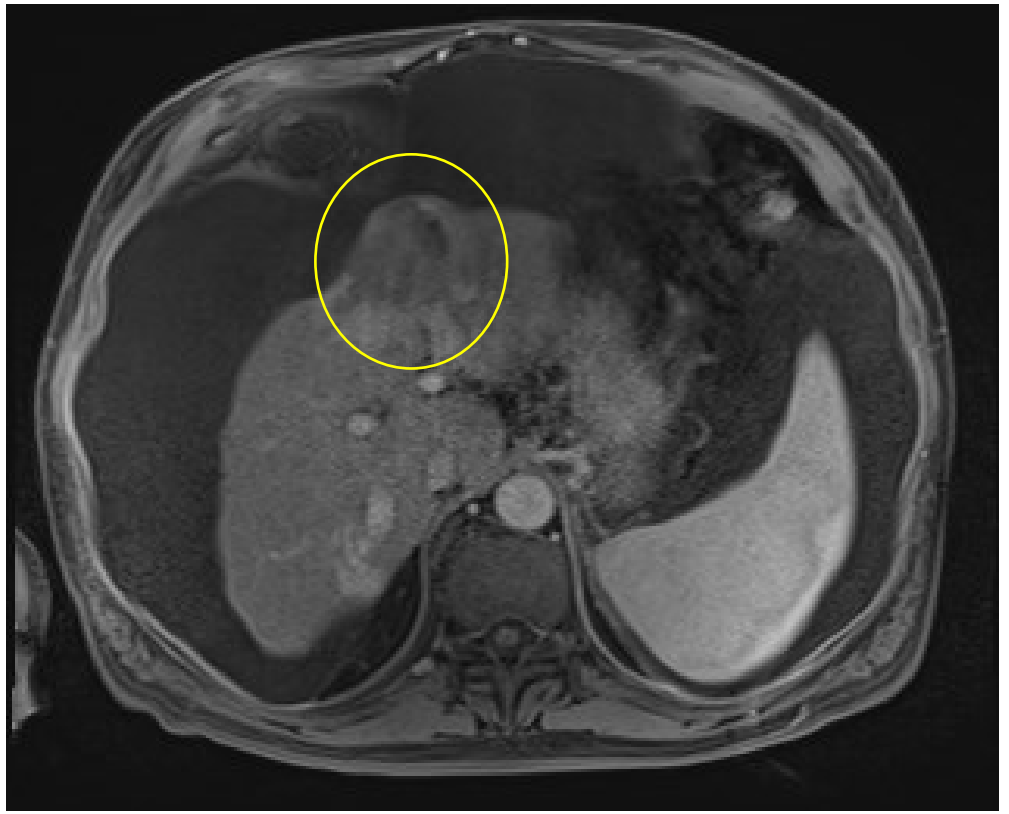

AND NOW BACK TO
OUR REGULARLY
SCHEDULED
PROGRAMMING

TACE Case Example

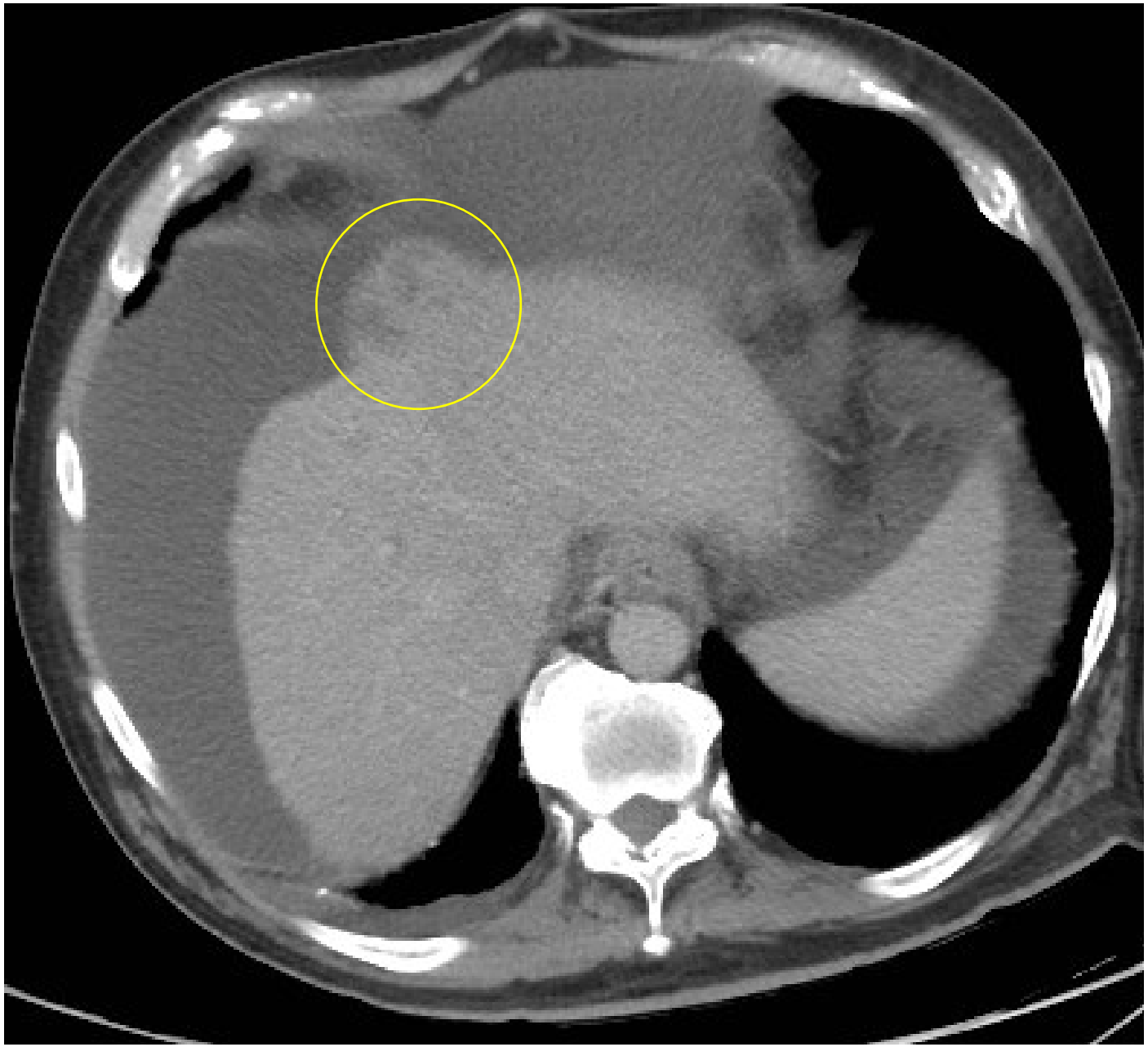
- 67 year old male with known diagnosis of HCC by imaging.
- MELD of 13 on presentation, Child Pugh B, ECOG – 1
- Tbili 0.7, Alk Phos – 189, AST – 12, ALT – 24, AFP – 62, Cr – 0.7
- Patient initially read outside of Milan at outside center and was deemed non-surgical.

Initial Imaging





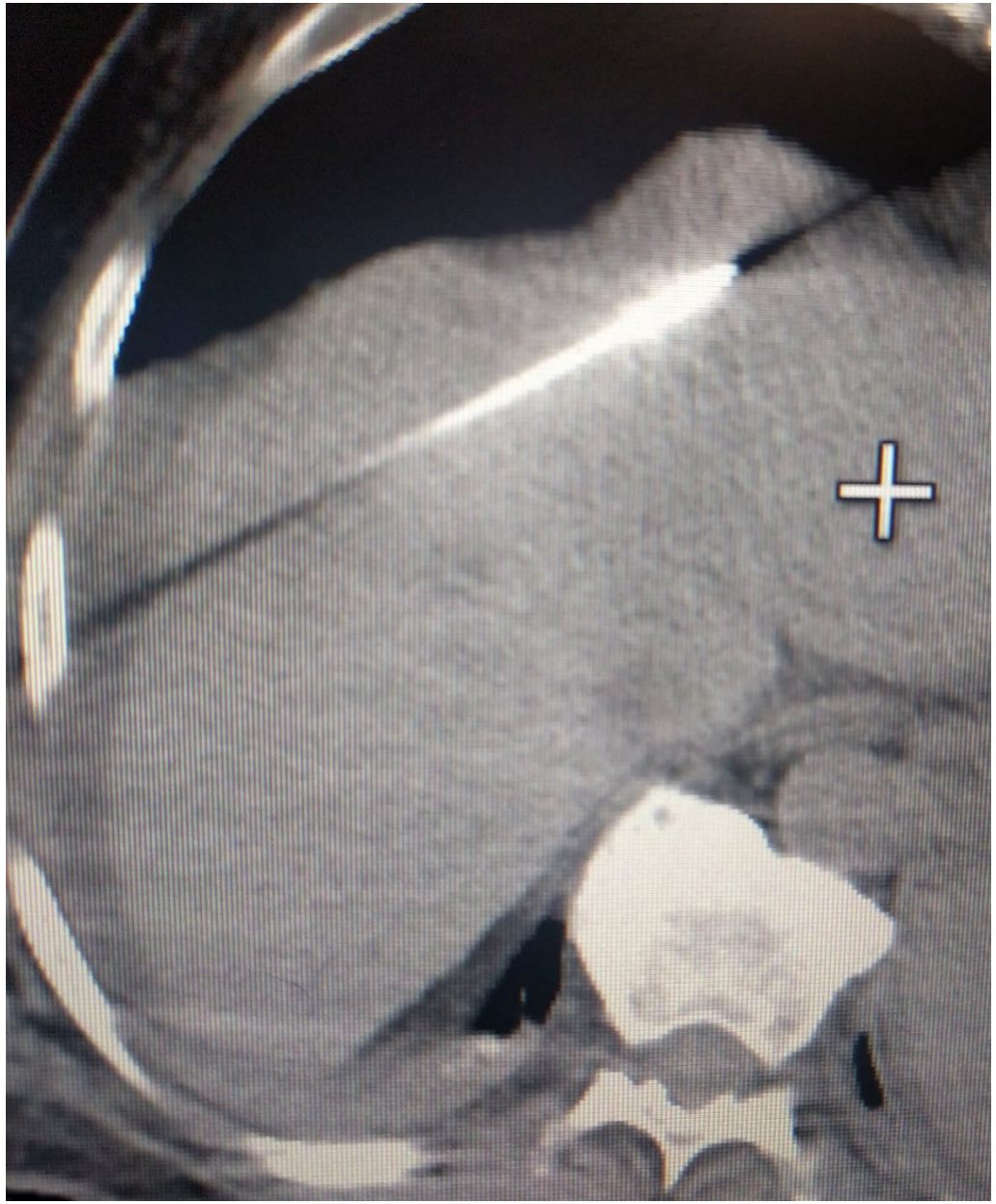
(bottom right) demonstrating enhancing residual lesion

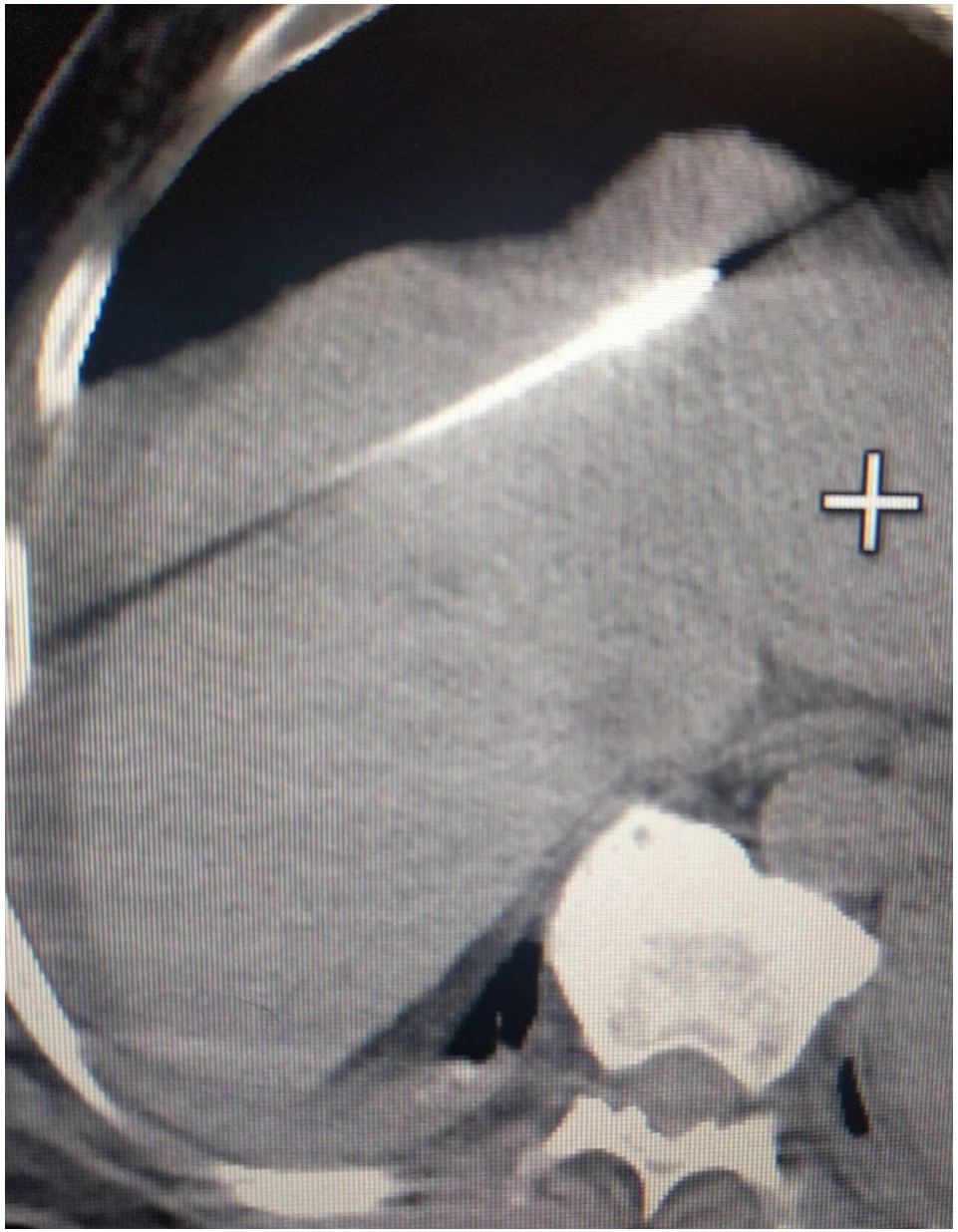


TACE Images – treated with 1 vial LC Beads

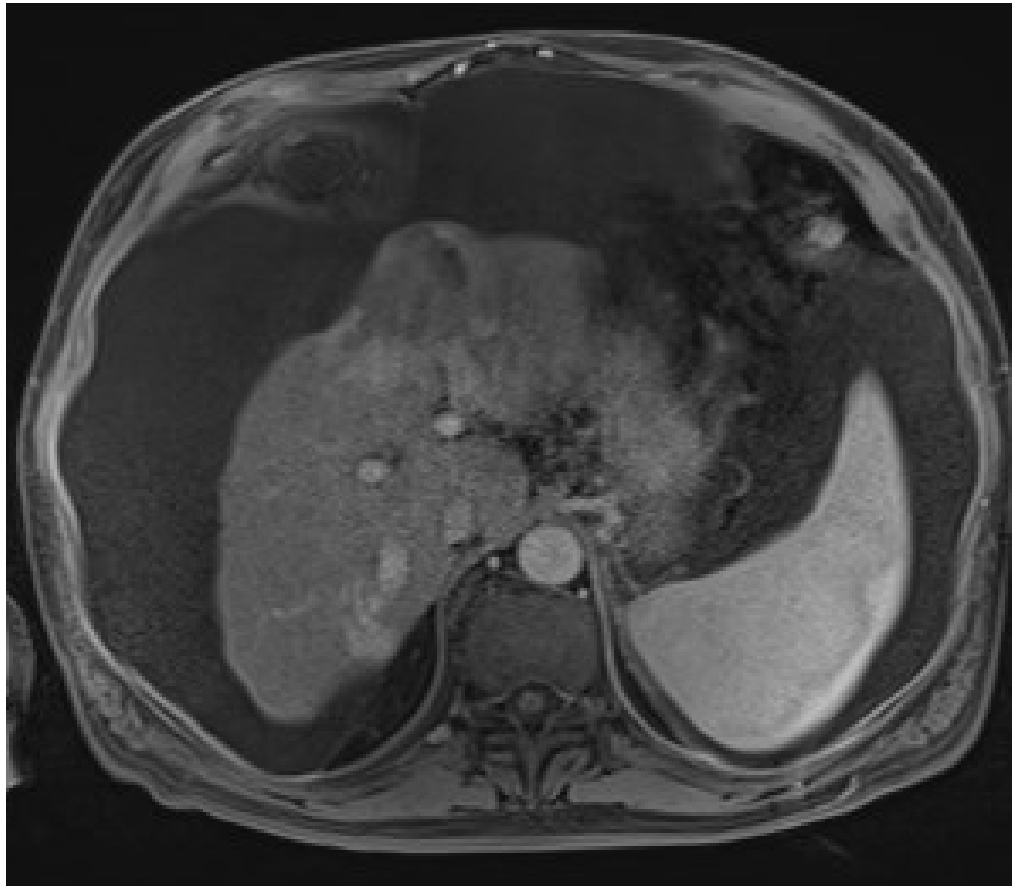
Post TACE CT 30 days later:

Post treatment changes: Internal nodular enhancing components “concerning for residual disease”





Post – Ablation CT and MRI thirty days later with no residual disease and continued surveillance recommended.



Patient follow-up:

- Patient activated on transplant list and after 6 months of surveillance was transplanted without complication in 5/2018.

Our Transpant Cohort 2012-2017

- 93 patients with HCC bridged to transplant
- Objective response to DEB-TACE highlights tumors with favorable biology (p<0.001).
- Nonresponders to treatment highlight an increased risk of posttransplantation HCC recurrence (35% vs 1% p<0.001).

Assessment of Response to Transcatheter Arterial Chemoembolization with Doxorubicin-eluting Microspheres: Tumor Biology and Hepatocellular Carcinoma Recurrence in a 5-year Transplant Cohort[1]

Radiology

Initial treatment response	
Complete response	30 (32)
Partial response	41 (44)
Stable disease	22 (24)
Local disease progression	0 (0)
Final treatment response prior to transplantation	
Complete response	41 (44)
Partial response	35 (38)
Stable disease	13 (14)
Local disease progression	4 (4)

What we began to notice…

- New proposals for allocation of liver transplant.
  - Changing from district models to acuity circles.

- Transplant listing times were starting to get longer.
  - 1-3 month waitlist times were now becoming 6+ months.
  - Patients were needing more interventions.

- It’s time for us to pivot…

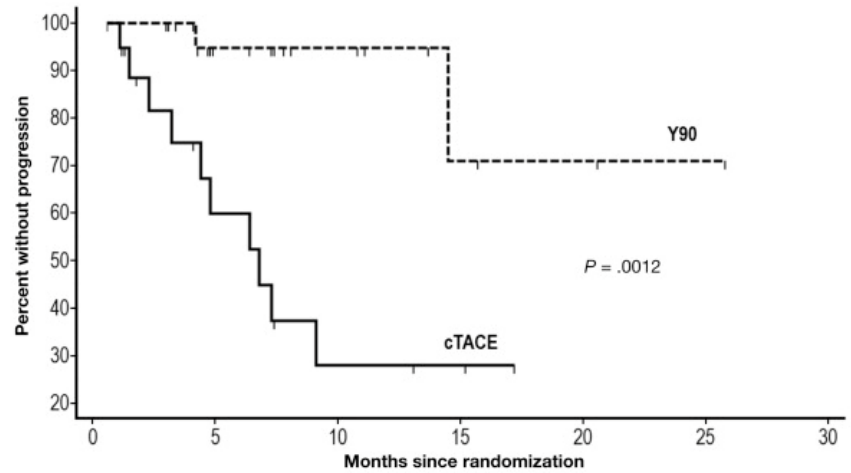
Intra-arterial Therapy (Y90 vs TACE)

Gastroenterology

Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma

Riad Salem,[1,2,3,*] **Andrew C. Gordon**,[1,*] Samdeep Mouli,[1] Ryan Hickey,[1] Joseph Kallini,[1] Ahmed Gabr,[1] Mary F. Mulcahy,[2] Talia Baker,[3] Michael Abecassis,[3] Frank H. Miller,[4] Vahid Yaghmai,[4] Kent Sato,[1] Kush Desai,[1] Bartley Thornburg,[1] Al B. Benson,[2] Alfred Rademaker,[5] Daniel Ganger,[6] Laura Kulik,[6] and Robert J. Lewandowski[1,2]

- Prospective, RCT: TACE or Y90
- Y90 provided longer TTP and lower toxicity
- No significant difference in mOS

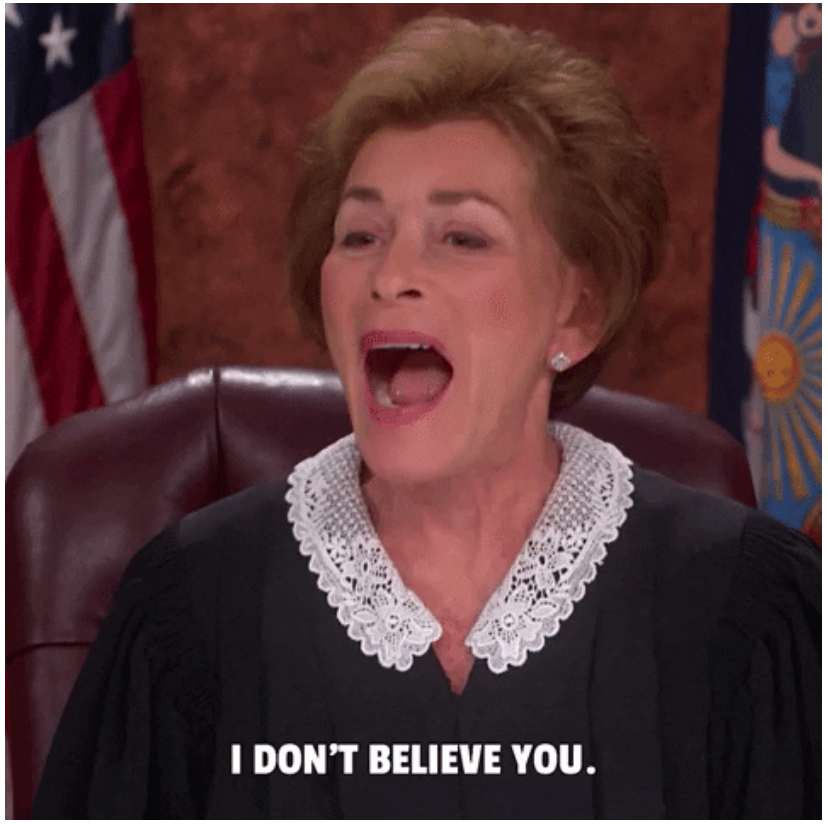


Number at risk

Group: cTACE						
21	8	3	2	0	0	0
Group: Y90						
24	12	7	3	2	1	0

	Y90	TACE	
TTP	>26 mos	6.8 mos	HR 0.12, P=0.0012
mOS	18.6 mos	17.7 mos	NS

The year is 2025... Time to follow advancements in science.

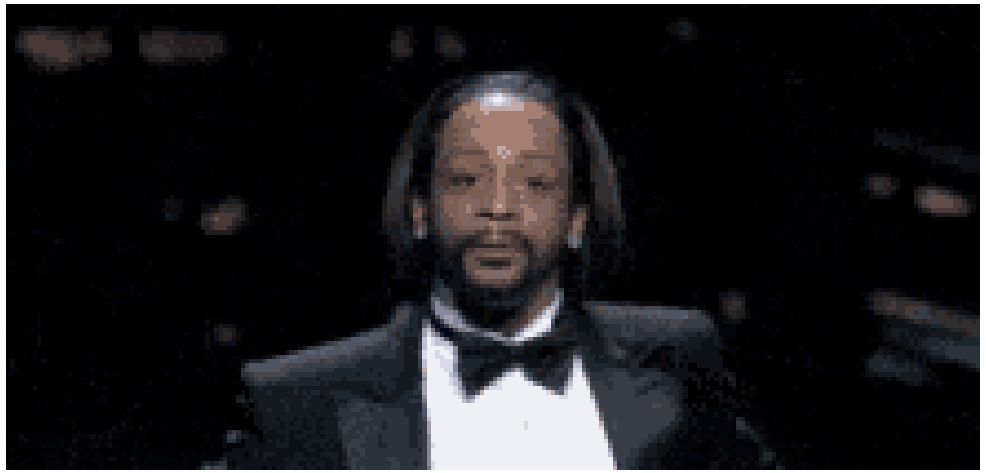


Ok… I still don't believe you.
Y90 vs TACE

Radiology

ORIGINAL RESEARCH · VASCULAR AND INTERVENTIONAL RADIOLOGY

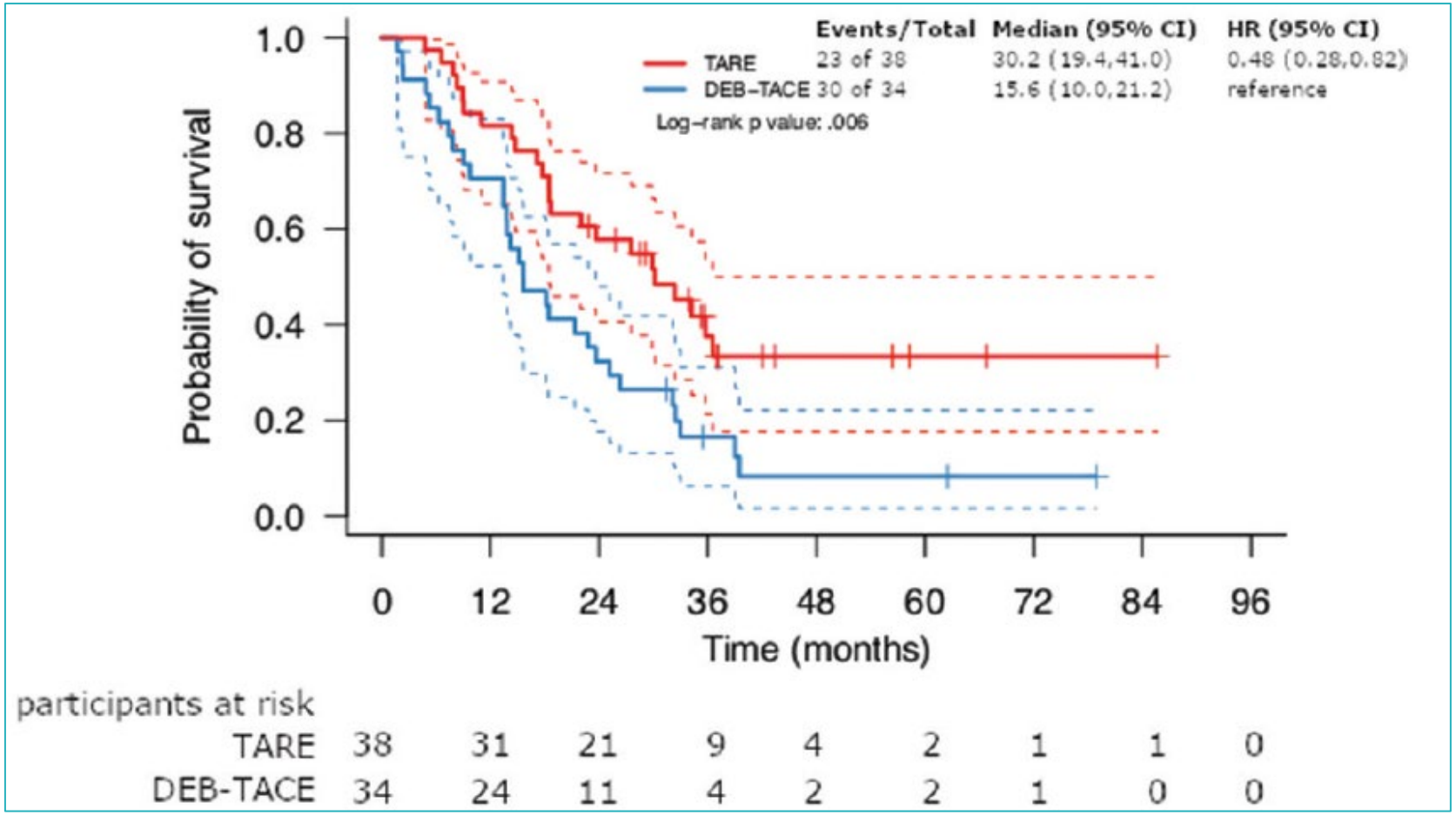
^{90}Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial



Results

- Secondary Endpoint: Median OS – ITT population

- **TARE**: 30.2 months
- **DEB-TACE**: 15.6 months
- **ITT:** HR 0.48, p = 0.006



Conclusion

Radiology

ORIGINAL RESEARCH · VASCULAR AND INTERVENTIONAL RADIOLOGY

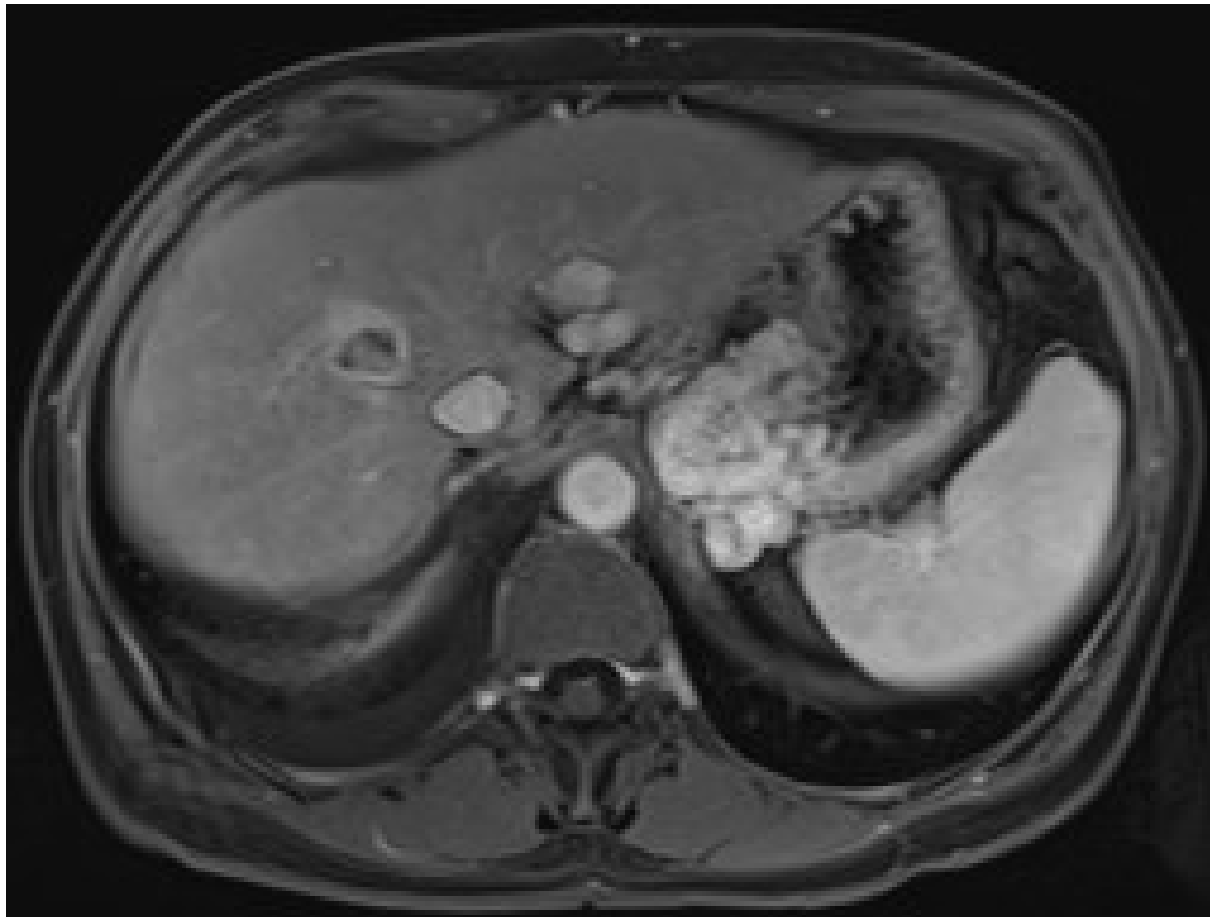
^{90}Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial

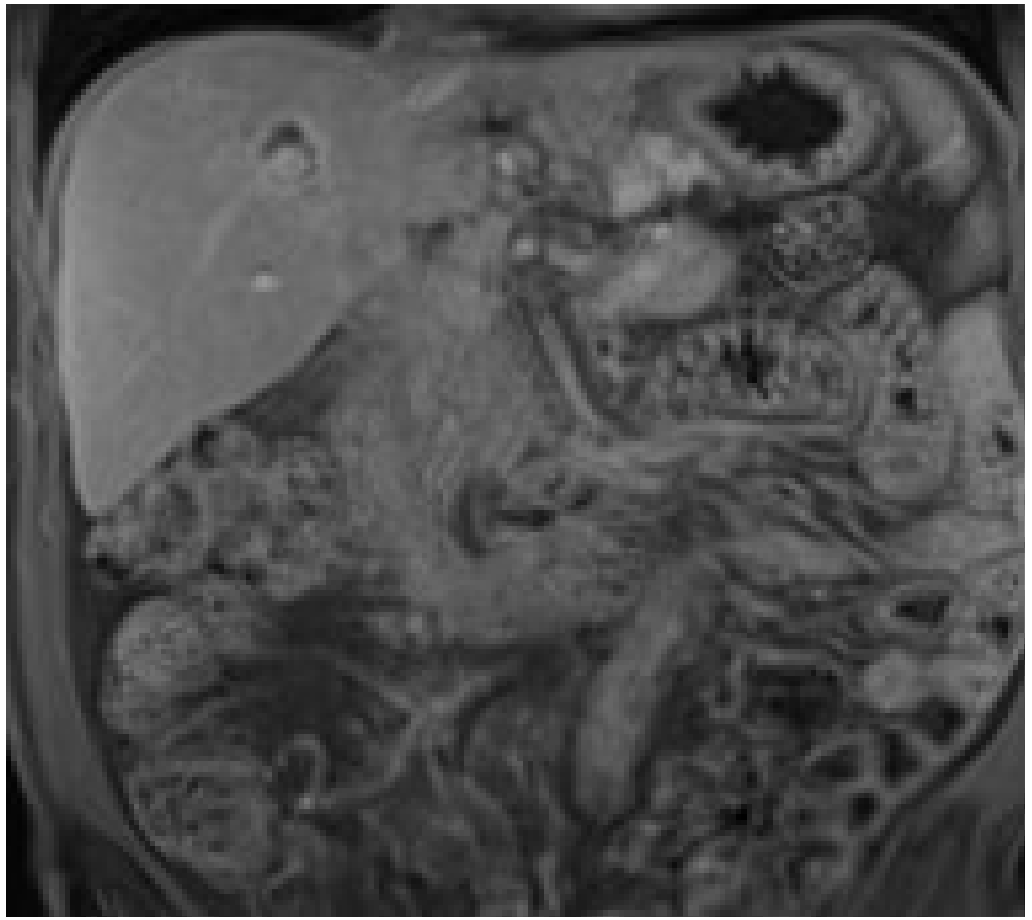
- Y-90 glass TARE resulted in significantly slower tumor progression compared to DEB-TACE for early/intermediate HCC not amenable to curative treatment
- TARE and DEB-TACE had equally high ORR
- Local tumor control was more durable with TARE
- OS was longer in TARE arm
- More patients underwent transplant in the TARE arm

Why We Changed Case Example

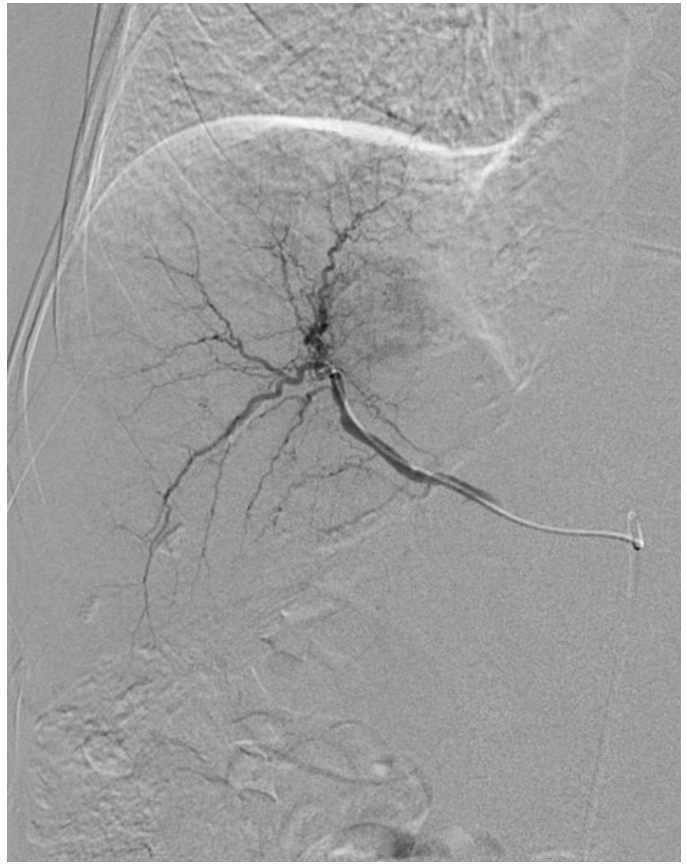
- 55 year old female with ESLD secondary to EtOH use
- CP B (8), MELD of 13, ECOG – 1
- Patient had single 2.5 cm lesion in segment 8 diagnosed by imaging
- AFP: 6, T Bili: 2.0, Albumin: 2.9, LFTs: normal
- Patient with history of prior Doxorubicin TACE with partial response to treatment

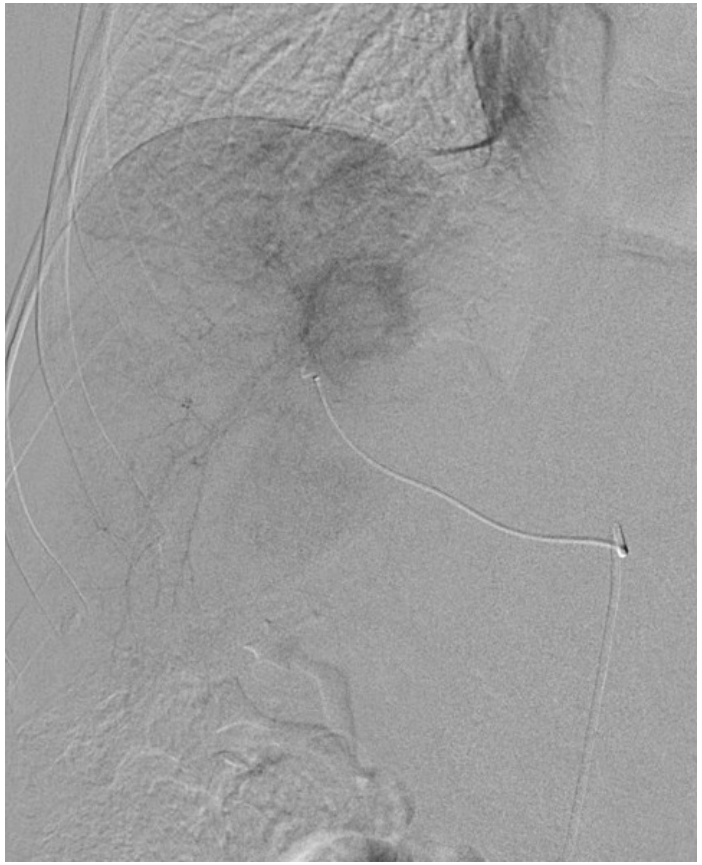
Post-TACE Imaging





Mapping Angiogram Images

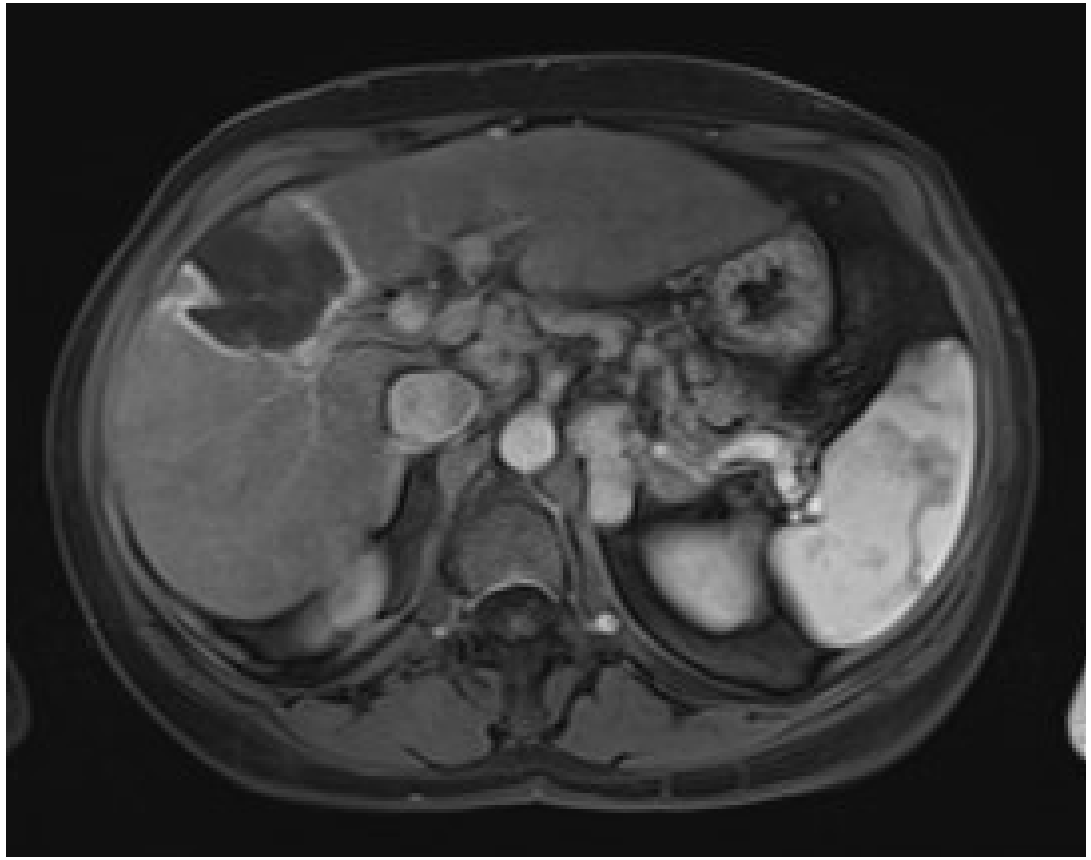


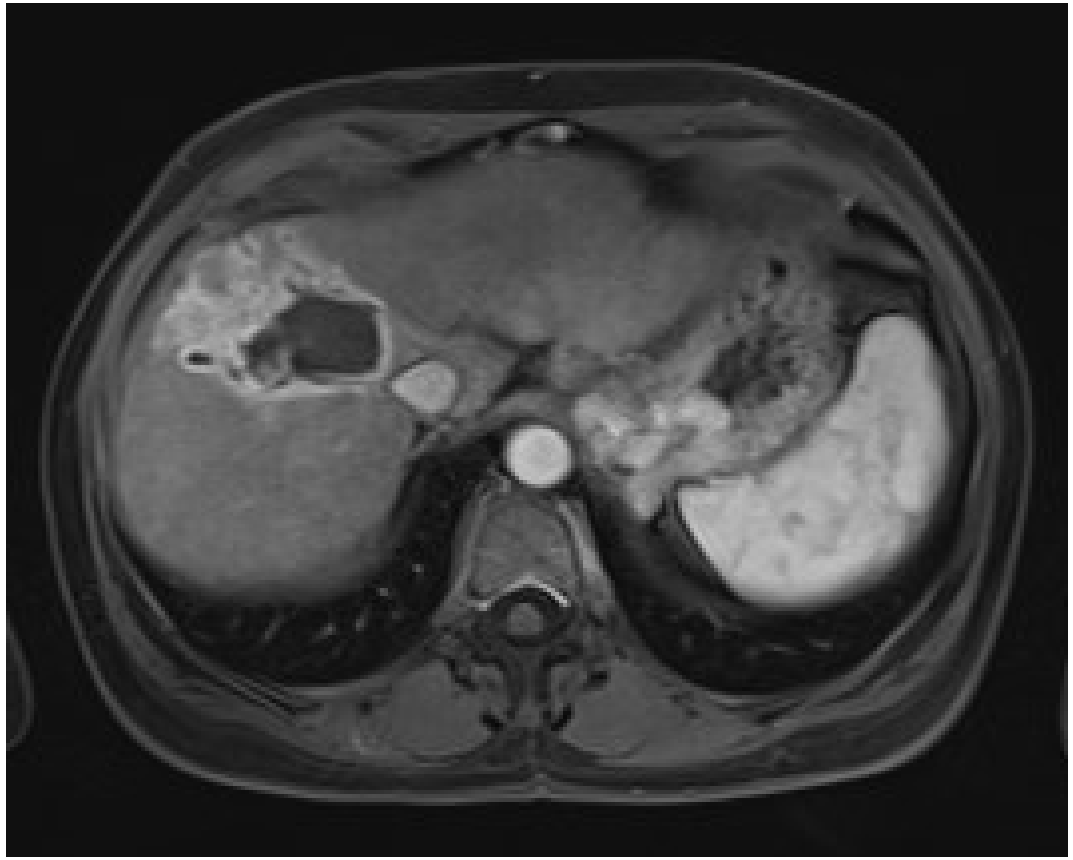


Procedure

- We proceeded to dose for selective radiation segmentectomy with a single 7 Gbq dose.
- First week administration on a Tuesday with an estimated 672 Gy administered to the segment.
- Treatment performed without complication and with same day discharge.

Post-Procedure MRI at 3 months





Patient Follow-up and Take Home Point

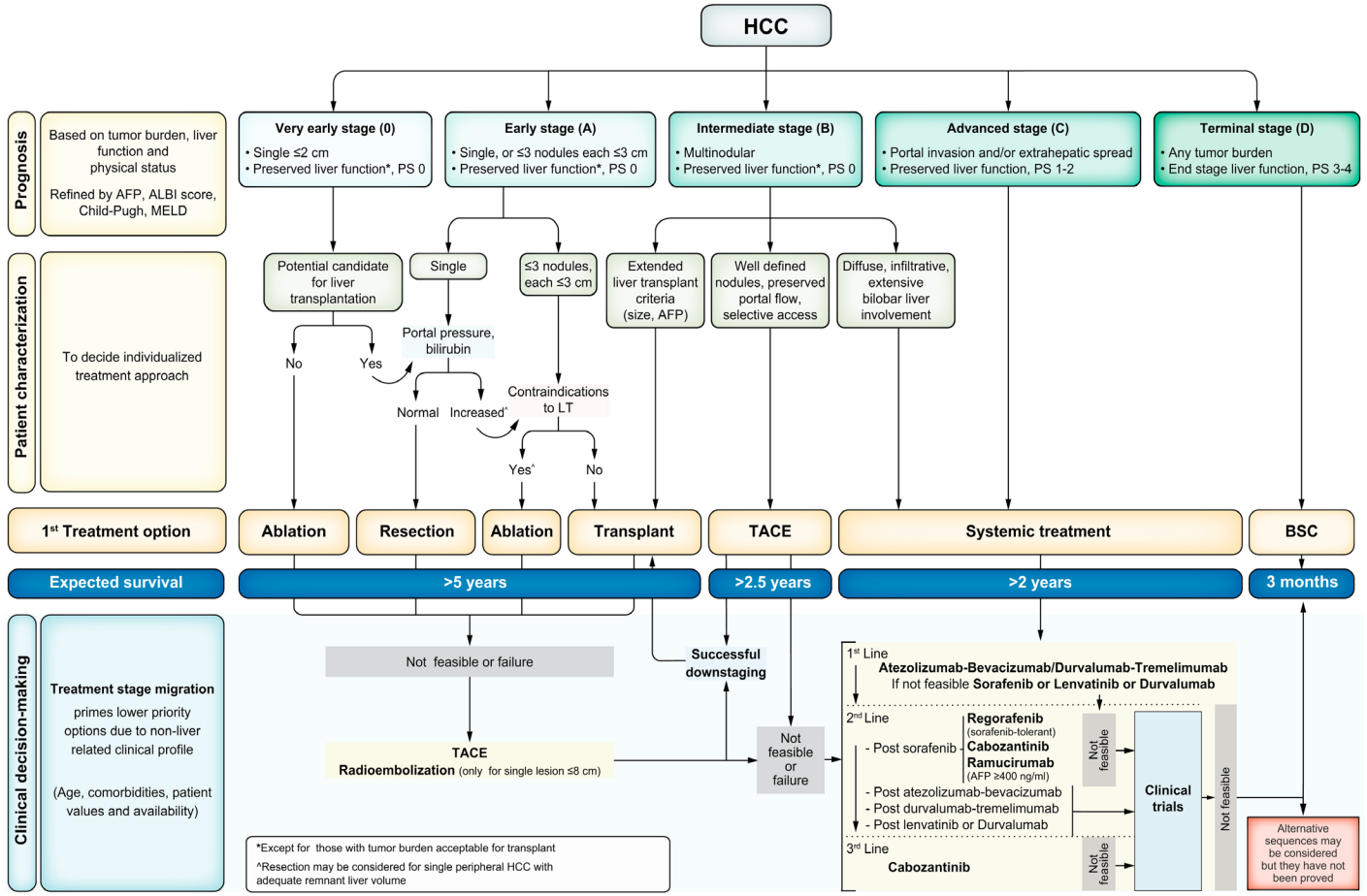
- Patient underwent liver transplant 3.5 months post-Y90 administration with pathology showing 100% tumor necrosis.

- Takeaways:
  - Segmentectomy is a good option for lesions that may be in a difficult location for ablation or when patient prefers to have arterial therapy.

  - Complete tumor necrosis can be achieved with segmentectomy.

Triaging Options

- Curative (Expected survival > 5 yrs)
- Palliative (Expected survival > 2.5 yrs for intermediate, > 2 yrs for advanced)
- Supportive



What about Neuroendocrine tumors?

- Current NCCN guidelines recommend TACE (or bland embolization) and radioembolization for patients with unresectable, liver-dominant, well-differentiated NETs
  - Progressive disease or symptomatic despite systemic therapy
- Meta-analyses and multi-institutional studies show TACE may be associated with improved OS compared to TARE
  - PFS and complication rates similar amongst modalities
- RETNET: prospective, RCT utilizing TACE, TAE, and TARE
  - Interim analysis does not favor a specific modality
  - Drug-eluting bead chemoembolization arm closed early 2/2 safety concerns

Ann Surg Oncol. 2021 Apr; 28(4):1950-1958.
J Am Coll Surg. 2020 Apr;230(4):363-370.
Eur Radiol. 2017 Dec;27(12):4995-5005.

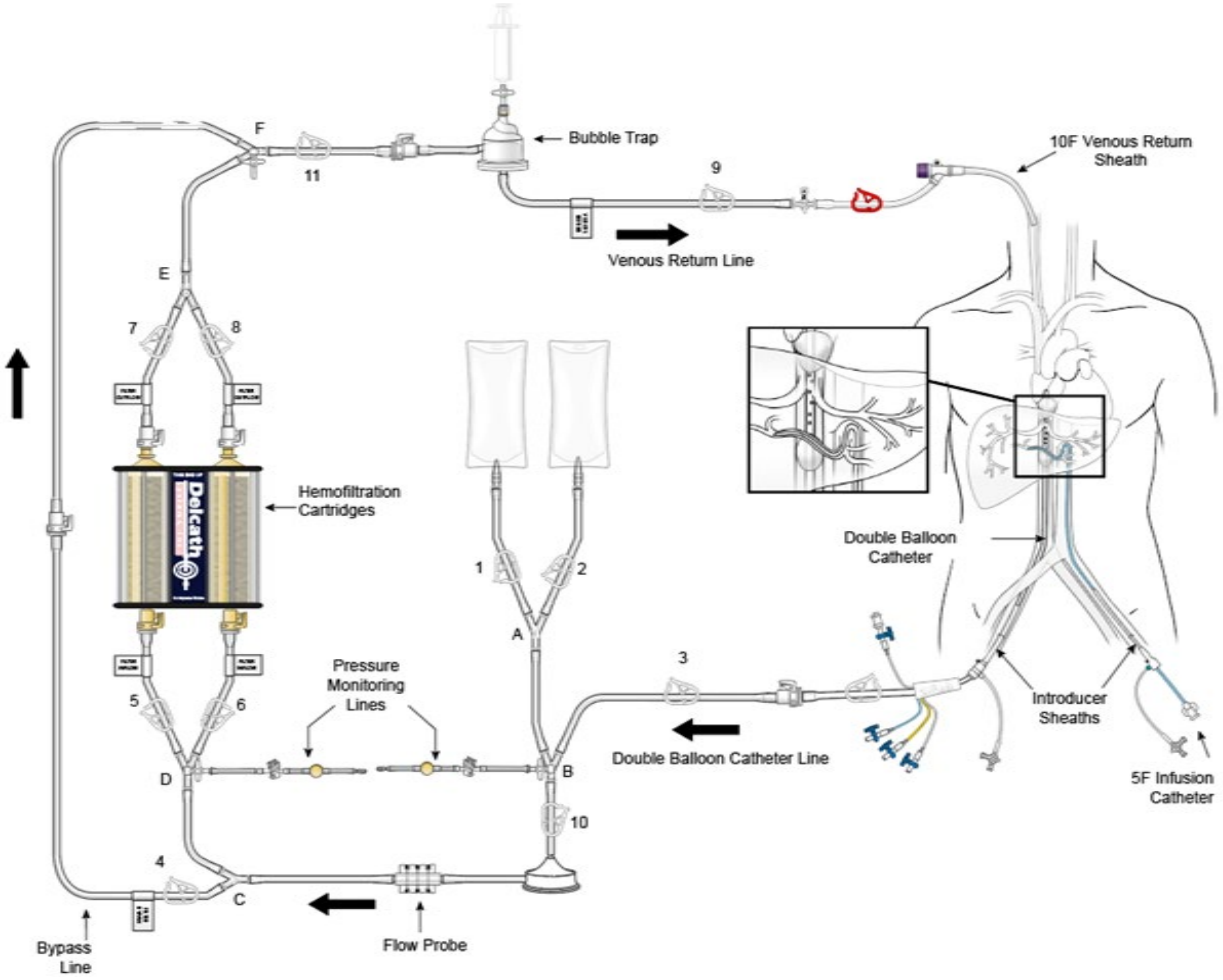
Moving on...

What else is new?!?!

- Histotripsy, IRE, PEF, PHP…

HEPZATO KIT

- Closed circuit of catheters and filters
- Delivers chemotherapeutic agent (melphalan) directly with simultaneous filtration of hepatic venous blood during drug infusion and washout
- Results in relatively high melphalan dose locally to intrahepatic tumors but also reduced systemic exposure.



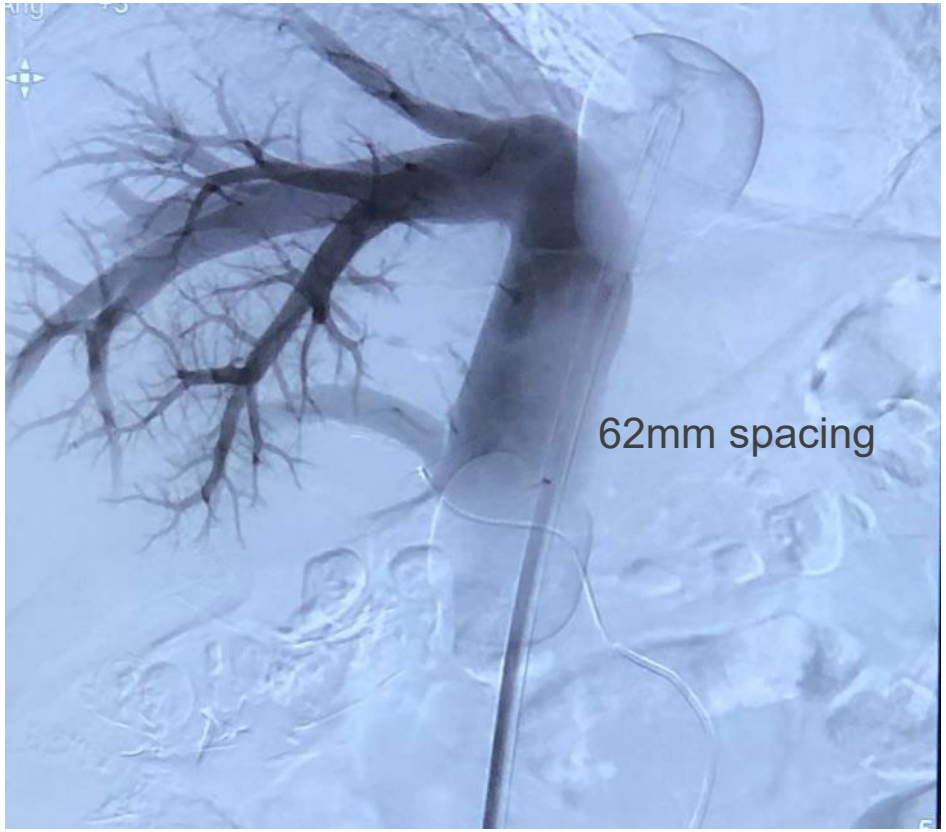
Selection of Balloon Spacing

The HEPZATO KIT comes available with two different lengths of balloon spacing: 50mm and 62mm:

Variables that affect the choice of balloon spacing length:

Variation in the length of the retro-hepatic segment of the inferior vena cava

Relative positions of hepatic and renal veins



Important: IR needs to decide which KIT (50mm or 62mm spacing) will be used for the PHP procedure **before** the actual PHP procedure

Delcath

IR Procedural Flow - **Catheter Location**


Interventional Radiologist

Based on evaluation of hepatic artery, two different infusion strategies can be utilized: lobar infusion or whole liver infusion.

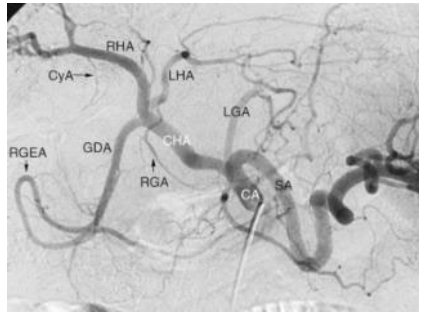
If performing a lobar infusion approach:

- The catheter is positioned to isolate a lobe
- The treatment is administered sequentially
- It requires HEPZATO dose splitting
- Dosing to each lobe is based on relative liver volume and is traditionally a 60% (right lobe) to 40% (left lobe) split.
- The catheter must be repositioned during HEPZATO infusion
- It is suggested to begin with the most difficult catheterization point in order to minimize catheter repositioning time

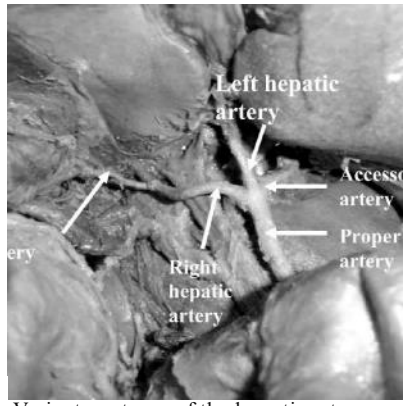
If performing a whole liver infusion approach:

Performing a whole liver infusion approach is dependent on arterial blood flow
Whole liver infusion may require minimal embolization.

Distal catheter placement to non-hepatic arterial branches can reduce requirements for embolization. adequate catheter positioning minimizes risk of infusion failure and reflux.



Embolotherapeutic Strategies for Hepatocellular Carcinoma: 2020 Update, Kishore et al, Cancers



Variant anatomy of the hepatic artery in adult Kenyans, European Journal of Anatomy, 2007, Kitungu et al.

Delcath

IR Procedural Flow - **Establishing Hemofiltration & Isolation**

Start ECF Bypass Circuit

When HEPZATO has been delivered to the procedural room and the connection of the hemofiltration circuit to catheters has been made, the perfusionist turns on the pump and then bypass can be started.

Bypass:

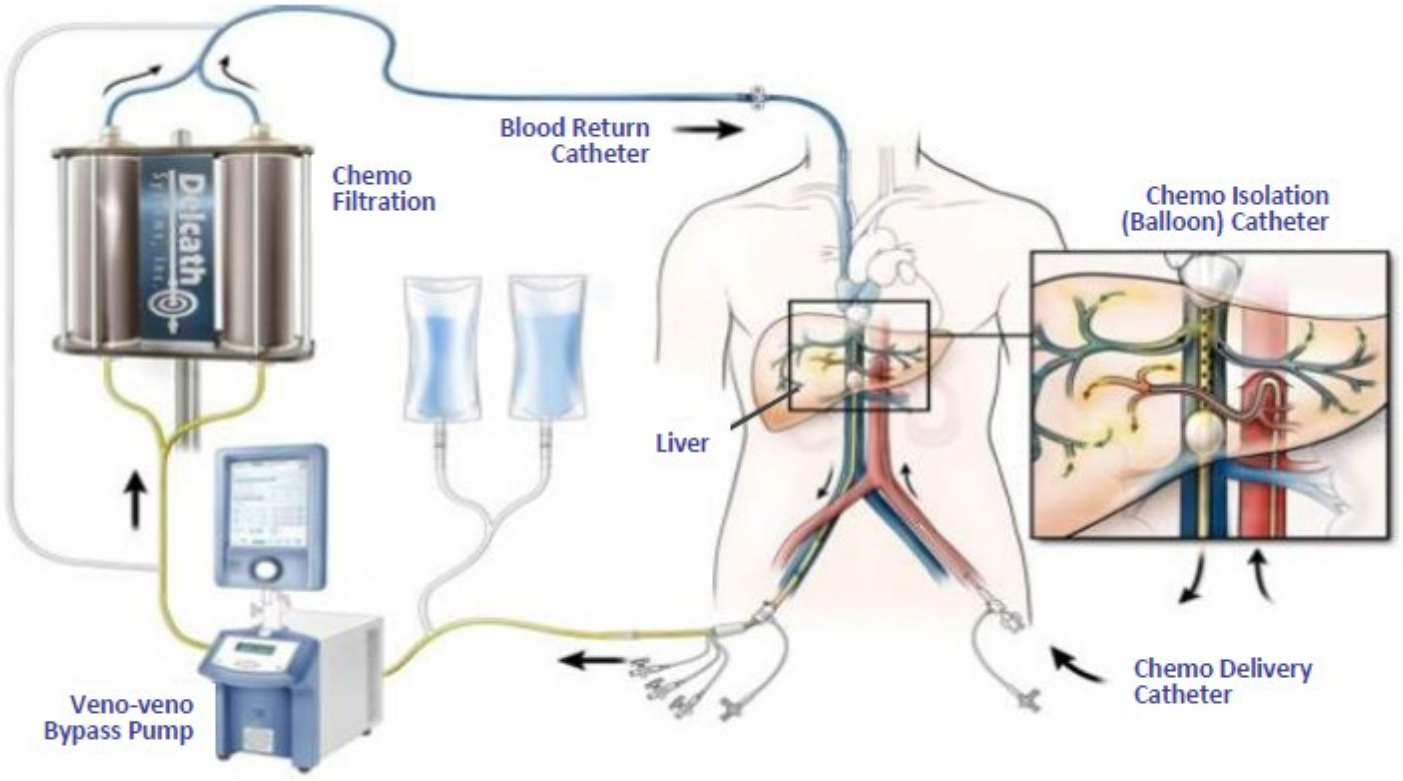
Venous blood aspirated from central lumen

Blood flows through fenestrations in DBC

Blood flows through the pump

Blood flows through the bypass line

Blood returns to the patient through the venous return sheath



During Hemofiltration and Isolation, the Perfusionist continuously monitors the pump pressures

Evidence for PHP

- Prospective phase II study in 35 patients with uveal melanoma liver metastases
- ORR: 72%
- Median OS: 19.1 months
  - Significantly longer in patients who responded to treatment (27.5 months vs 11.9 months, p<0.001)
- 1-year OS of 77% and 2-year OS of 43%
- PFS: 7.6 months
- hPFS: 11.2 months

Percutaneous Hepatic Perfusion with Melphalan in Patients with Unresectable Ocular Melanoma Metastases Confined to the Liver: A Prospective Phase II Study

T Susanna Meijer [1], Mark C Burgmans [2], Eleonora M de Leede [3], Lioe-Fee de Geus-Oei [2 4], Bas Boekestijn [2], Henricus J M Handgraaf [3], Denise E Hilling [3], Jacob Lutjeboer [2], Jaap Vuijk [5], Christian H Martini [5], Arian R van Erkel [2], Rutger W van der Meer [2], Fred G J Tijl [6], Frank M Speetjens [7], Ellen Kapiteijn [7], Alexander L Vahrmeijer [3]

Ann Surg Oncol. 2021 Feb;28(2):1130-1141.

What about mixing treatments together?

Why Add Y90 to immunotherapy in HCC?

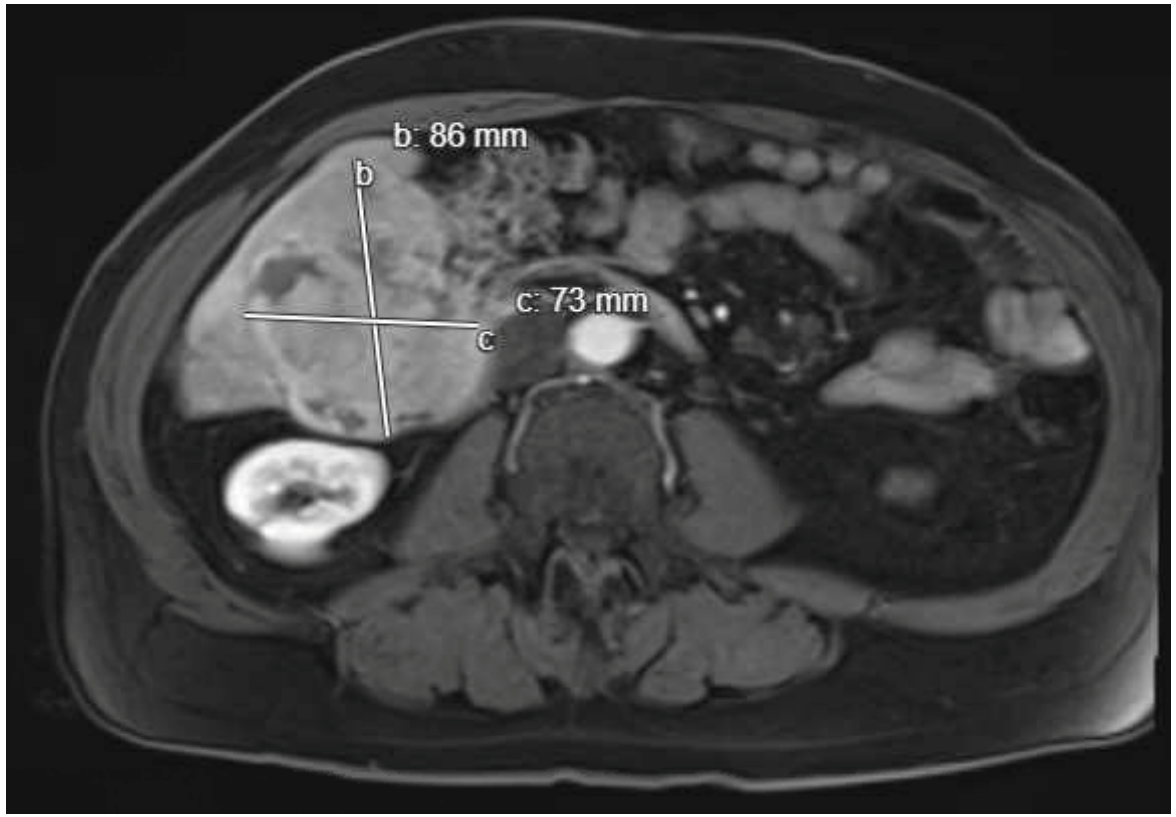
Tumor Microenvironment

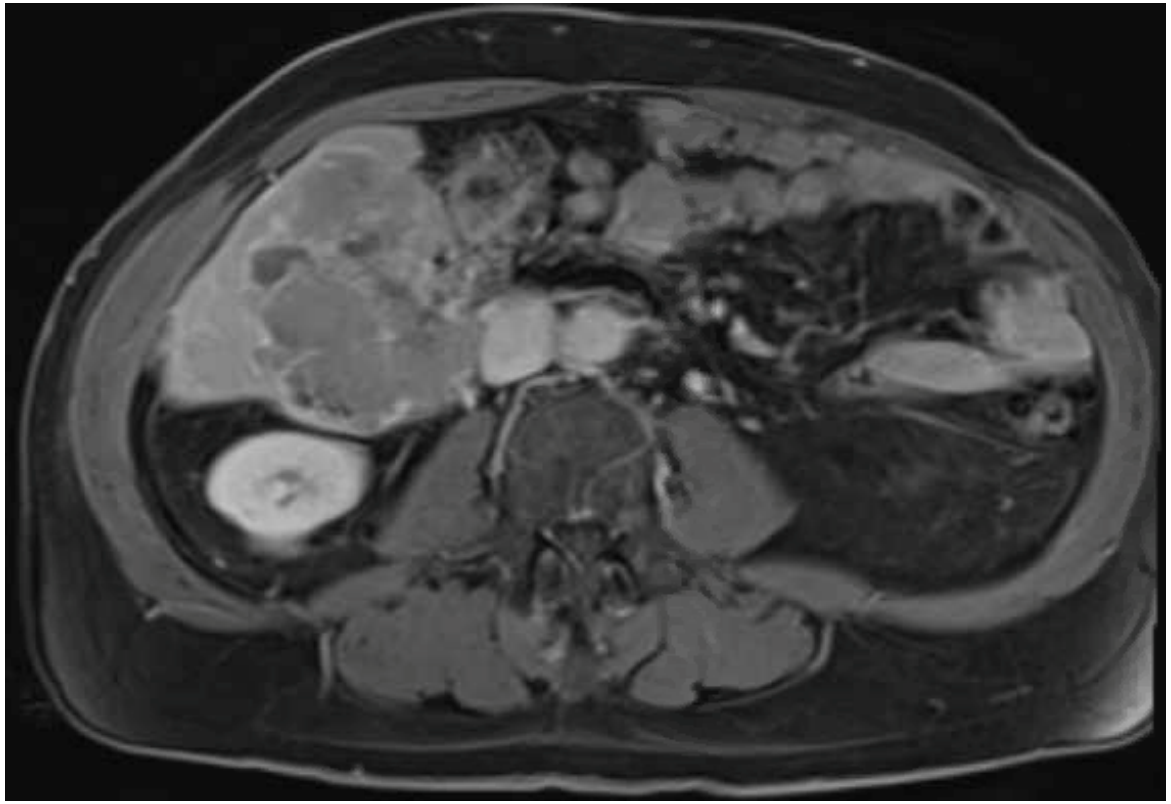
Brandi N et al, *Int J Mol Sci 2023,24,8598*

Combination Case Example

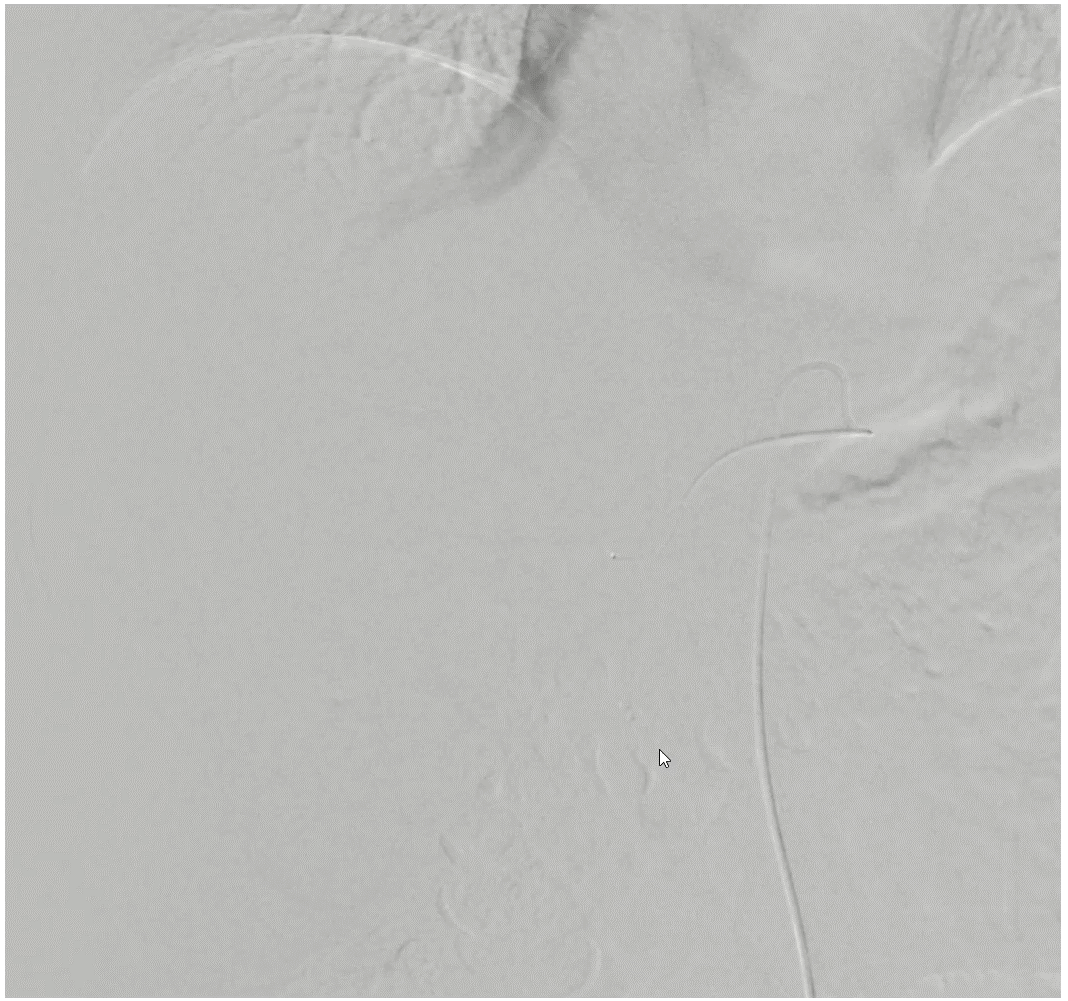
- 70 yo M with HCV cirrhosis found to have a 9cm mass in seg V
- MELD-Na 6
- Total Bilirubin 0,4, Albumin 3.8
- AFP 16

Imaging





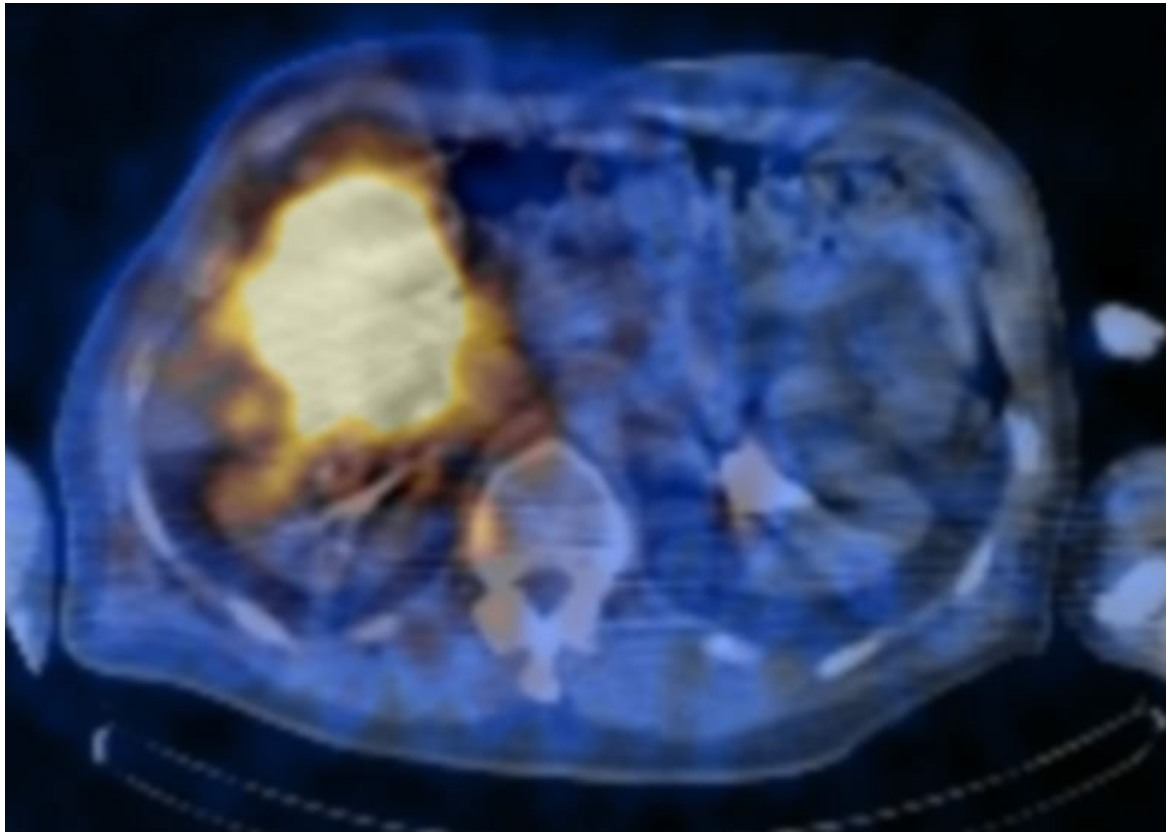
Mapping



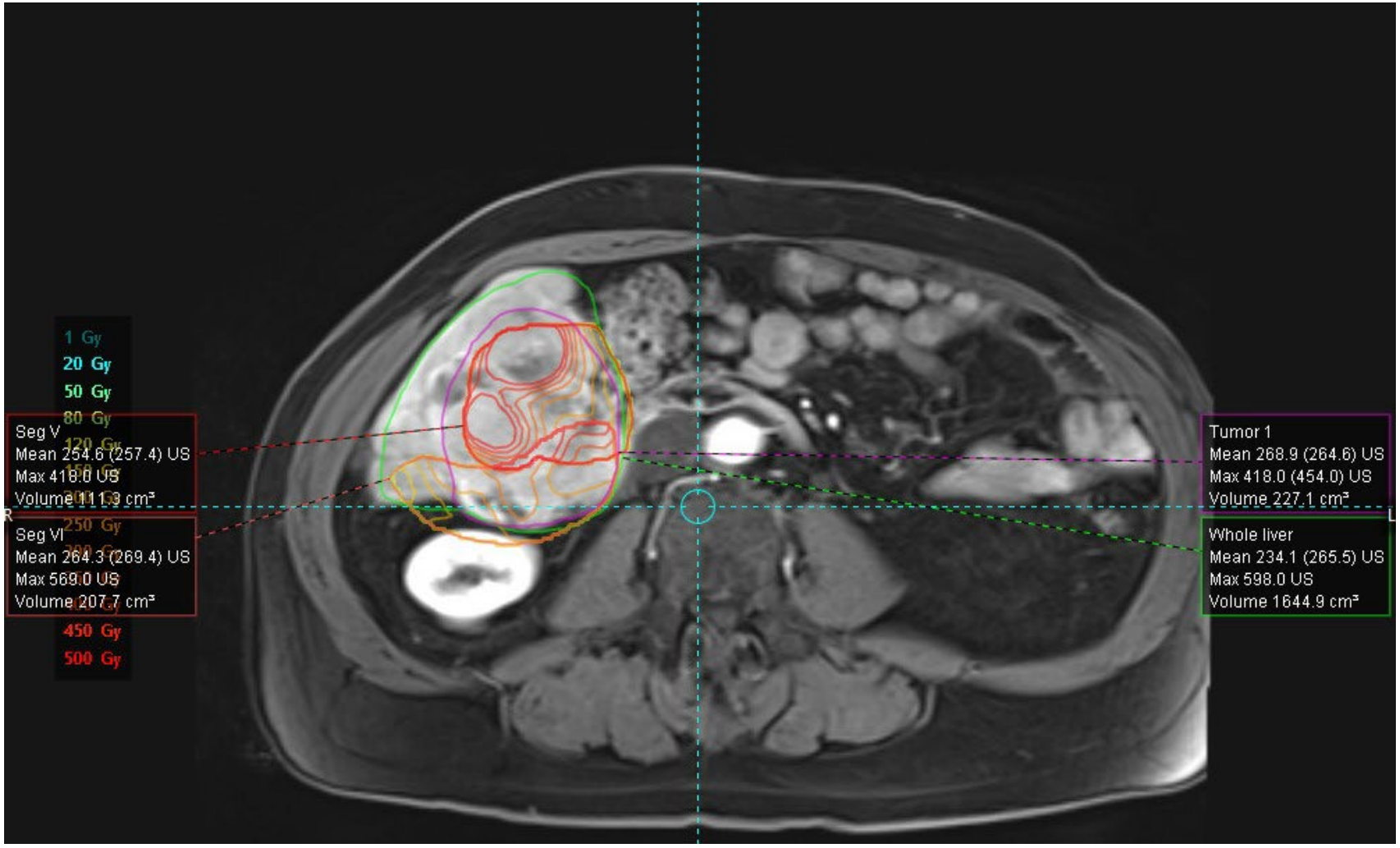
Delivery

- Perfused volume: 289mL (207mL + 82mL)
- LSF: 6.9%
- Target Dose: 550Gy (483Gy + 732Gy)

- We selected a 5GBq vial (W1 Wed) to be delivered to a subsegmental branch of segment VI and 3GBq vial (W1 Wed) to be delivered to a subsegmental branch of segment V



Delivery



Whole liver volume	1644.9	cm³	
Lung Shunt Fraction	6.9	%	*Manually entered*
Previous dose to the lungs	0.0	Gy	
Residual Fraction	2.0	%	*Default*

	Seg V	Seg VI
Volume, cm³	111.3	207.7
Perfused Fraction, %	6.8	12.6
Calculate	☑	☑
☑ Summation mode		
Activity, GBq	1.36	2.26
Perfused tissue absorbed dose, Gy	541.2	482.0
Perfused tumor absorbed dose, Gy	519.0	539.6
Perfused viable tumor absorbed dose, Gy		
Perfused normal tissue absorbed dose, Gy	668.0	408.9

⚠ VOI quality check: overlaps accepted

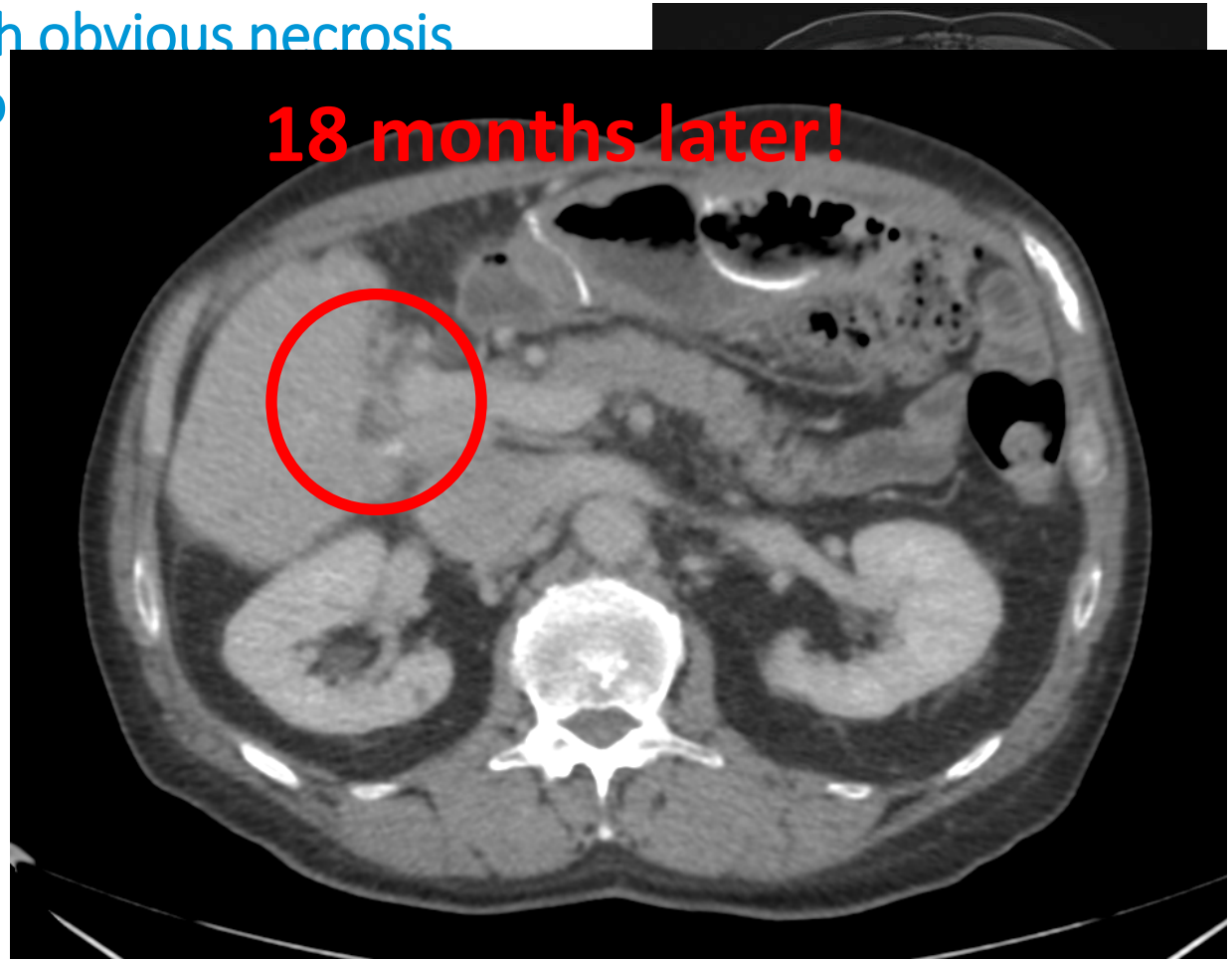
✓ Volume consistency check: OK

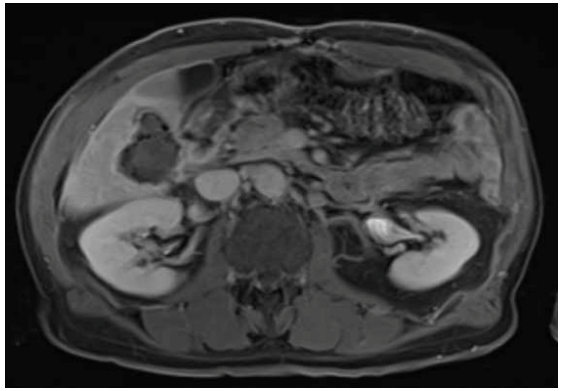
Totals

Num. Perfused Volumes	**2**	
Required activity	**3.62**	**GBq**
Perfused fraction	**17.9**	**%**
Perfused tissue absorbed dose	**545.2**	**Gy**
Perfused tumor absorbed dose	**595.6**	**Gy**
Perfused viable tumor absorbed dose		**Gy**
Perfused normal tissue absorbed dose	**442.3**	**Gy**
Whole liver normal tissue absorbed dose	**33.7**	**Gy**
Current lung absorbed dose	**12.2**	**Gy**
Cumulative lung absorbed dose	**12.2**	**Gy**

Follow-up Imaging and Discussion

- 6 month MRI: CR with obvious necrosis throughout the tumo
or recurrence.





Ochsner's Combination Therapy Data

- 40 patients with median f/u of 12 months
  - Predominantly Child-Pugh A (96%)
  - Predominantly HCV cirrhosis (76%)
  - BCLC-C tumor burden (51%)
  - Median tumor size 7.7cm

- Target lesion: 82% ORR, 51% CR
- Overall response: 59% ORR, 41% CR
- 2-yr OS: 55%

- No difference in AEs, delays, or discontinuation based on regimen
- Sequencing had no effect on response or TTP
- Achieving CR strongly associated with TTP ($p<0.001$) and PFS ($p<0.001$)

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Results

- Treatment-related AEs (Grade 3-4): 35% (14/40)
  - Steroid use: 28%
  - Treatment delays: 31%
  - Discontinuation: 10%

Supplemental Table 1. All Adverse Events

	Cohort (n = 40)	
All AEs	**Any Grade**	Grade 3 or 4
Fatigue, n (%)	23 (58)	0 (0)
Hyponatremia, n (%)	19 (48)	2 (5)
AST increase, n (%)	19 (48)	3 (8)
ALT increase, n (%)	15 (38)	2 (5)
Platelet count decrease, n (%)	19 (48)	0 (0)
Decrease appetite, n (%)	18 (45)	0 (0)
Bilirubin increase, n (%)	15 (38)	3 (8)
Rash, n (%)	14 (35)	0 (0)
Hypertension, n (%)	12 (30)	0 (0)
Nausea, n (%)	12 (30)	0 (0)
Hypothyroidism, n (%)	8 (20)	0 (0)
Asthenia, n (%)	8 (20)	0 (0)
Vomiting, n (%)	8 (20)	0 (0)
Constipation, n (%)	8 (20)	1 (3)
Abdominal pain, n (%)	7 (18)	0 (0)
Edema, n (%)	7 (18)	0 (0)
Pruritus, n (%)	7 (18)	0 (0)
Weight decrease, n (%)	7 (18)	0 (0)
Pyrexia, n (%)	5 (13)	0 (0)
Diarrhea, n (%)	5 (13)	1 (3)
Cough, n (%)	4 (10)	0 (0)
Proteinuria, n (%)	4 (10)	0 (0)
Mucositis, n (%)	2 (5)	0 (0)
Epistaxis, n (%)	2 (5)	0 (0)
Alopecia, n (%)	1 (3)	0 (0)
Insomnia, n (%)	1 (3)	0 (0)
Dizziness, n (%)	1 (3)	0 (0)
Pneumonitis, n (%)	1 (3)	1 (3)
Bowel perforation, n (%)	2 (5)	2 (5)
AEs that Led to Treatment Change		
Total AEs, n (%)	39 (98)	14 (35)
AEs that led to discontinuation, n (%)	3 (8)	
AEs that led to delay in treatment, n (%)	10 (25)	
AEs that led to death, n (%)	1 (3)	
Immune-mediated AE requiring steroid use, n (%)	11 (28)	

Abbreviations: Adverse events (AEs), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT).

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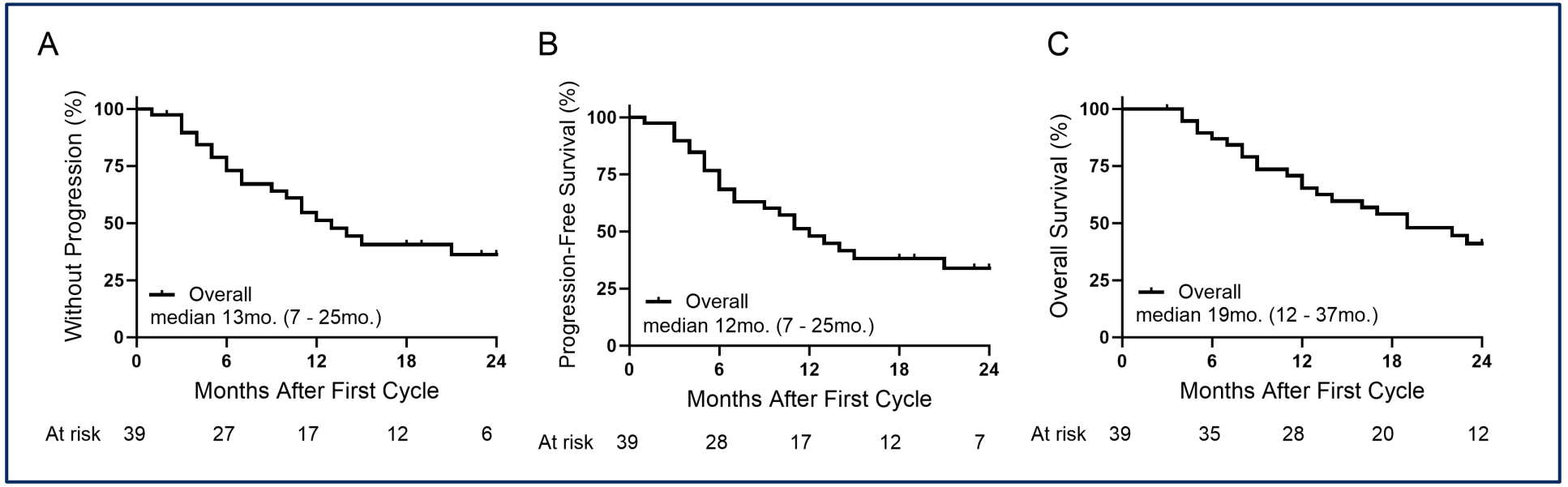
Survival Outcomes

- Median TTP: 13 months
- Median PFS: 12 months
- Median OS: 19 months



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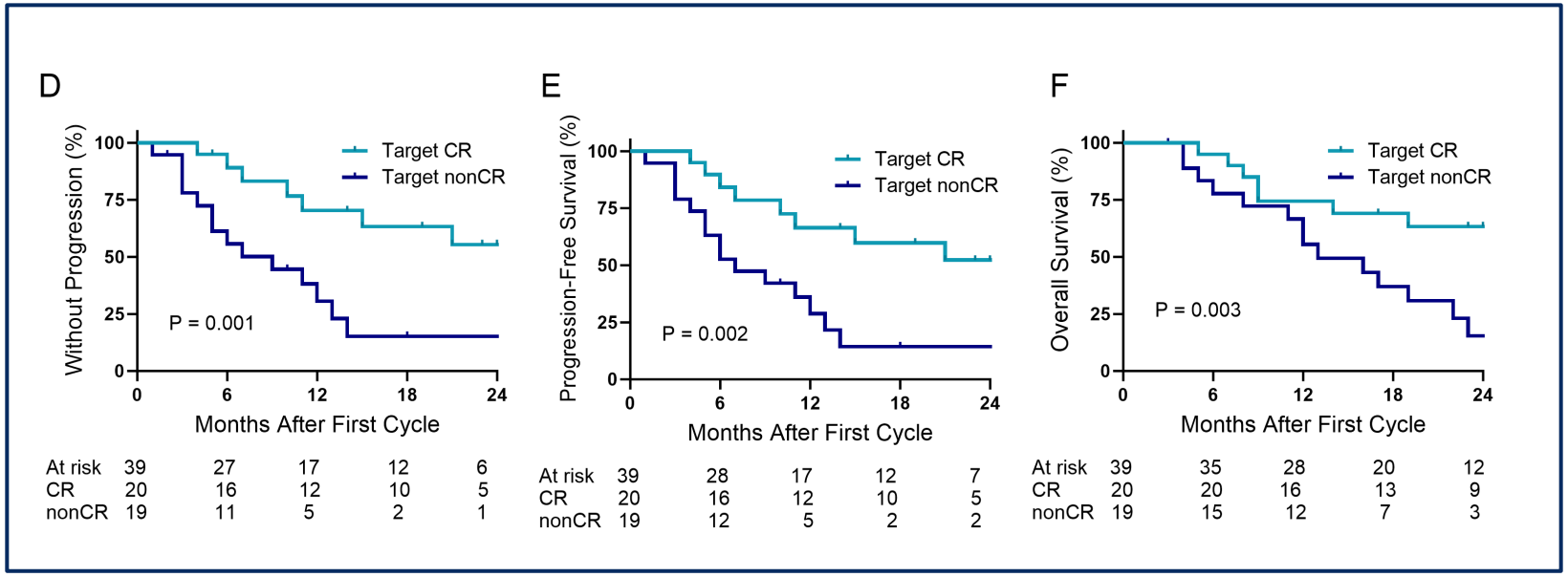
Survival Outcomes by Response

- Target CR -> improved TTP (p=0.001), PFS (p=0.002), and OS (p=0.003)
- Overall CR -> stronger TTP (p<0.001), PFS (p<0.001), and OS (p<0.001)
- Median OS: not met for CR



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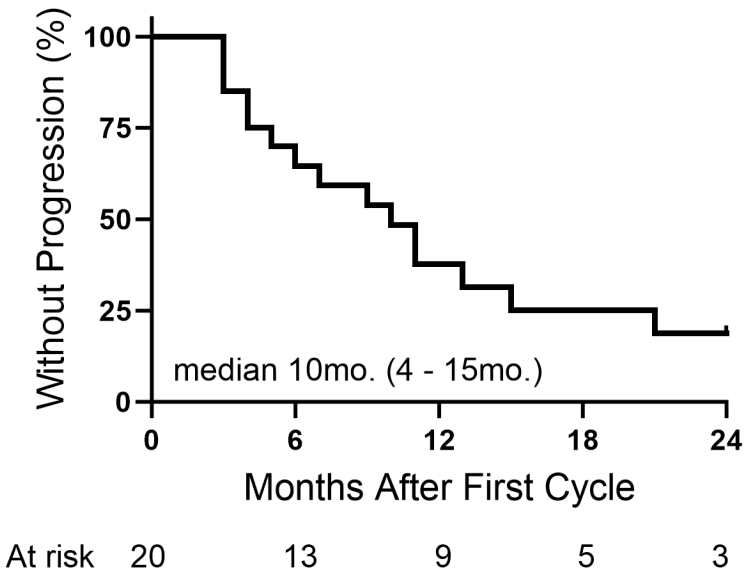
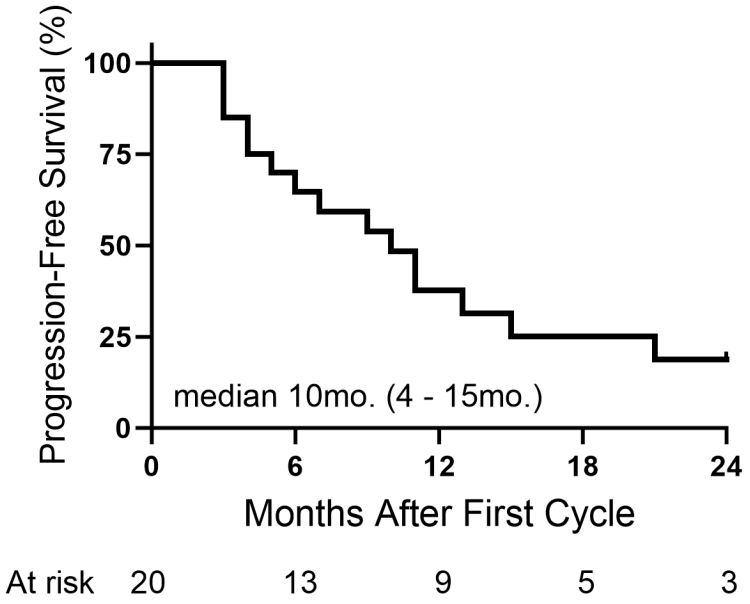
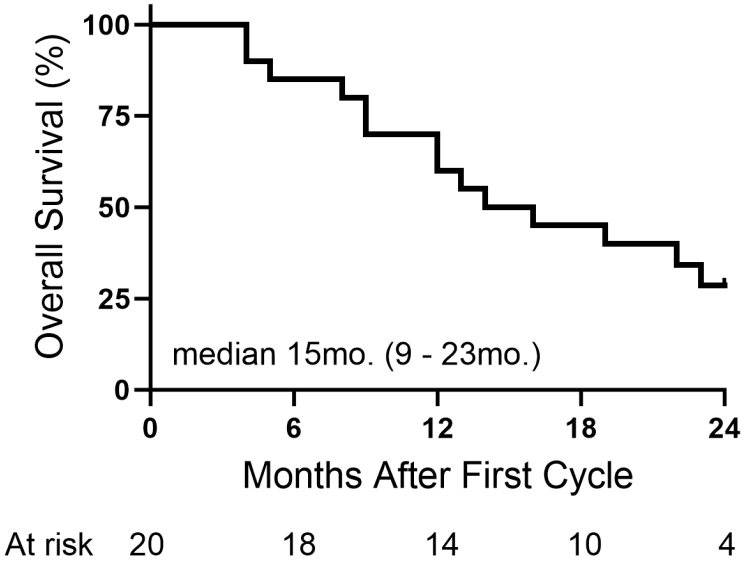
Survival Outcomes for Advanced HCC

- **Median TTP: 10 months**
- **Median PFS: 10 months**
- **Median OS: 15 months**







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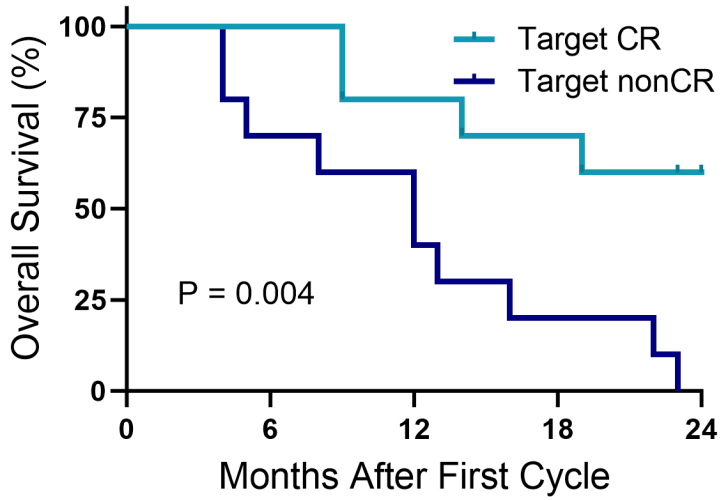
Survival Outcomes for Advanced HCC by Response

- TTP by response: 15 months CR vs 5.5 months non-CR (p=0.015)
- PFS by response: 15 months CR vs 5.5 months non-CR (p=0.015)
- OS by response: median not reach for CR vs 12 months non-CR (p=0.004)



At risk	20	18	14	10	4
CR	10	10	10	8	4
nonCR	10	8	6	3	0

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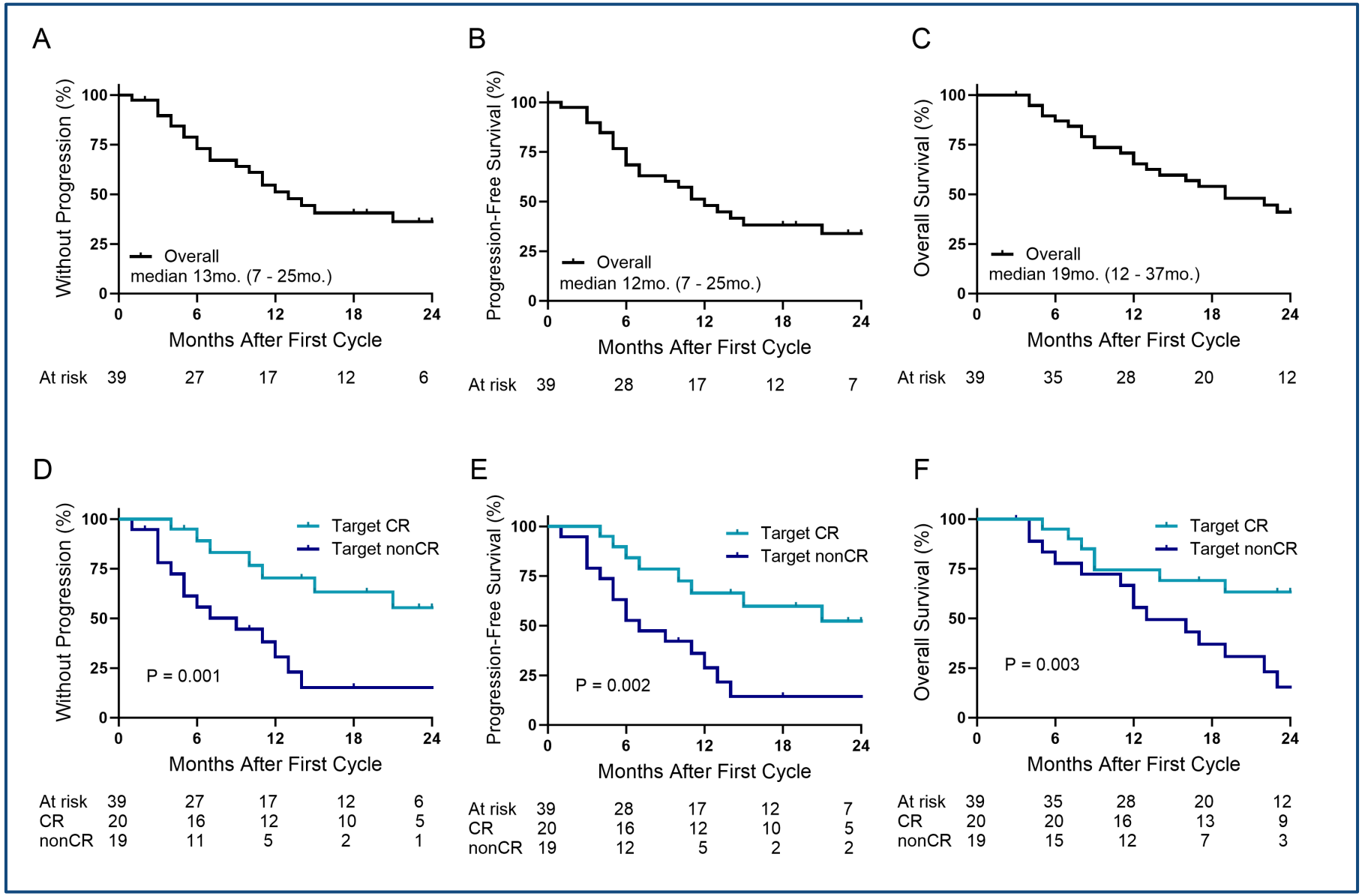
When Combination Works… it works well!



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Thank you for your time and attention!


Ranked #1
in the Nation in
Liver Transplants
D6
D5

Thank you!

Ochsner