



Hepatocellular Carcinoma Debate: Management of Barcelona Clinic Liver Cancer (BCLC) Stage B Liver Confined Advanced Hepatocellular Carcinoma (HCC)

Panel & Disclosures

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City of Hope

- *No relevant financial relationships.*

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- *Grant/Research Support for AstraZeneca*
- *Consultant for Coherus, Eisai, Exelixis, Genentech, Ipsen, Lexicon, Merck, and Mina Therapeutics.*

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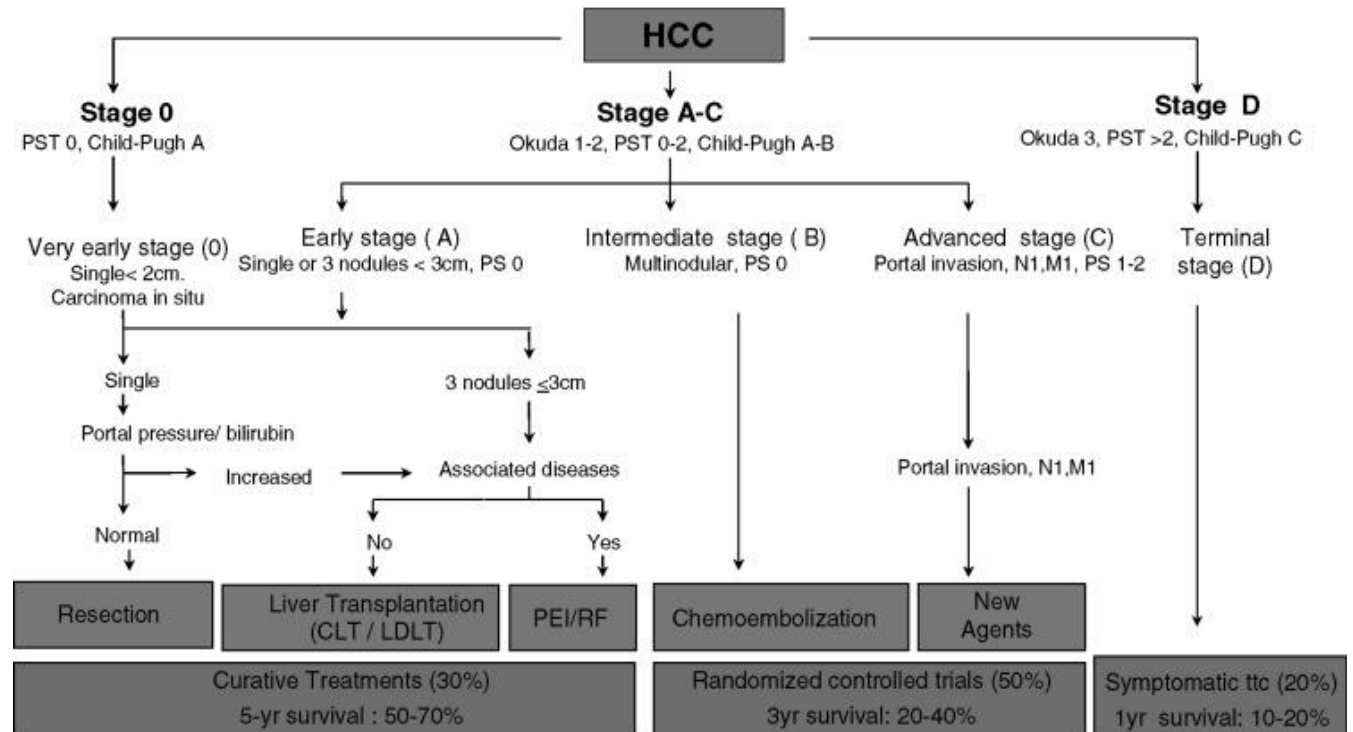
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BCLC (Barcelona Clinic Liver Cancer)

1999

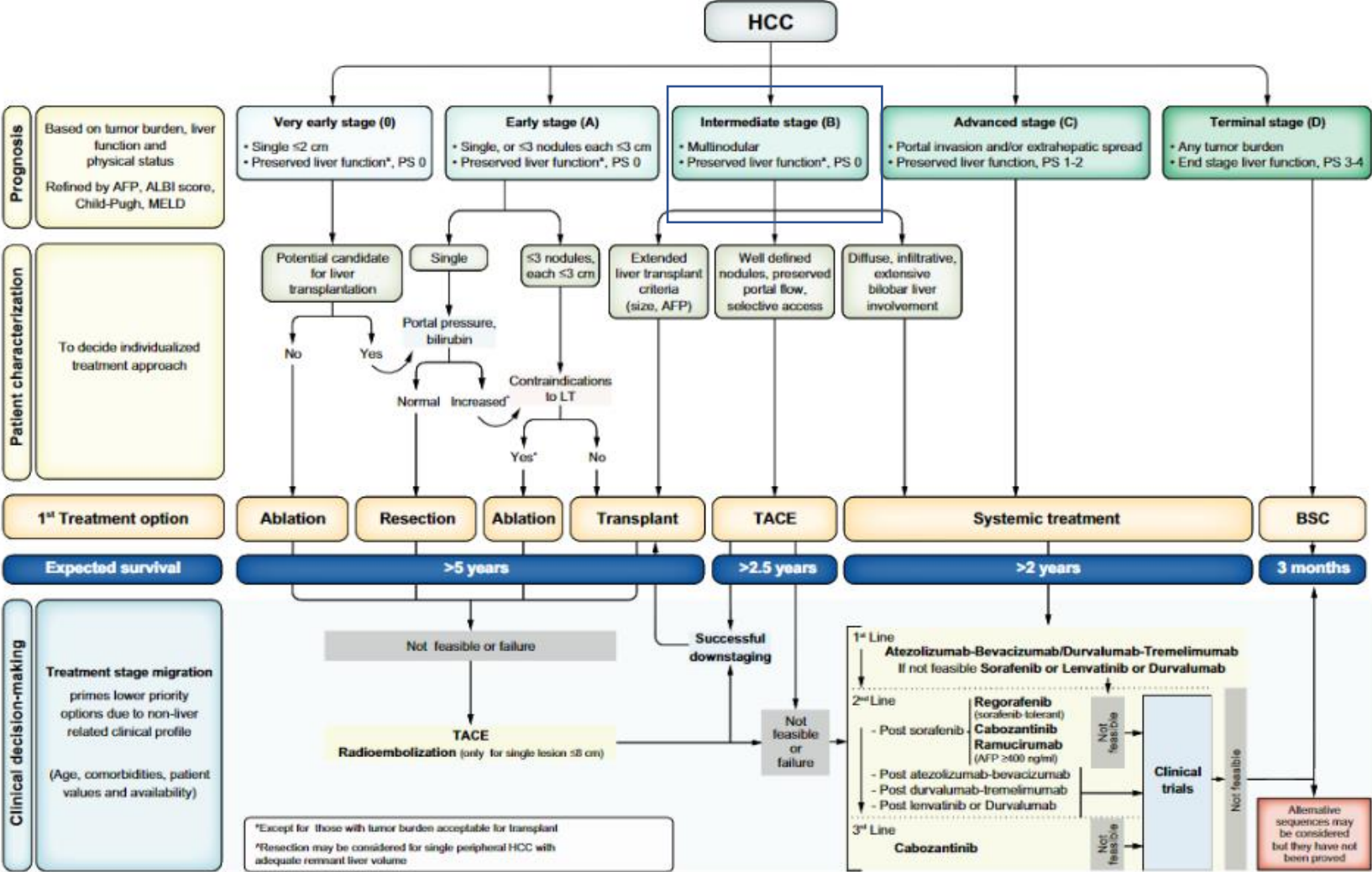


BCLC Staging and treatment schedule



BCLC (Barcelona Clinic Liver Cancer)

Today



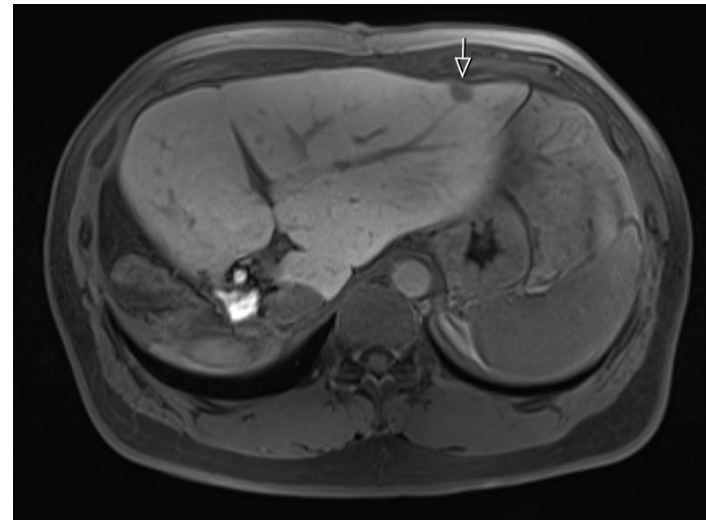
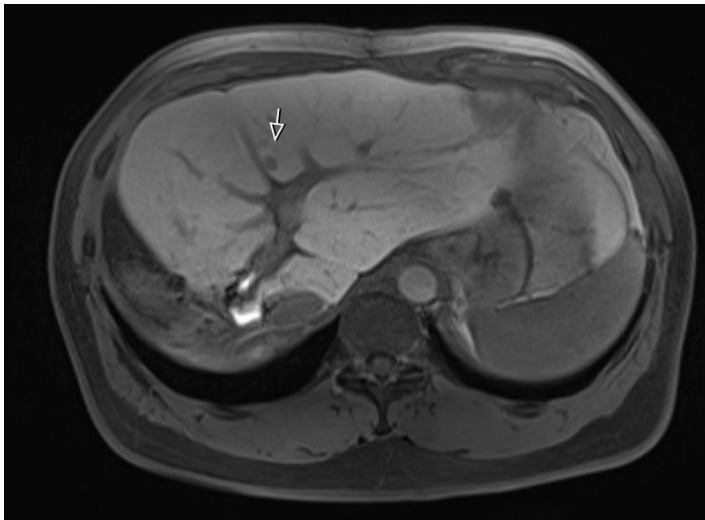
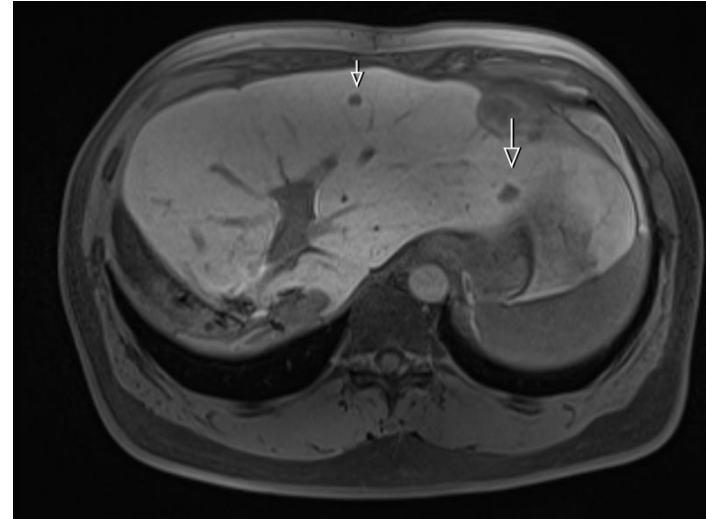
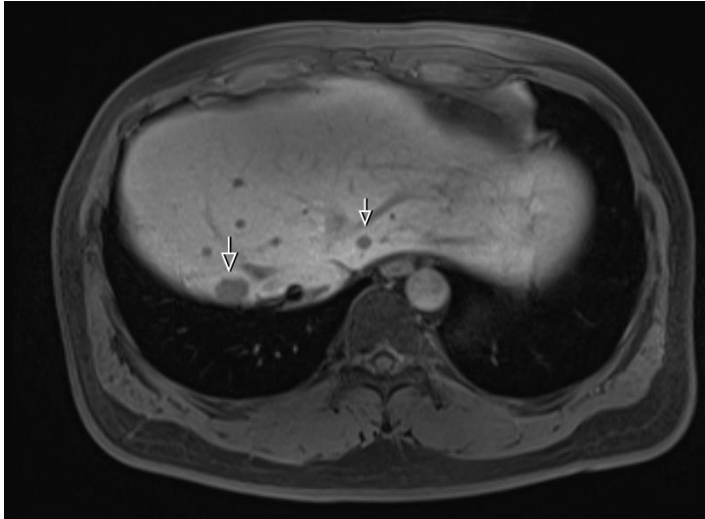
BCLC- B

- What do we do for “potentially downstage to transplant” patients?
- How many tumors is too many tumors?
- How do ancillary factors impact treatment decisions (AFP, PS, liver function)?
- Is there a role for combined systemic and local regional therapy?

Case 1

- 44 y/o man with chronic Hep B
 - 2014 right hepatectomy for 7.5 cm hepatocellular carcinoma
 - 2016 left liver recurrence treated with ablation
 - 2017 multifocal recurrence in liver remnant (13 lesions total)
 - Plt 157, INR 1, liver enzymes normal, tbili 0.6, afp 41

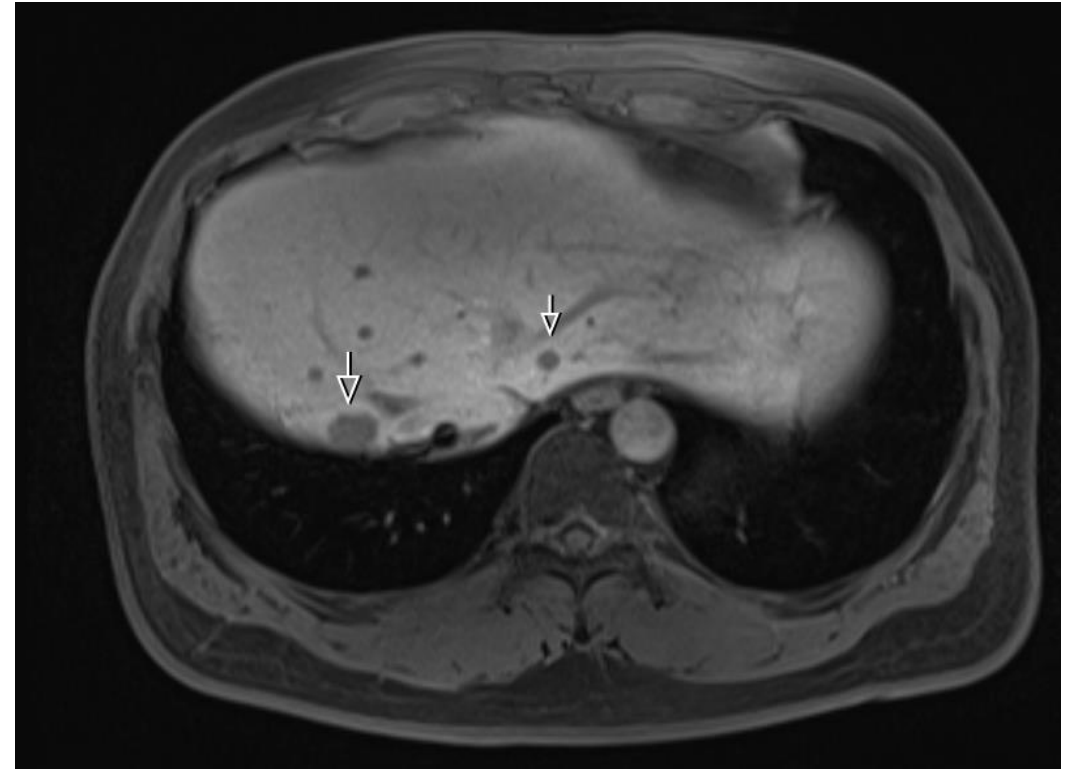
Case 1



Case 1

- Options

- Systemic therapy: 2017 vs 2022
- Arterial Therapy
- Ablative therapy
- Transplant

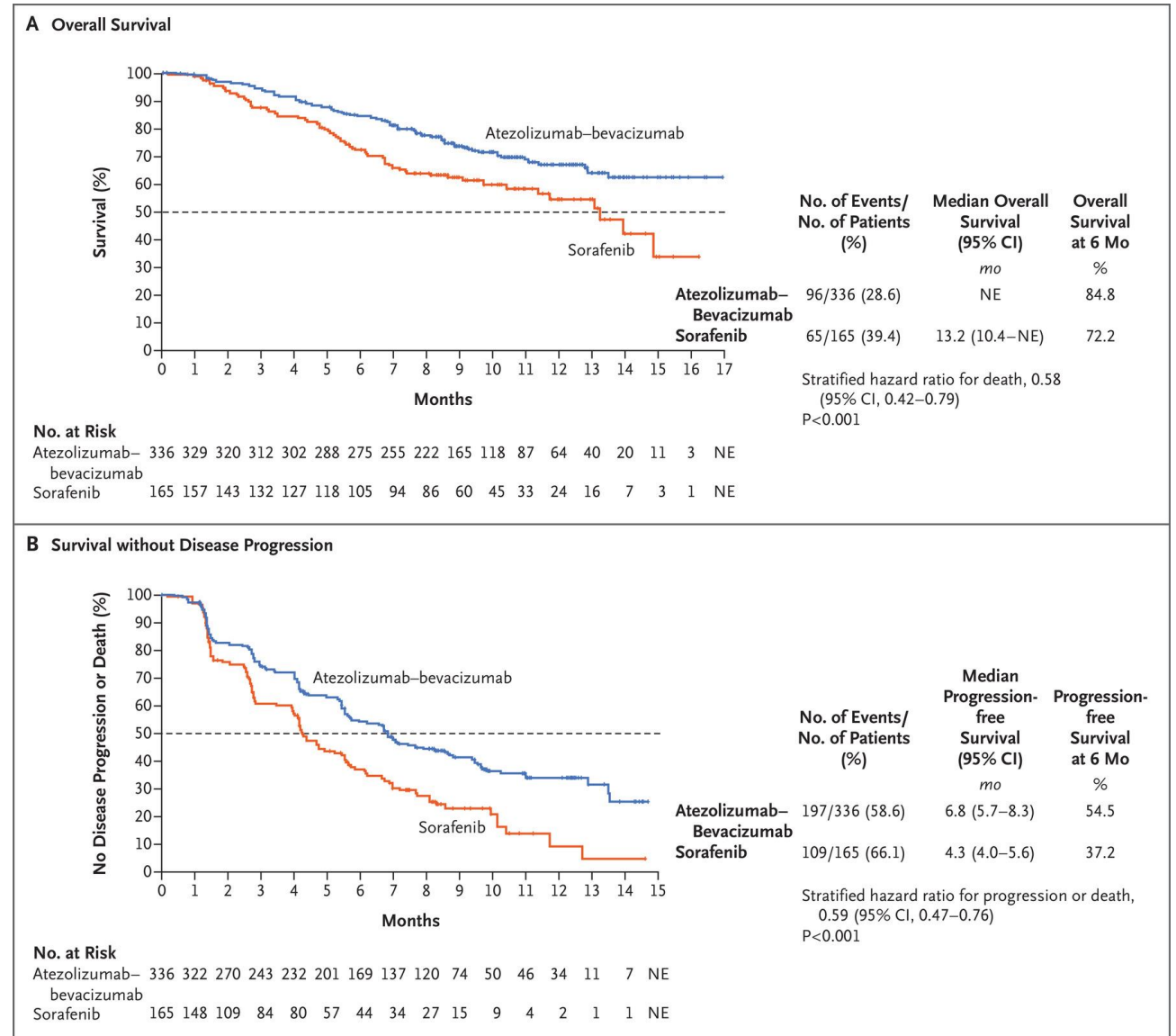


Case 1

■ What do we know about SOC systemic therapy?

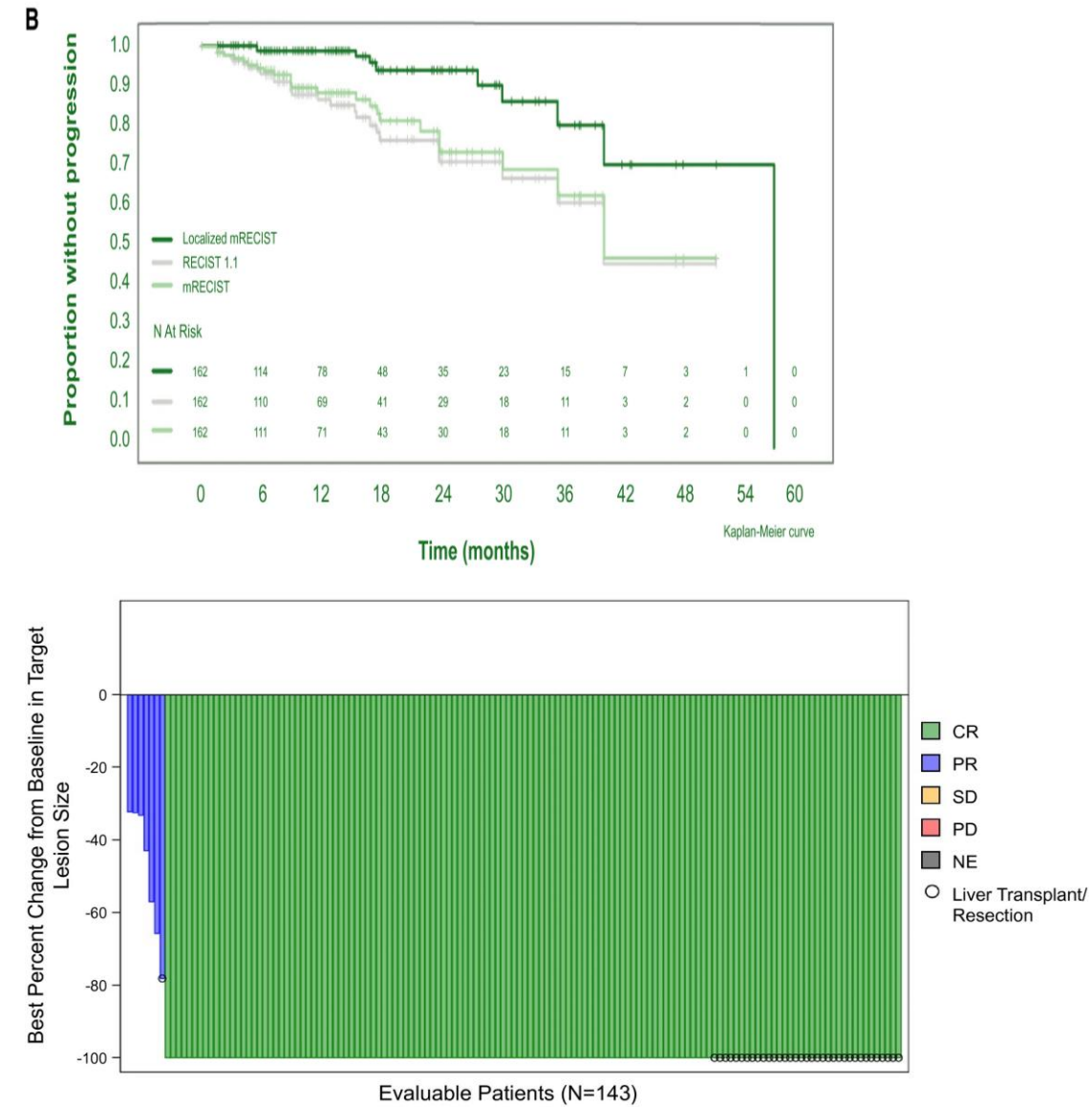
○ IMBRAVE 150

- Median PFS 6.8 months
- ORR 27.3%
- Grade 3-4 toxicity in 56%
- Grade 3-4 HTN in 15%



Case 1

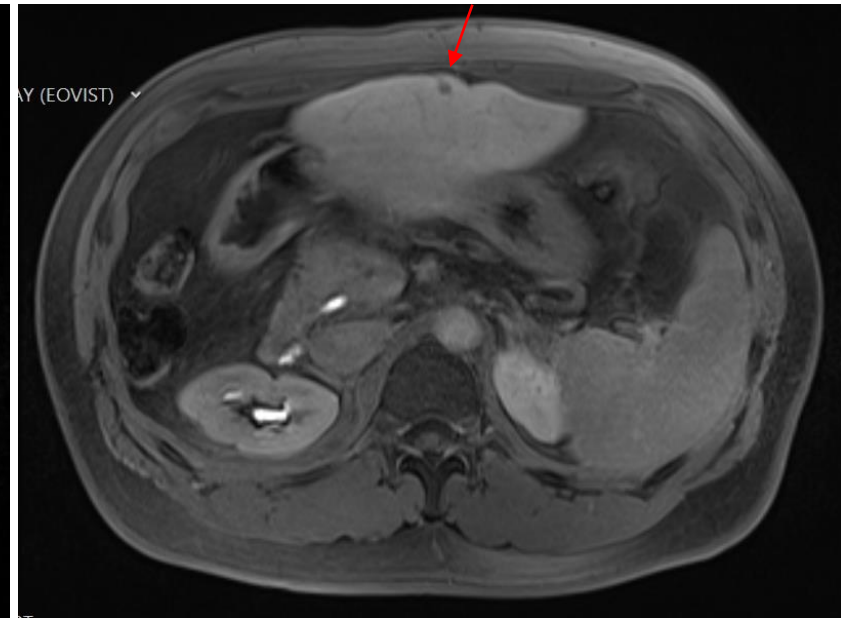
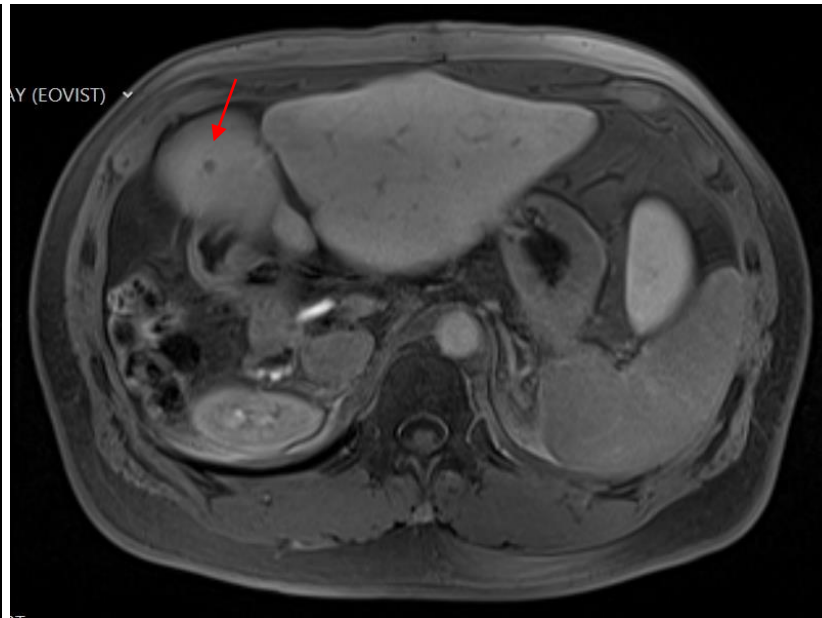
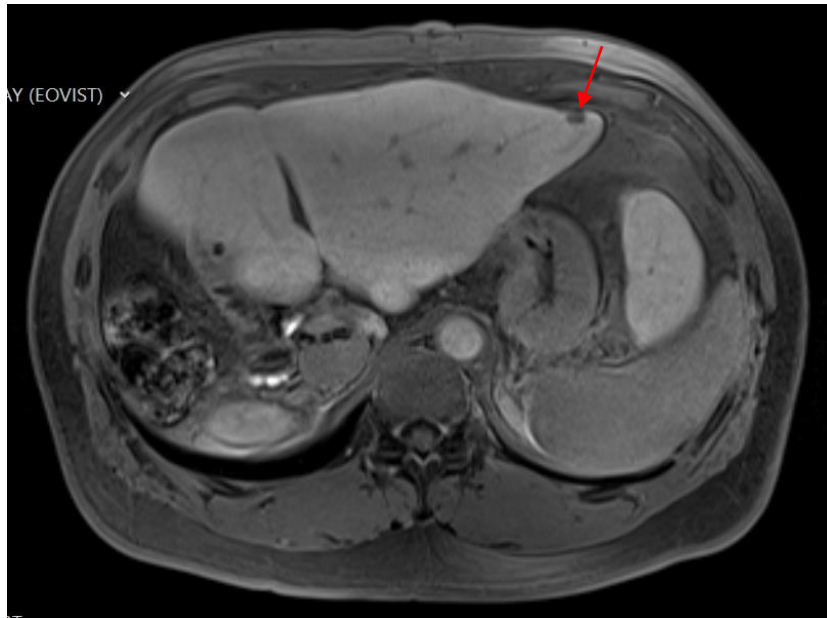
- What do we know about local regional therapy?
 - Legacy study – multicenter single arm
 - Solitary tumor size up to 8cm treated with Y90
 - ORR 88.3%
 - PFS 93.9% at 24 months
 - 19% grade 3 events
 - <1% grade 4 events



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 - 6/2017: Y90 1Gbq to entire liver remnant.
 - 5/2019: 3 sites of less than 1 cm recurrence

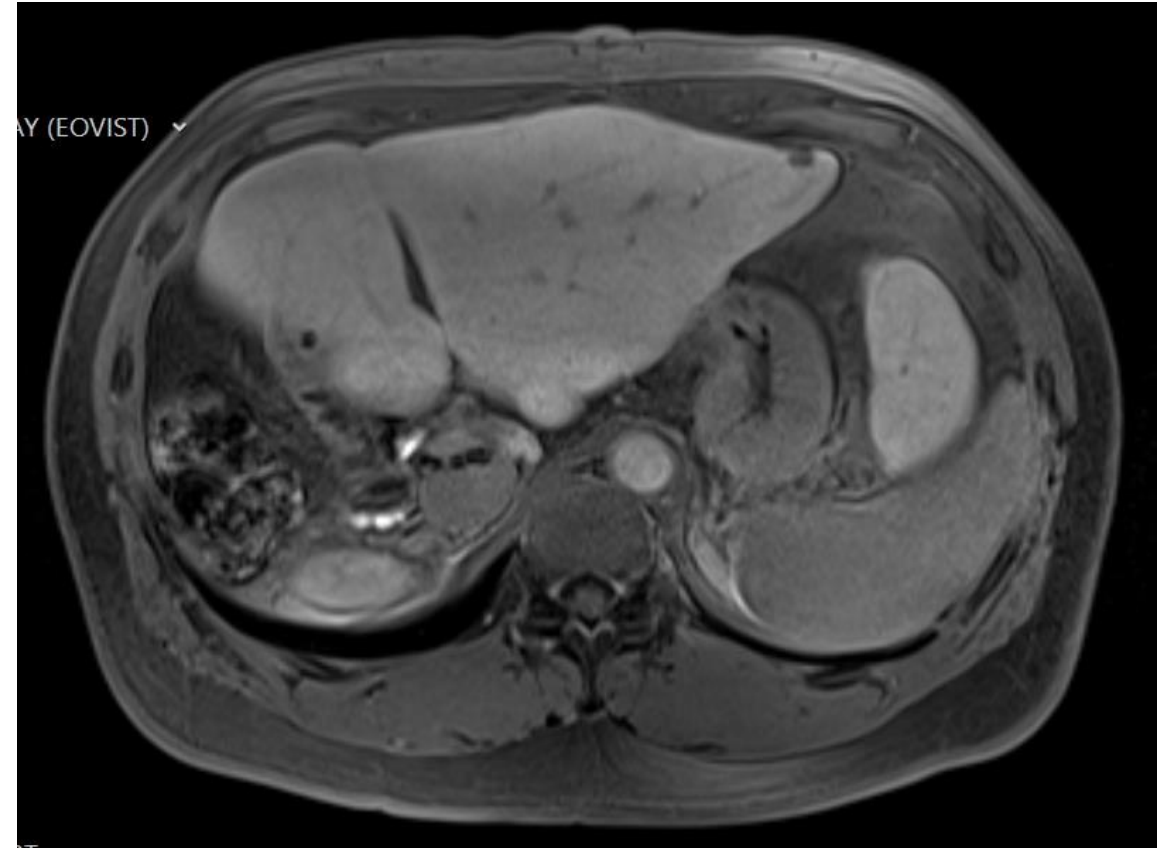
Case 1



Case 1

- Options

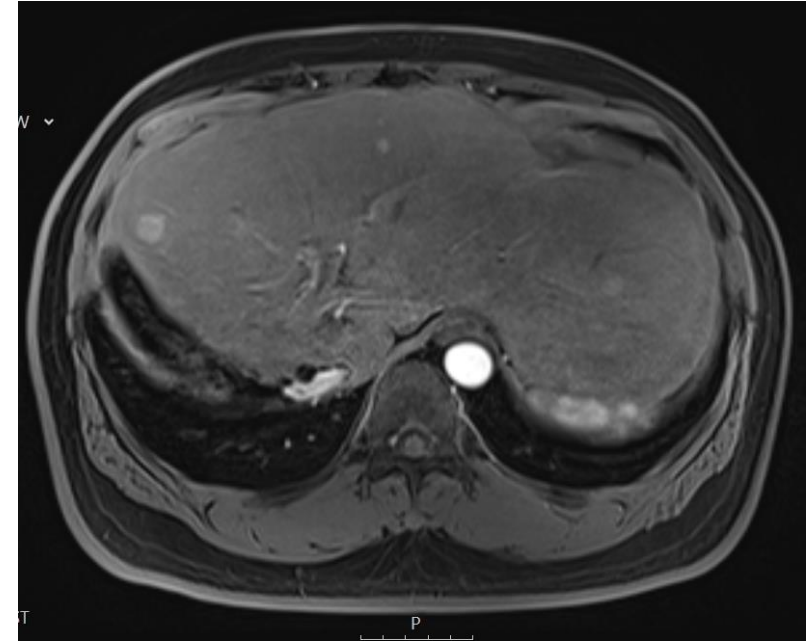
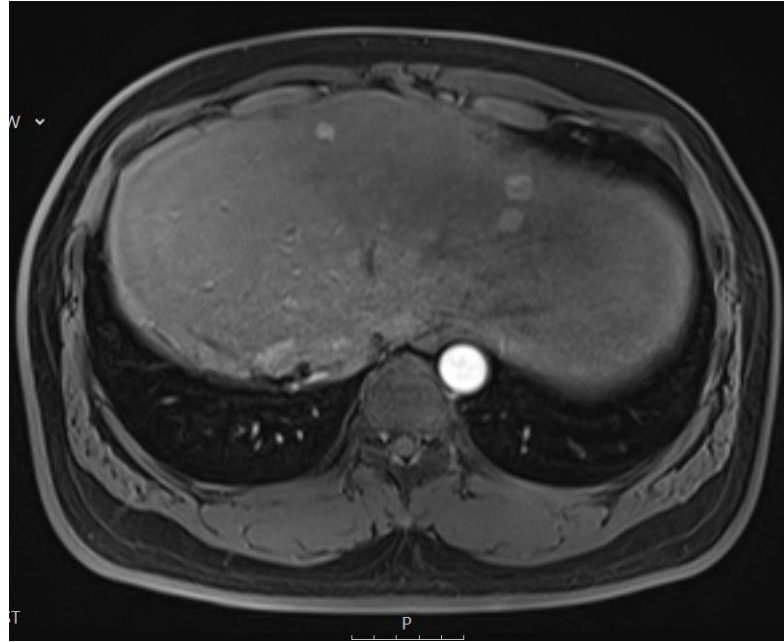
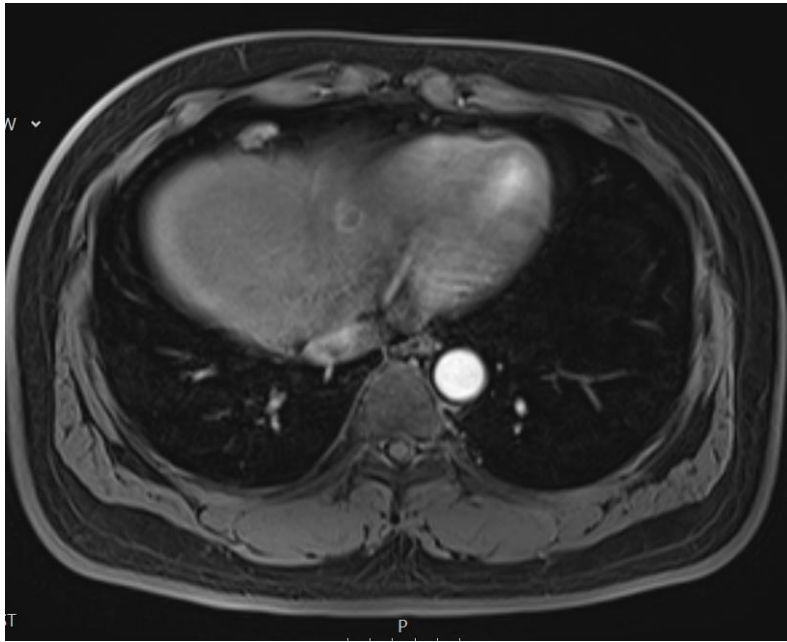
- Systemic therapy: 2019
- Arterial Therapy
- Ablative therapy
- Transplant



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 - 5/2019: 3 sites of less than 1 cm recurrence
 - 6/2019 & 11/2019: ablation of 3 tumors
 - 4/2021: multifocal recurrence

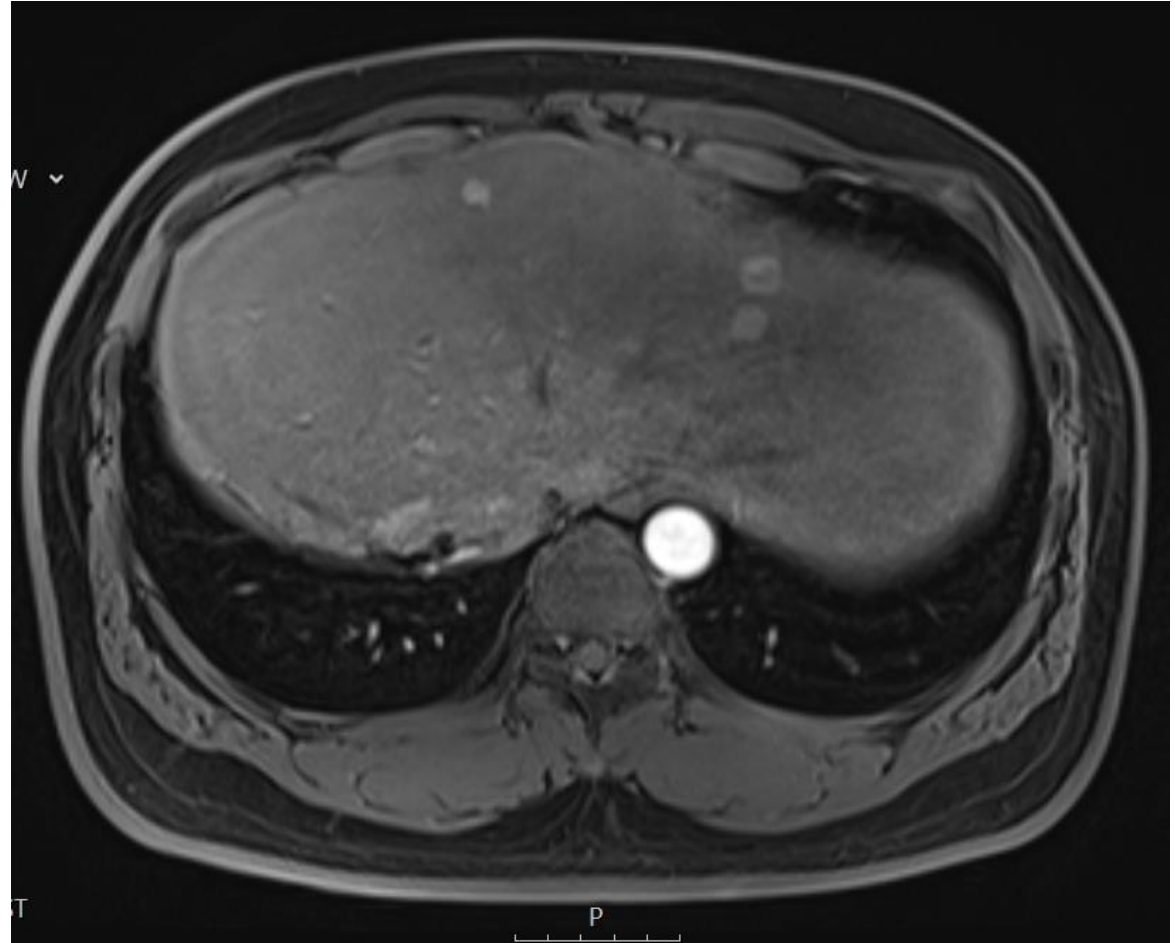
Case 1



Case 1

- Options

- Systemic therapy: 2021
- Arterial Therapy
- Ablative therapy
- Transplant



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 - 6/2017: Y90 1Gbq to entire liver remnant.
 - 5/2019: 3 sites of less than 1 cm recurrence
 - 5/2019: Systemic therapy with TKI plus immune checkpoint inhibitor based therapy
 - 2/2022: progression
 - 3/2022: Clinical trial with additional immune based therapy
 - 7/2022: progression
 - 8/2022- Repeat Y90



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Assistant Professor

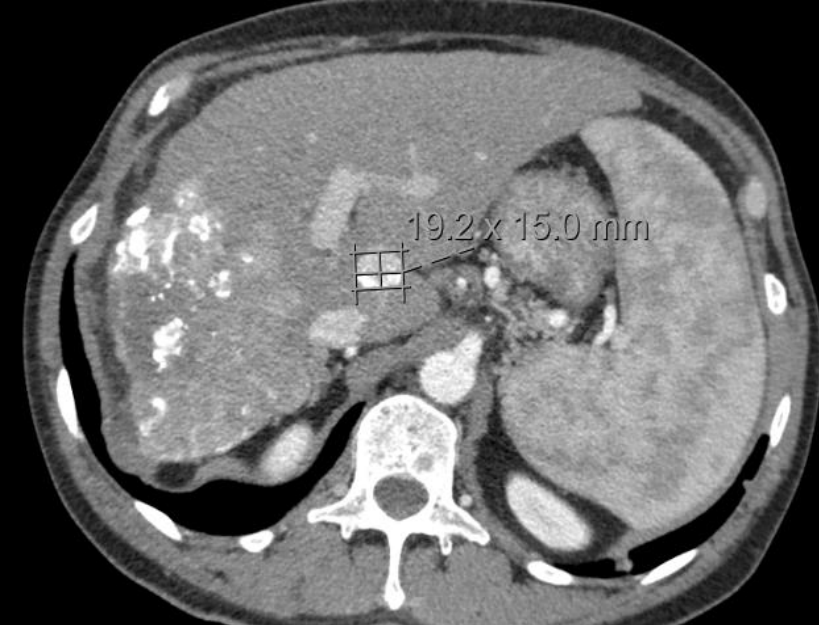
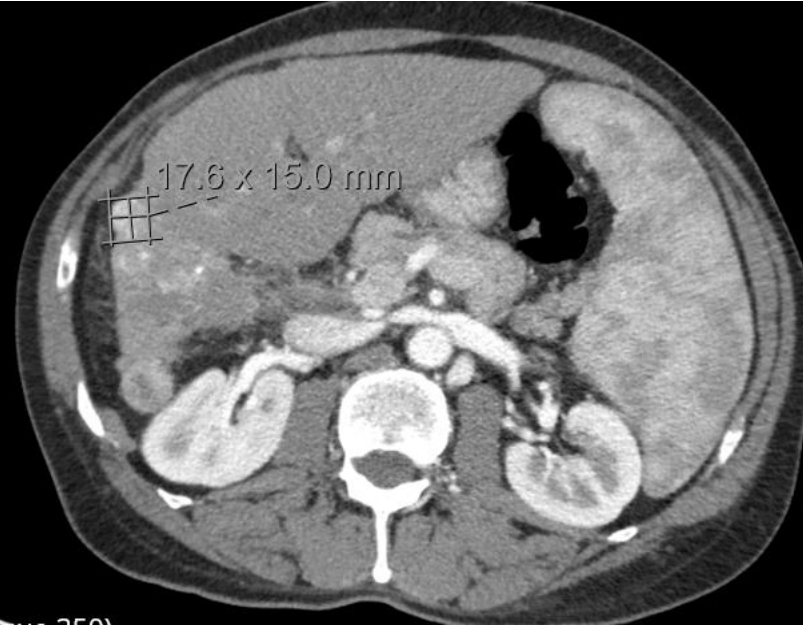
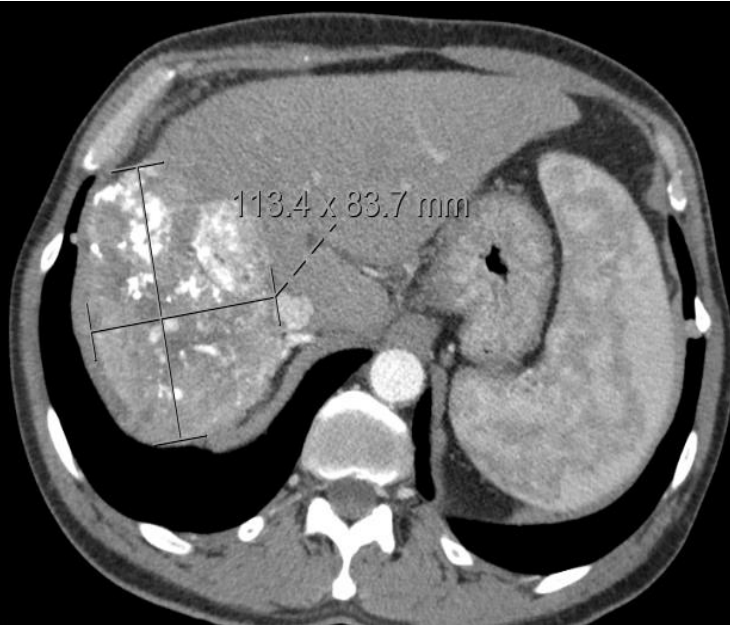
Department of Radiation Oncology

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City of Hope

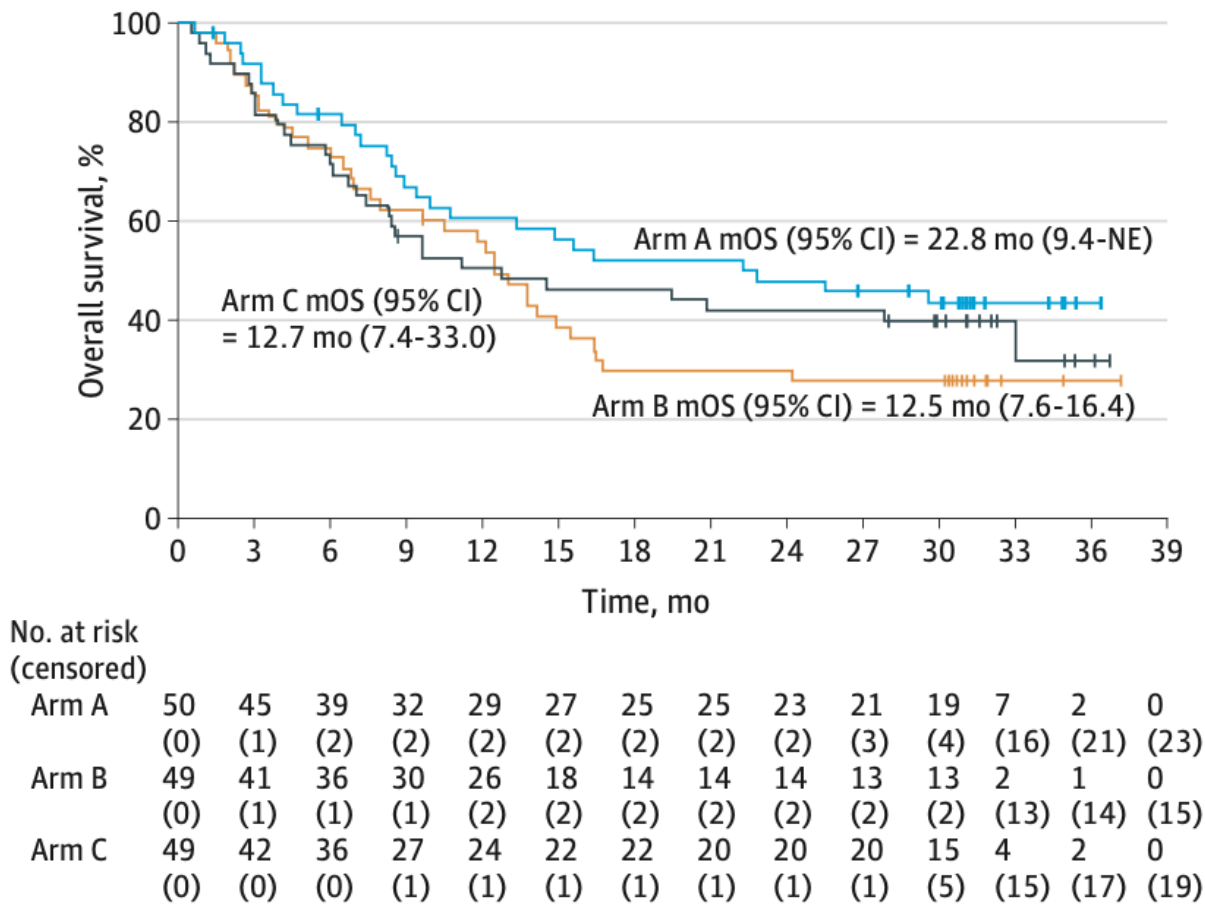
Case 2

- 66 y/o man with chronic Hepatitis C and Child Pugh A5, BCLC B HCC
 - Previously treated with TACE at an OSH
 - April 2021- AFP rose to 487
 - Triphasic CT-abdomen showed a partially calcified large mass in R hepatic lobe measuring 11.3 x 8.7 cm. A small satellite lesion in the inferior lateral right hepatic lobe measures 1.76 x 1.5cm. A second satellite lesion at the junction of the caudate and left hepatic lobes measures 1.9 x 1.5cm.



Checkmate 040

A All participants



Arm A: Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg every 3 weeks (4 doses) → followed by Nivolumab 240 mg intravenously every 2 weeks.

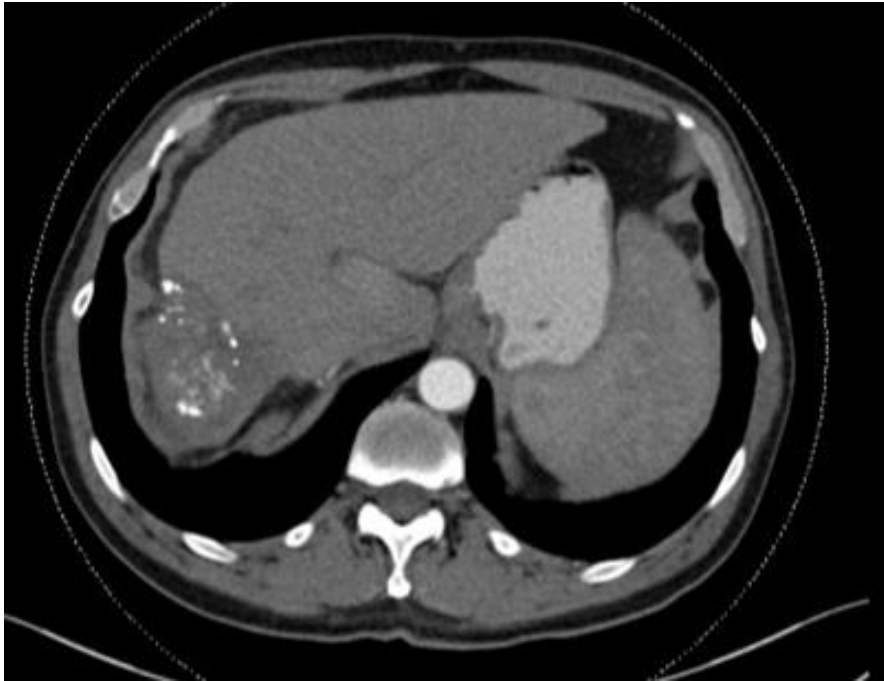
Arm B: Nivolumab 3 mg/kg plus Ipilimumab 1 mg/kg every 3 weeks (4 doses) → followed by Nivolumab 240 mg intravenously every 2 weeks.

Arm C: Nivolumab 3 mg/kg every 2 weeks plus Ipilimumab 1 mg/kg every 6 weeks

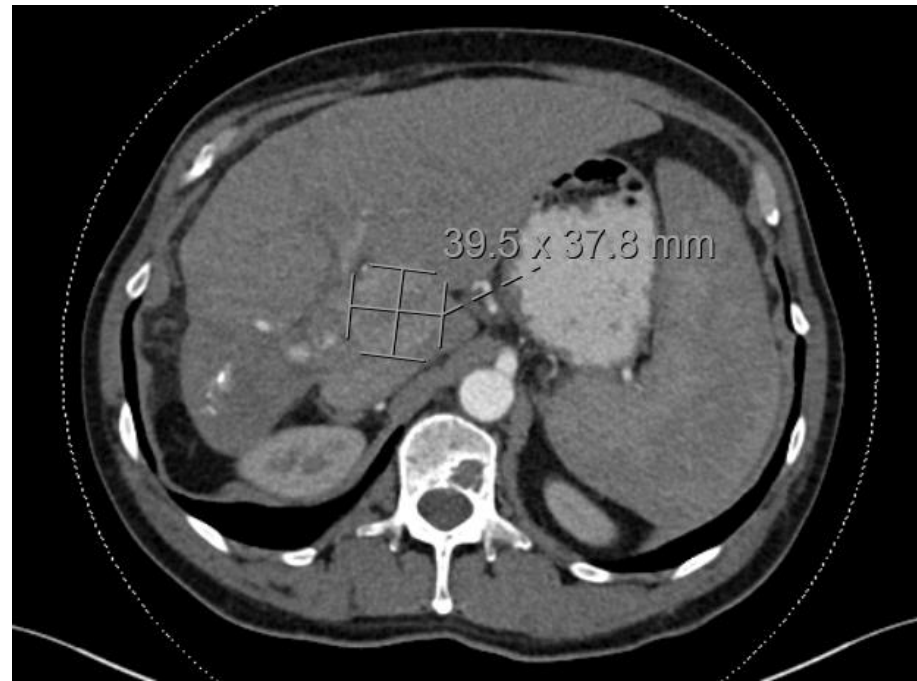
Results:
mOS = 22.8 months (Arm A)
12.5 months (Arm B)
12.7 months (Arm C)

Case 2: Triphasic CT-abdomen (Dec 2021)

Impressive response to Nivolumab + Ipilimumab -- > but caudate lobe lesion persists



Post-treatment appearance of the posterior right hepatic lobe with heterogeneous calcification now measuring 6.3 x 4.8cm.



Caudate lobe mass is larger now measuring 4 x 3.8 cm arterially enhancing with venous washout.

ASTRO Liver Cancer Guidelines

Practical Radiation Oncology® (2022) 12, 28–51



Clinical Practice Guideline

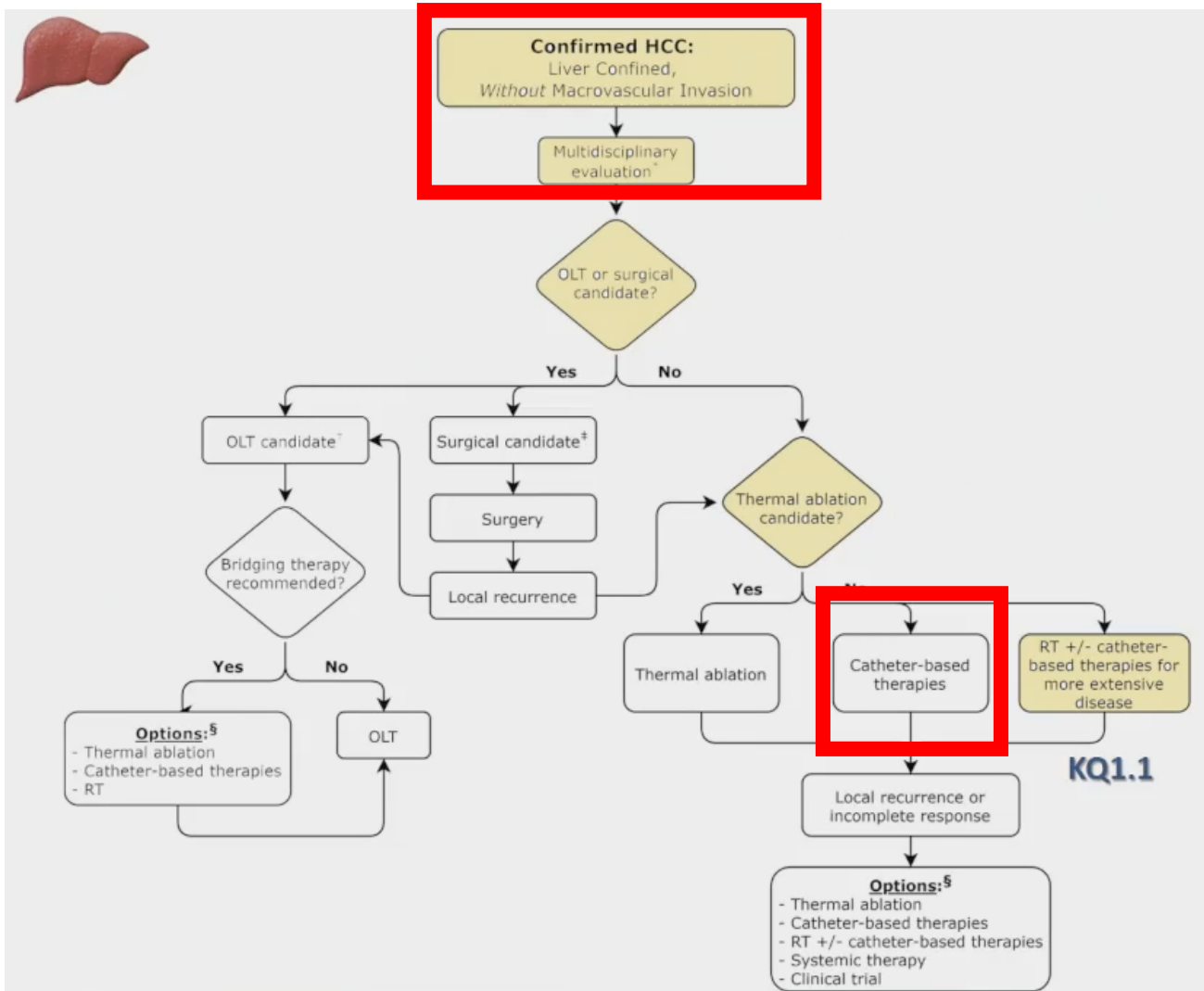
External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline



Smith Apisarnthanarax, MD,^{a,*} Aisling Barry, MD,^b Minsong Cao, PhD,^c Brian Czitio, MD,^d Ronald DeMatteo, MD,^e Mary Drinane, MD,^f Christopher L. Hallemeier, MD,^g Eugene J. Koay, MD, PhD,^h Foster Lasley, MD,ⁱ Jeffrey Meyer, MD, MS,^j Dawn Owen, MD, PhD,^g Jennifer Pursley, PhD,^k Stephanie K. Schaub, MD,^a Grace Smith, MD, PhD, MPH,^h Neeta K. Venepalli, MD, MBA,^l Gazi Zibari, MD,^m and Higinia Cardenes, MD, PhDⁿ

^aDepartment of Radiation Oncology, University of Washington, Seattle, Washington; ^bDepartment of Radiation Oncology, Princess Margaret Cancer Center, Toronto, Ontario, Canada; ^cDepartment of Radiation Oncology, University of California, Los Angeles, California; ^dDepartment of Radiation Oncology, Duke University, Durham, North Carolina; ^eDepartment of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania; ^fDepartment of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; ^gDepartment of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; ^hDepartment of Radiation Oncology, UT—MD Anderson Cancer Center, Houston, Texas; ⁱDepartment of Radiation Oncology, GenesisCare, Rogers, Arkansas; ^jDepartment of Radiation Oncology and Molecular

Case 2: Algorithm for HCC w/o MVI



Discuss options at GI Multi-Disciplinary Tumor Board

1. Surgery (Transplant or Resection)

- Because of this patient's age and comorbidities... he was not a candidate for transplant or surgical resection.

2. Thermal Ablation

- Due to the size of his lesion, he was not a candidate for thermal ablation.

3. Catheter-Based Therapy (i.e. TARE or TACE)

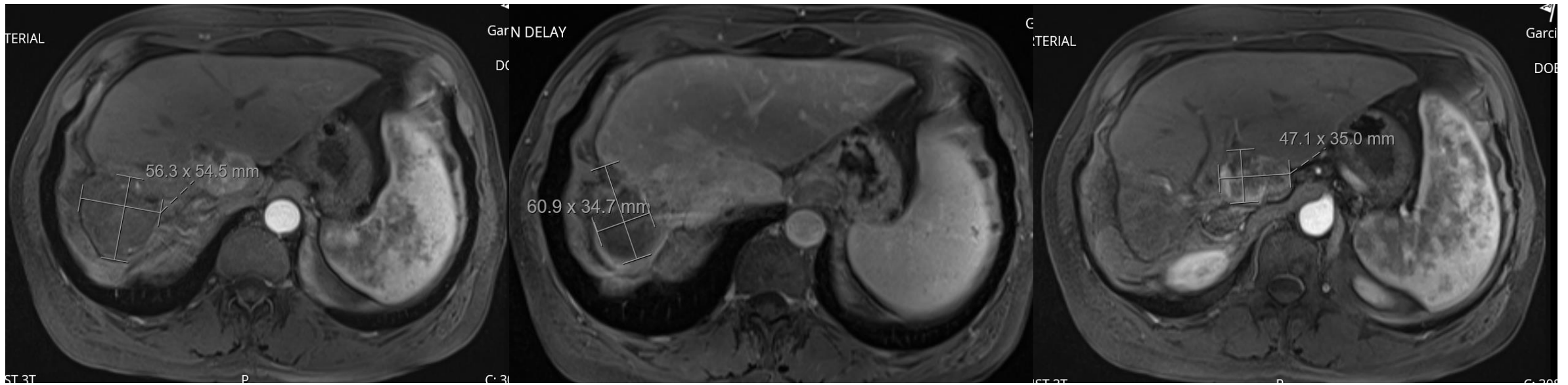
4. Radiation +/- Catheter-Based Therapy

Case 2

- 66 y/o man with chronic Hepatitis C and Child Pugh A5, BCLC B HCC
 - Previously treated with TACE at an OSH
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 - Triphasic CT-abdomen shows a partially calcified large mass in R hepatic lobe which measures 11.3 x 8.7 cm. A small satellite lesion in the inferior lateral right hepatic lobe measures 1.76 x 1.5cm. A second satellite lesion at the junction of the caudate and left hepatic lobes measures 1.9 x 1.5cm.
 - June 2021- started on ipilimumab and nivolumab
 - Dec 2021- CT-abdomen showed an increase in size of caudate lobe tumor
 - Jan 2022- Yttrium-90 trans-arterial radioembolization of the caudate lobe tumor with SIR microspheres

Case 2: MRI-liver after TARE (March 2022)

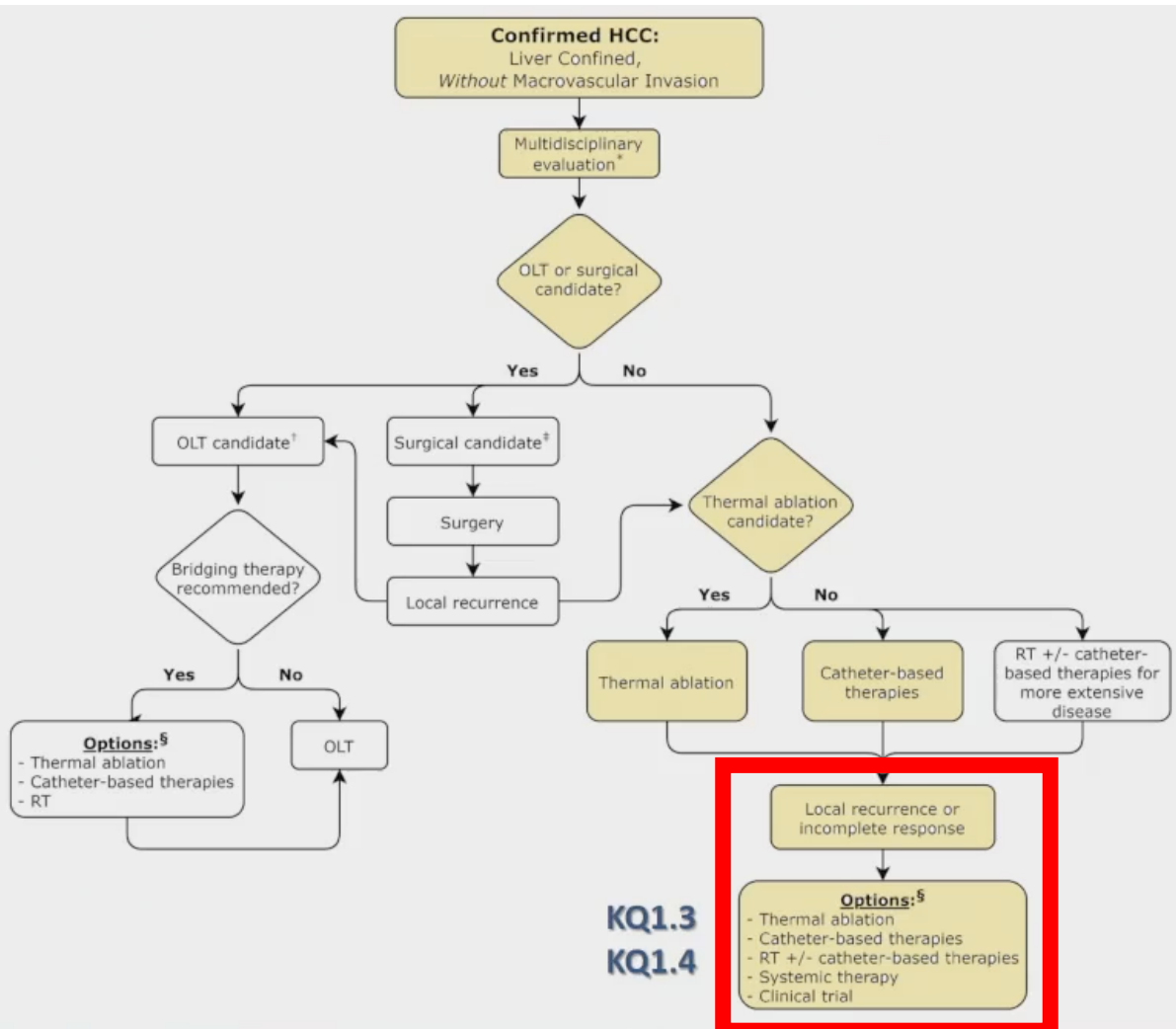
MRI showed about 20-30% necrosis of caudate lobe lesion after TARE.



Atrophy of the posterior right hepatic lobe, now measuring 5.6 x 5.5cm as compared to the partially calcified mass seen on the prior examination measuring 6.1 x 3.5 cm.

Heterogeneously enhancing mass of the caudate lobe measures 4.4 x 3.7 cm, previously 4.6 x 3.5 cm. This lesion has 20-30% necrosis.

HCC s/p TARE → Incomplete response → Consolidative RT



For patients with liver-confined HCC who had an incomplete response to thermal ablation or catheter-based therapies*, EBRT is recommended as a consolidative treatment option.

- Median survival = 22-42 months
- Local control > 89%



How to deliver Radiation for HCC?

Case 2: SBRT for Early Stage HCC

- Multiple retrospective phase I and II studies support EBRT as a definitive option in early stage HCC
- Patients with small tumors (<6cm), 1-5 lesions, Child Pugh A-B7
- 2-5 year local control rates $\geq 90\%$



SYSTEMATIC REVIEW | VOLUME 145, P63-70, APRIL 01, 2020

Comparisons between radiofrequency ablation and stereotactic body radiotherapy for liver malignancies: Meta-analyses and a systematic review

Jeongshim Lee • In-Soo Shin • Won Sup Yoon • Woong Sub Koom • Chai Hong Rim  

SYSTEMATIC REVIEW | VOLUME 131, P135-144, FEBRUARY 01, 2019

Clinical feasibility and efficacy of stereotactic body radiotherapy for hepatocellular carcinoma: A systematic review and meta-analysis of observational studies

Chai Hong Rim ¹ • Hyun Ju Kim ¹ • Jinsil Seong   • Show footnotes

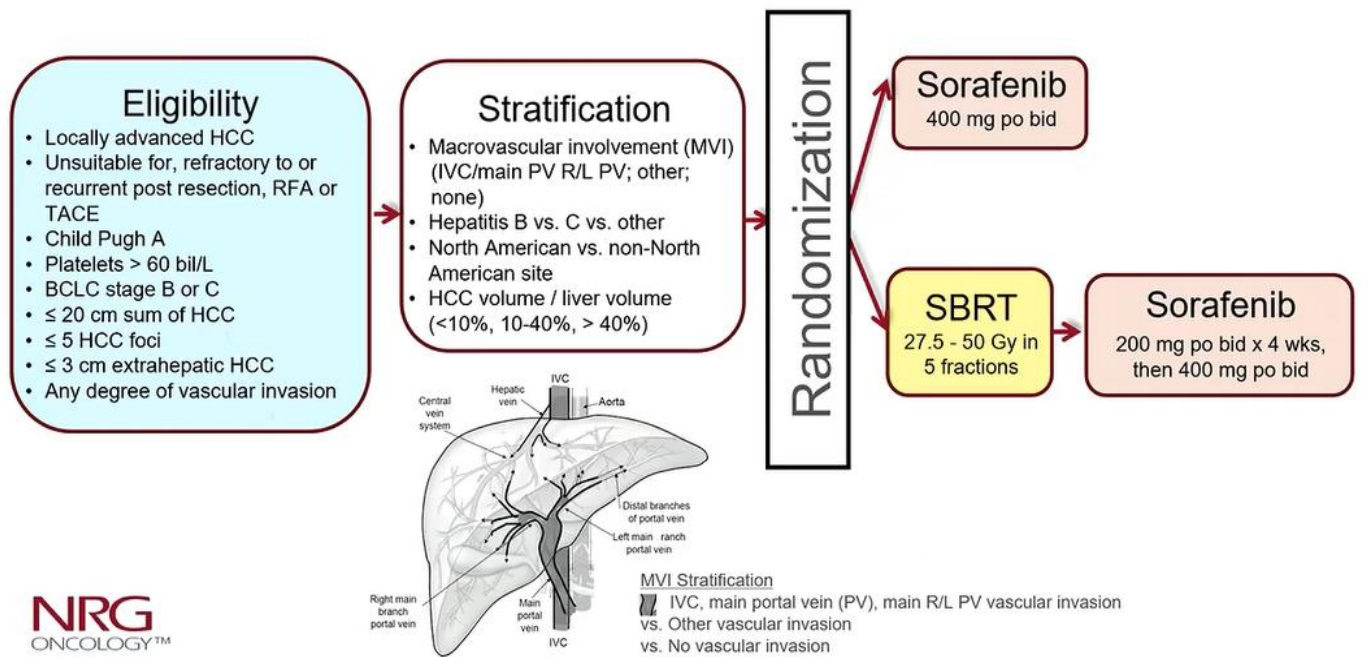
No difference in OS or LC between RFA vs. SBRT

Pooled data on SBRT:

- 3 yr OS = 48%
- LC = 84%

NRG/RTOG 1112

NRG/RTOG 1112 Schema

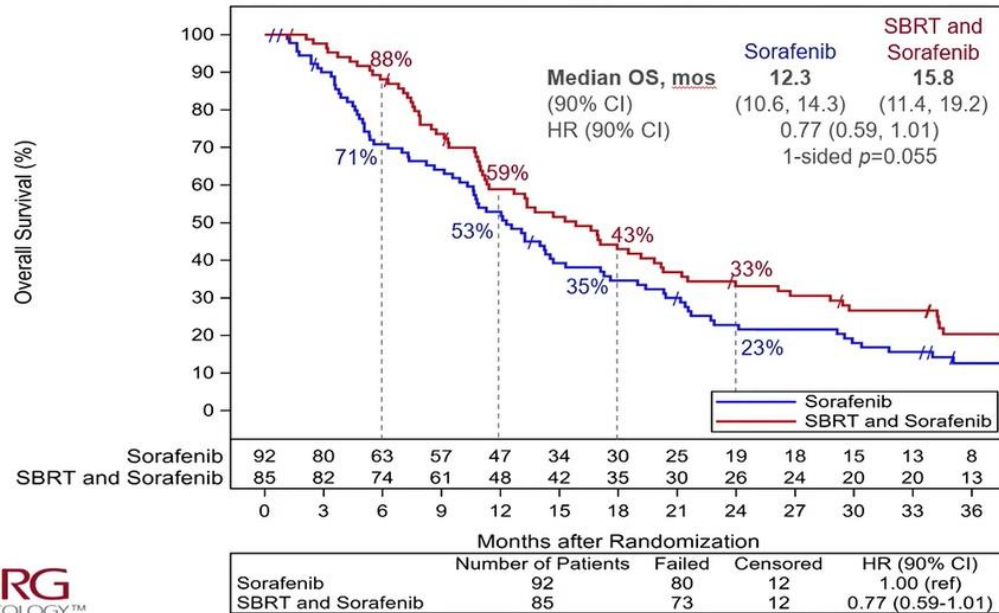


- Randomized phase III study of sorafenib vs SBRT followed by sorafenib in HCC.
- 193 patients with new or recurrent locally advanced HCC who were ineligible for surgical resection or other locoregional therapies due to underlying clinical factors or because their cancer was refractory or recurrent
- BCLC stage B or C
- Large tumors were permitted, up to 15cm and total volume up to 20cc, up to 5 lesions
- 74% had macrovascular invasion

Dawson et al, 2022 ASTRO

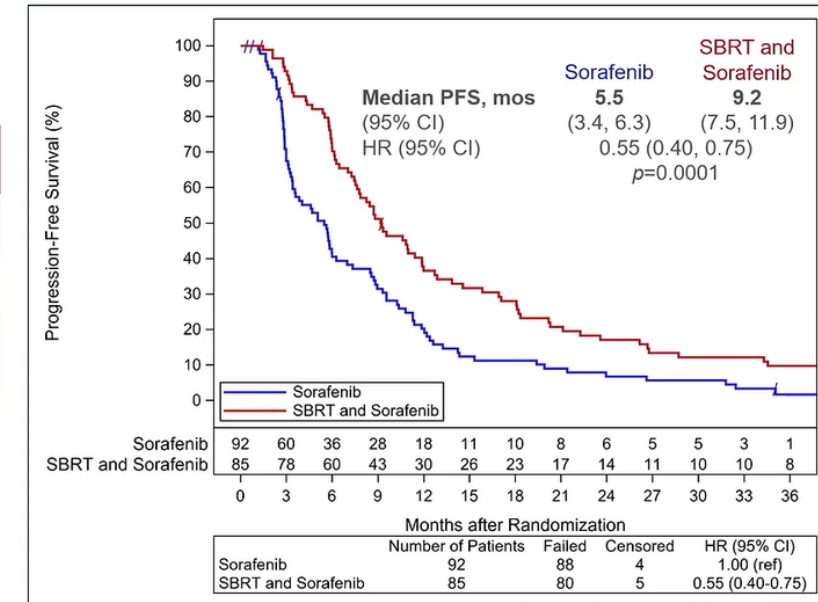
Results from RTOG 1112

Overall Survival



Progression-Free Survival

Estimate (95% CI)	Sorafenib (n=92)	SBRT and Sorafenib (n=85)
6-month	41% (30%, 51%)	71% (62%, 81%)
12-month	20% (12%, 29%)	37% (26%, 47%)
18-month	11% (5%, 18%)	28% (18%, 38%)
24-month	7% (2%, 12%)	17% (9%, 25%)



Median follow: all patients – 13.2 months; alive patients – 33.7 months

NRG/TOG 1112

NRG/TOG 1112

- Overall survival was longer for patients receiving SBRT and sorafenib, compared to sorafenib alone (15.8 vs. 12.3 months; one-sided $p = 0.055$).
- This was statistically significant after controlling for clinical prognostic factors such as performance status and the degree of vascular invasion ($p=0.042$).
- Progression-free survival was improved with the addition of SBRT, from 5.5 months to 9.2 months ($HR = 0.92$, $p<0.001$).

Dawson et al, 2022 ASTRO

Case 2: Selecting the Radiation Prescription

- Determining the dose/fractionation depends on:
 - Child Pugh score (baseline liver function)
 - Size of lesion
 - Location of lesion
 - Liver- Gross tumor volume (GTV) dose constraint
 - Duodenum dose constraint

Case 2: Dose & Fractionation for SBRT

Practical Radiation Oncology (2015) 5, e443-e449



Original Report

Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy



Foster D. Lasley MD^a, Edward M. Mannina MD, MPH, MS^b, Cynthia S. Johnson MS^c, Susan M. Perkins PhD^c, Sandra Althouse MS^c, Mary Maluccio MD, MPH^d, Paul Kwo MD^e, Higinia Cárdenes MD, PhD^{b,*}

^aMercy Radiation Oncology, Oklahoma City, Oklahoma

^bDepartment of Radiation Oncology, Indiana University School of Medicine, Indianapolis, Indiana

^cDepartment of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana

^dDepartment of Surgery, Indiana University School of Medicine, Indianapolis, Indiana

^eDepartment of Gastroenterology, Indiana University School of Medicine, Indianapolis, Indiana

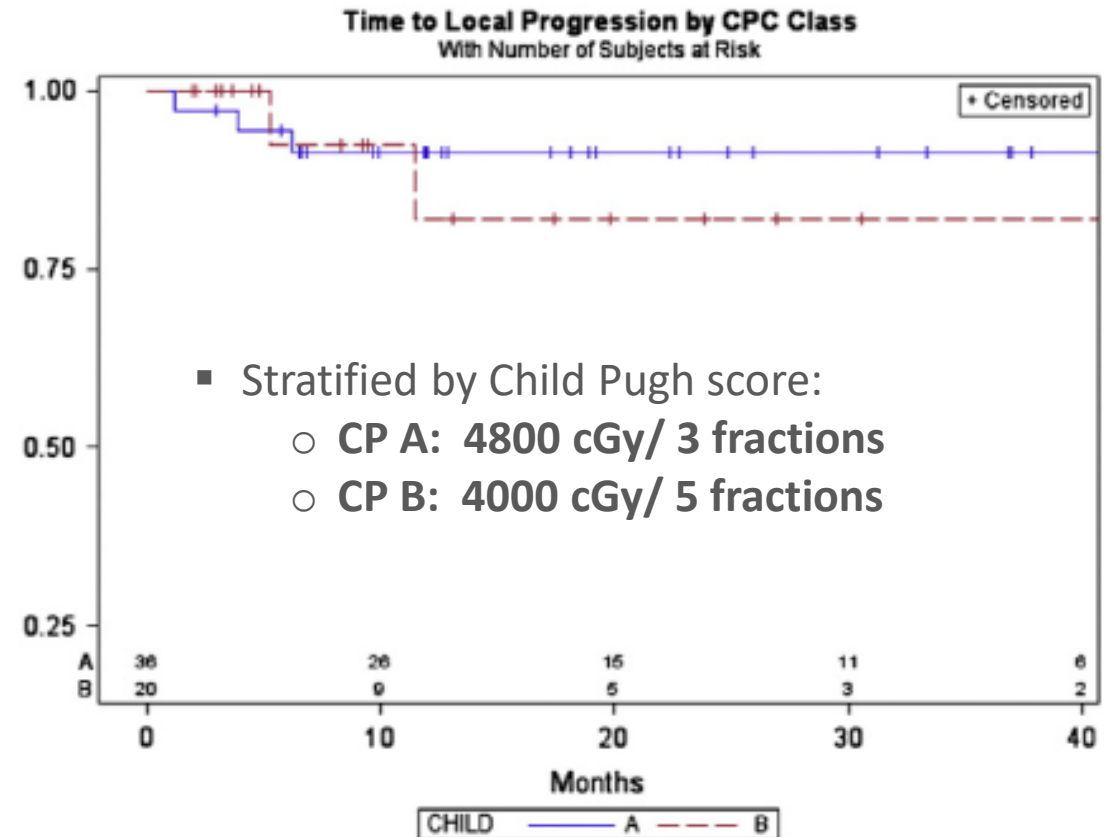


Figure 1 Local control by Child-Pugh class (CPC).

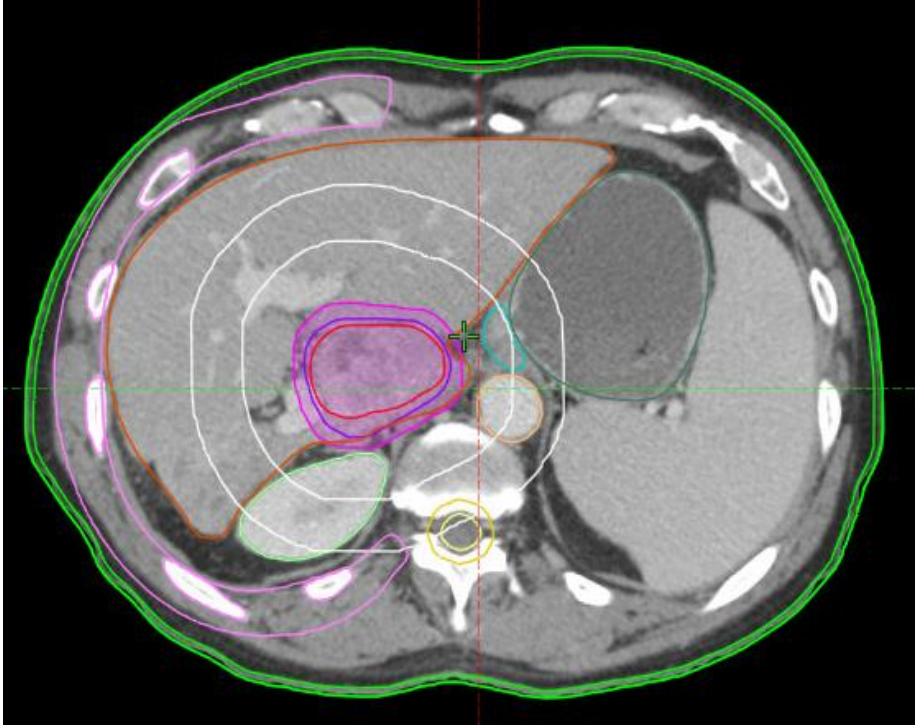
Case 2: Reducing dose to OARs

- Preparation for simulation
 - NPO for 3 hours prior to CT-sim
 - IV contrast CT (triple phase)
 - Zofran before each treatment
- Motion Management
 - Free breathing ITV (if < 1cm motion on 4DCT) +/- abdominal compression
 - Free breathing with gating (30 to 70 phase of respiratory cycle) +/- abdominal compression
 - Breath hold
- Daily image guidance (Cone Beam CT)

Case 2

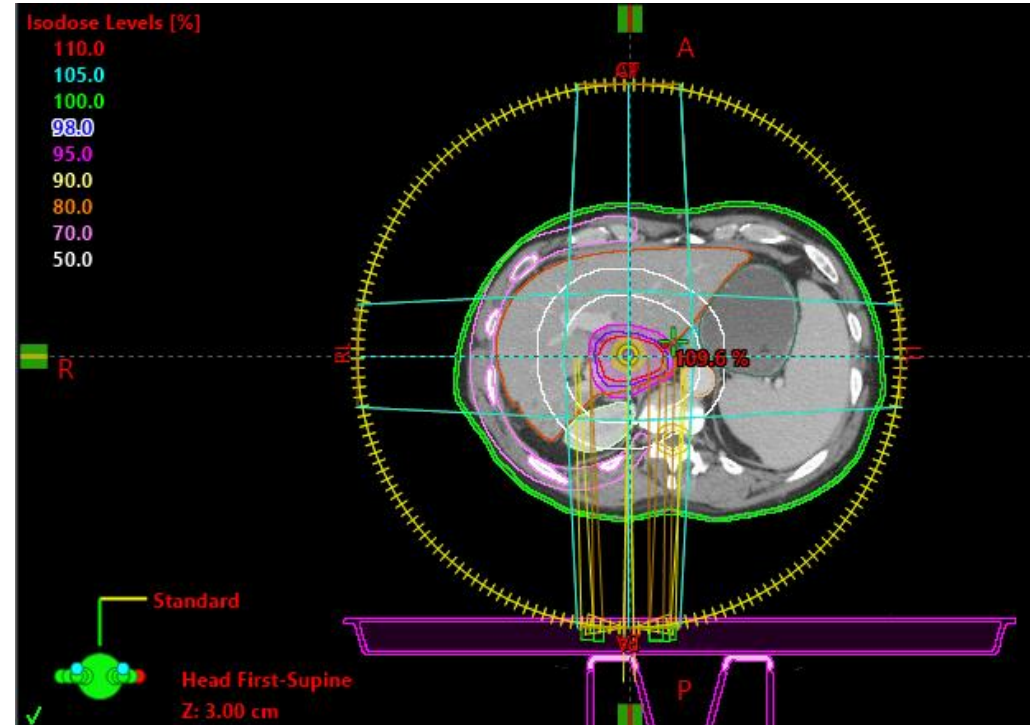
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 - March 2022- MRI showed 20-30% necrosis of caudate lobe lesion after TARE.
 - March 2022- SBRT to caudate lobe tumor

Case 2: SBRT to caudate lobe



Prescription:

40 Gy in 5 fractions every other day
Breath hold with daily CBCT
VMAT plan using 6X FFF



Dose constraints:

Liver – GTV : $V_{21.5\text{Gy}} < 700\text{cc}$
Duodenum: Max < 35 Gy, $V_{26.5\text{Gy}} < 5\text{cc}$
Spine: Max < 28 Gy, $V_{22\text{Gy}} < 0.35\text{ cc}$

Case 2: Follow-up Imaging after SBRT (June 2022)



The arterial phase enhancing lesion of the caudate lobe has decreased in size since 3/2022. Measured on the arterial phase, it currently spans 3.4 x 2.5 cm axial dimension, previously 4.7 x 3.5 cm. This lesion spans ~ 2.4 cm craniocaudal dimension on the portal venous phase, previously 3.9 cm.

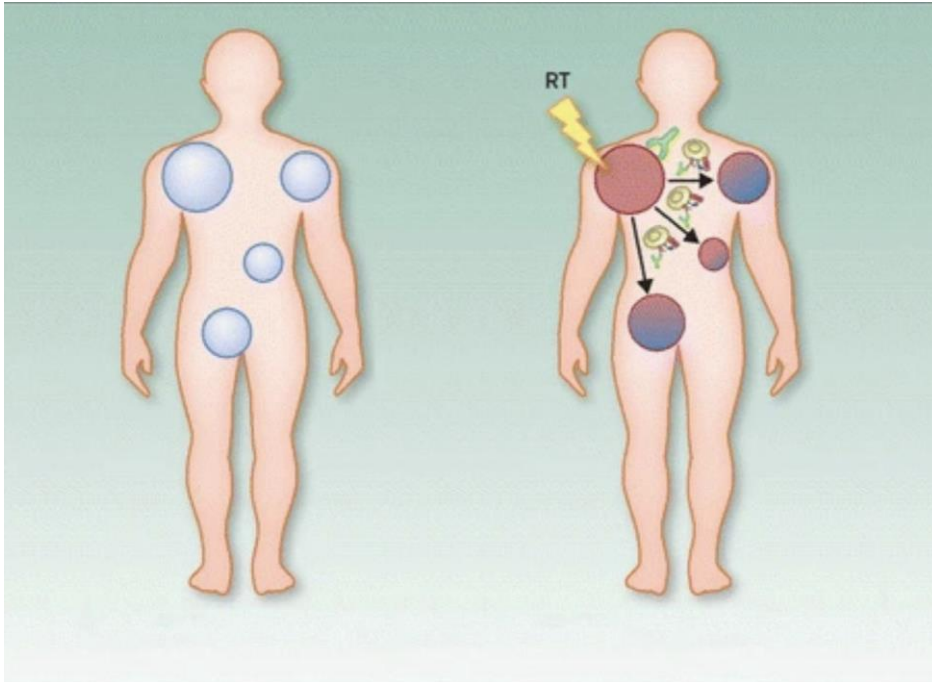
The majority of the residual lesion enhances and demonstrates portal venous phase washout. 20 min delayed postcontrast demonstrates a larger abnormality spanning ~ 6 cm and extending into the left lobe. This corresponds to the radiotherapy treatment zone.

Case 2:Future Research Questions

- What is the appropriate sequence of Nivolumab/Ipilimumab and radiation (SBRT)?
- What is the optimal length of time between the delivery of TARE and SBRT?
- What are the best ways to assess response to combined ICI and RT (iRECIST vs. RECIST)?
- What other innovative therapeutic combinations could improve outcomes for our patients with HCC?

Questions?

Abscopal Effect



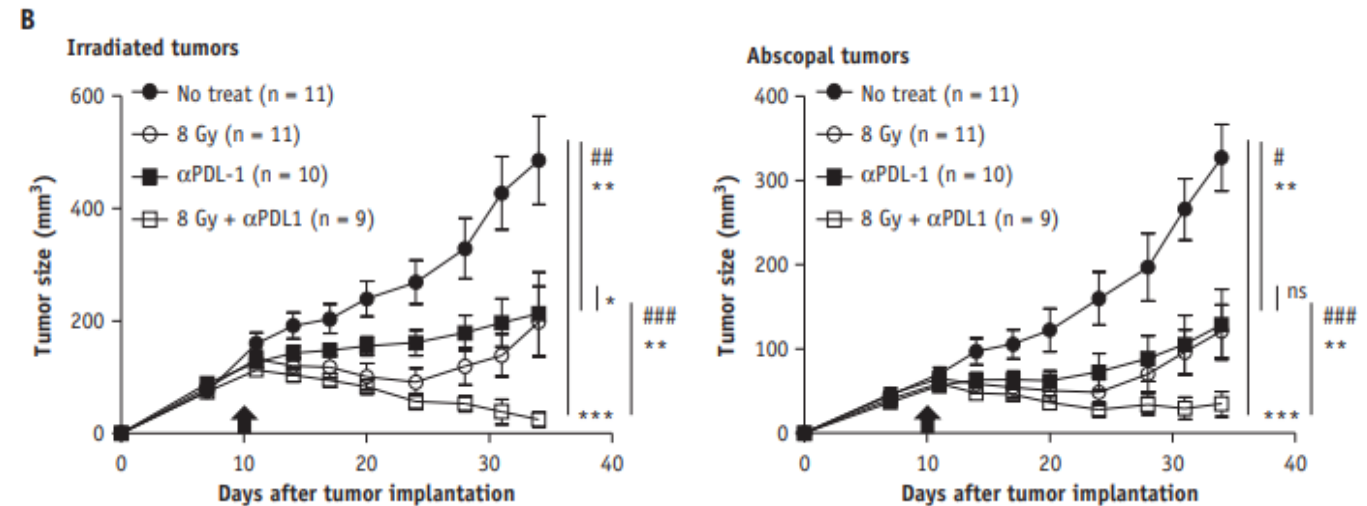
© 2016 American Association for Cancer Research

CCR Focus

AAGR

- Is there a role for the radiation-induced abscopal effect in the treatment of HCC?

Pre-clinical murine model of HCC treated with 8 Gy + α -PD-1 Ab



Park et al, Int J Radiat Oncol Bio Phys. 2021.