The Other Primary Liver Cancer

My Approach to Intrahepatic Cholangiocarcinoma

Susan Shamimi-Noori, MD

University of Pennsylvania

Susan.Shamimi-Noori@pennmedicine.upenn.edu

CIO

Faculty Disclosures

- Consultant for Boston Scientific Inc. and Sirtex Medical

- Conventional chemoembolization and radioembolization will be discussed. Both treatment modalities make use of off label products for the treatment of intrahepatic cholangiocarcinoma.

The Other
Primary Liver Cancer

My approach to ICC

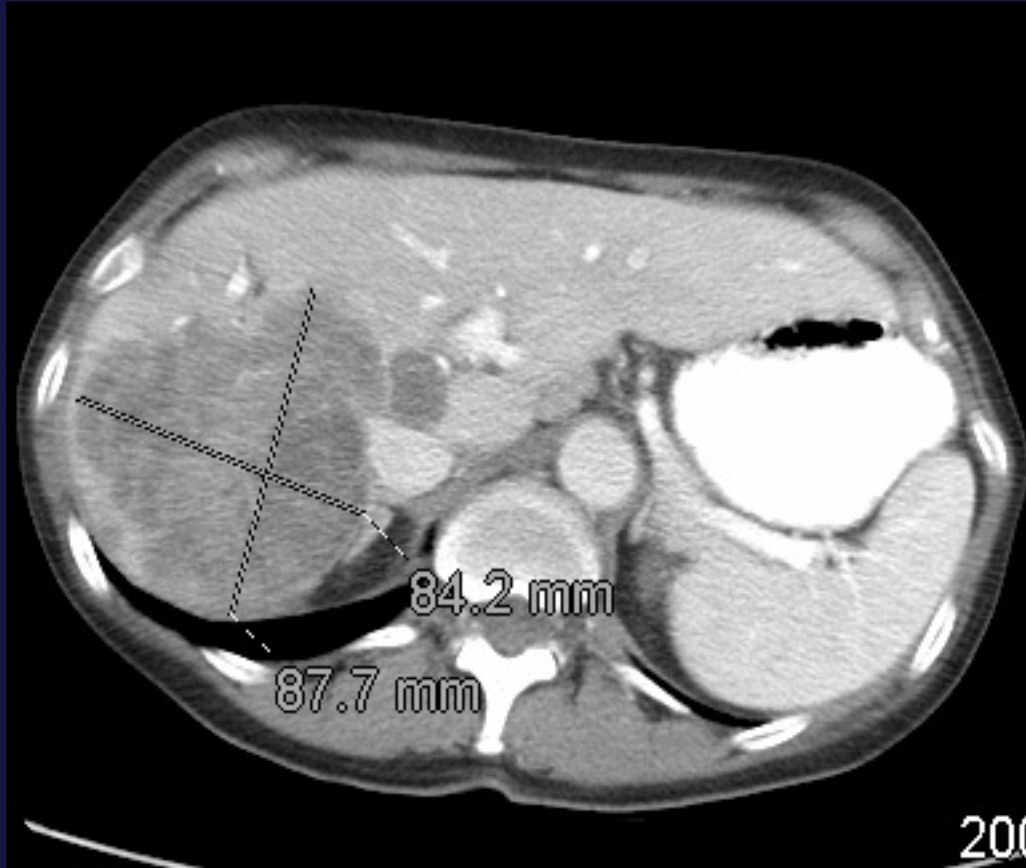
Susan Shamimi-Noori MD

Assistant Professor of Radiology

University of Pennsylvania

Susan.Shamimi-Noori@pennmedicine.upenn.edu

72-y/o M w/ abnormal LFTs



- CT findings:
  - 8.4 cm RHL mass with satellite lesions
  - Posterior RPV segmental branch tumor thrombus
  - No extrahepatic metastases
- CP A, ECOG 0
- Labs:
  - TB 0.9
  - Alb 4.2
  - INR 1.1
  - Plt 179
  - Cr 0.7
  - CA 19-9 455

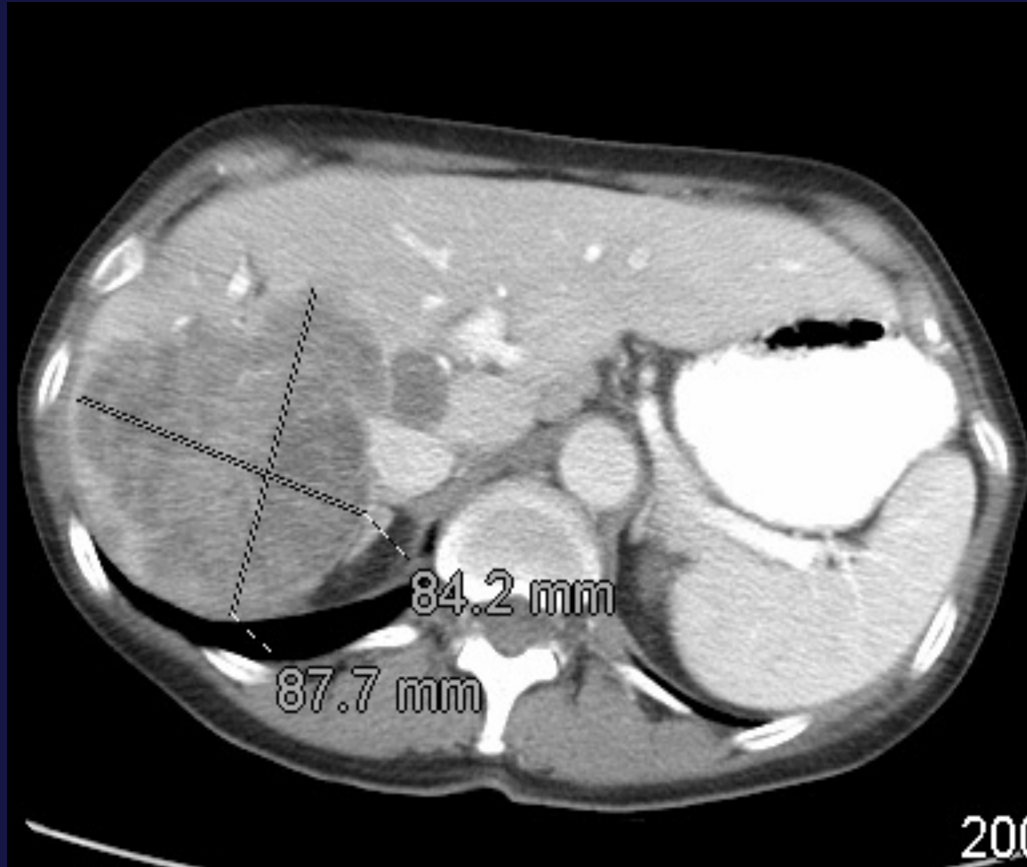
Penn IR

ICC: DIAGNOSIS

- Imaging
  - Variable tumor vascularity – not definitive
  - Arterial peripheral rim enhancement with delayed progressive enhancement
- Biopsy
  - Core biopsy needed for definitive diagnosis
- Tumor markers
  - CA-19-9 > 129 U/ml → 79% sensitive, 98% specific for ICC
  - Can have (+) CEA, CA-125
  - Mixed hepatocellular-cholangiocellular carcinoma → (+) AFP

Yang J. *World J Gastroent.* 2008.

Penn IR



Biopsy

Adenocarcinoma of pancreaticobiliary origin,

likely cholangiocarcinoma

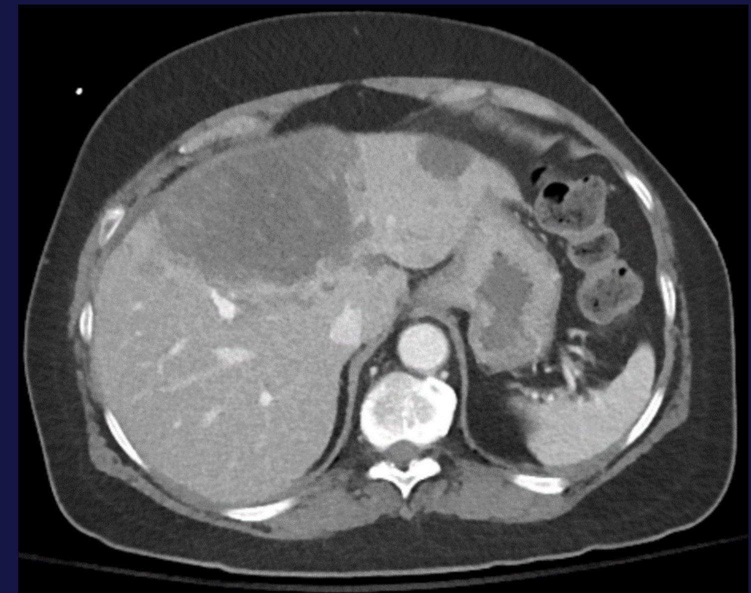
ICC: NATURAL HISTORY

Usually diagnosed in advanced stages

- Not screened like HCC

Metastases

- Intrahepatic
- Vascular
- Lymphatic
- Bone



Untreated, median overall survival ~ 3 months

Park, et al. *Gut Liver.* 2009.

Penn IR

NCCN 2021 Guidelines
Intrahepatic Cholangiocarcinoma

Resectable
- Staging laparoscopy or resection + regional lymphadenectomy

Unresectable

Metastatic

- Systemic therapy
  - Gemcitabine/Cisplatin (category 1)
  - 2nd line - FOLFOX
- Clinical Trial
- EBRT w/ concurrent fluoropyrimidine (unresectable only)
- Locoregional therapy
  - EBRT
  - Arterial directed
- Best supportive care

https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

Penn IR

EASL Guidelines

Intrahepatic cholangiocarcinoma (iCCA)

TNM stage I	TNM stage II	TNM stage III	TNM stage IV
Single tumor	Single or multinodular vascular invasion (VI)	Visceral peritoneum perforation, local hepatic invasion	Periductal invasion, N1, M1
Resectable (30-40%)		Unresectable (60-70%)	
		Intrahepatic disease only	Extrahepatic disease
Curative resection	Non-curative resection	Local-regional therapy*	Gemcitabin and cisplatin*
Observation	Enroll in studies of adjuvant therapy		
5-yr survival R0: 40% **5-yr survival N1 and VI: 20%**		**RF/TACE: median survival 15 mo** **Chemotherapy: median survival 12 mo**	

Bridgewater, et al. *J Hepatology*. 2014.

1st Line Data

Penn IR

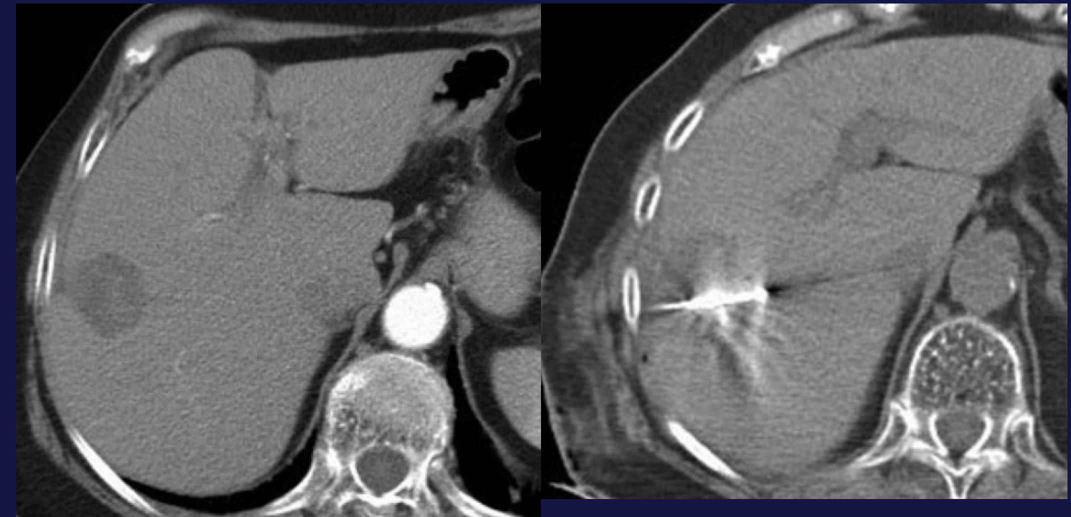
Percutaneous Ablation

- Median OS ~ 30 months
- Outcomes depend on tumor size
- Majority recur

Fu, et al. *J Vasc Interv Radiol.* 2012. (retrospective,17 pts)
- Patients ineligible for surgery
- Median OS 33 mo, 29% 5 yr survival

Han, et al. *JVIR.* 2015. (meta-analysis, 84 pts)
- 82% 1 yr, 47% 3yr, 24% 5 yr survival

Diaze-Gonzalez, et al. *JVIR.* 2020. (retrospective, 27 pts)
- 92.6% complete radiologic necrosis
- mOS 30.6 mo
  - 94.5 mo (single $\leq$ 2 cm)
  - 24.3 mo (single >2 cm)
- 77.8% with recurrence → TTR 10.1 mo



Penn IR

1st Line Systemic Therapy

ABC-02 Trial

- cisplatin + gemcitabine vs gemcitabine alone (RCT 412 pts)
  - Median OS: 11.7 mo vs 8.1 mo
  - PFS: 8 mo vs 5 mo
  - No significant increased toxicity for gem-cis

Penn IR

1st line
Gem/Cis + TARE

Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma
A Phase 2 Clinical Trial

JAMA Oncol. 2020;6(1):51-59.

Julien Edeline, MD, PhD; Yann Touchefeu, MD; Boris Guiu, MD, PhD; Olivier Farge, MD, PhD;
David Tougeron, MD, PhD; Isabelle Baumgaertner, MD; Ahmet Ayav, MD, PhD; Boris Campillo-Gimenez, MD, PhD;
Luc Beuzit, MD; Marc Pracht, MD; Astrid Lièvre, MD, PhD; Samuel Le Sourd, MD; Karim Boudjema, MD, PhD;
Yan Rolland, MD; Eveline Boucher, MD, PhD; Etienne Garin, MD, PhD

MISPHEC Trial (RCT, 41 pts)

- 22 mo mOS
- 75% 12 mo, 45% 24 mo OS
- 39% RR, 98% DCR (RECIST @ 3 mo)
- 14 mo mPFS → 55% 12 mo, 30% 24 mo PFS rates
- 22% downstaged to surgical intervention

Penn IR

1st line
Gem/Cis + TARE

Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma
A Phase 2 Clinical Trial

JAMA Oncol. 2020;6(1):51-59.

Julien Edeline, MD, PhD; Yann Touchefeu, MD; Boris Guiu, MD, PhD; Olivier Farge, MD, PhD; David Tougeron, MD, PhD; Isabelle Baumgaertner, MD; Ahmet Ayav, MD, PhD; Boris Campillo-Gimenez, MD, PhD; Luc Beuzit, MD; Marc Pracht, MD; Astrid Lièvre, MD, PhD; Samuel Le Sourd, MD; Karim Boudjema, MD, PhD; Yan Rolland, MD; Eveline Boucher, MD, PhD; Etienne Garin, MD, PhD

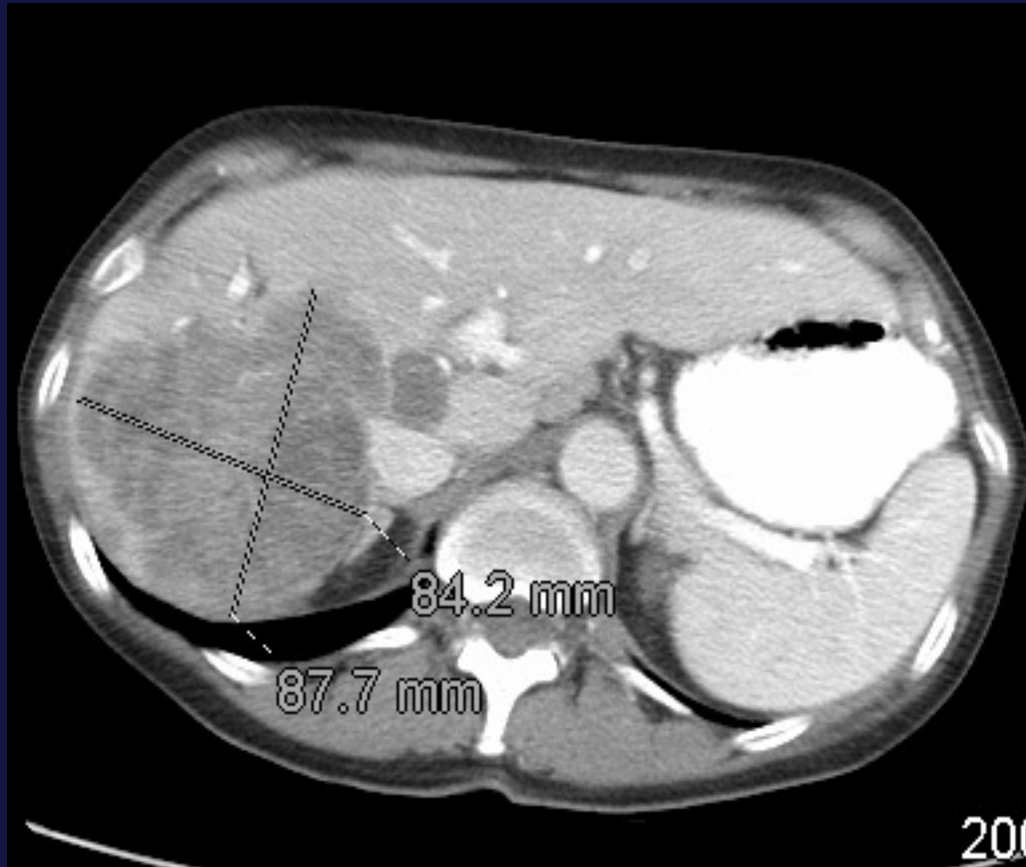
- Gemcitabine plus cisplatin given D1 and D8 of 21D cycle x 6 cycles
- TARE cycle 1 (D3-21) +/- cycle 3 (D3-21)
- Gemcitabine dose decreased for cycle concomitant and cycle after TARE

Penn MDTT first line therapy

→ TARE on ~D10 of cycle

(before nadir in 3rd week/optimize CBC profile)

Penn IR

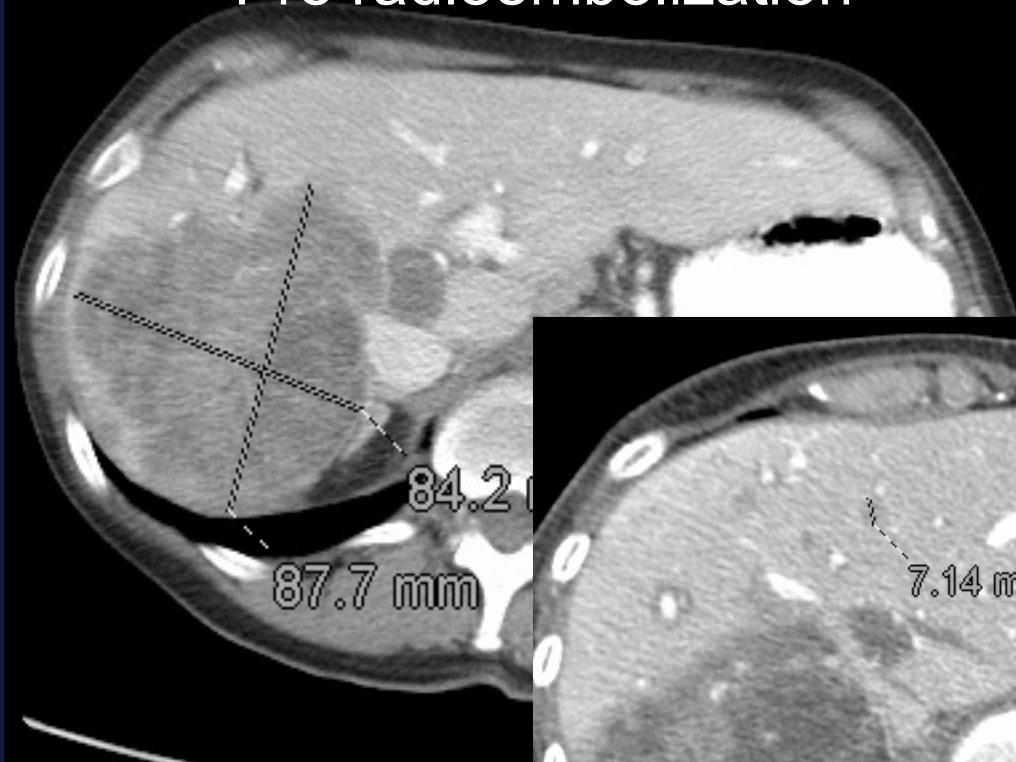


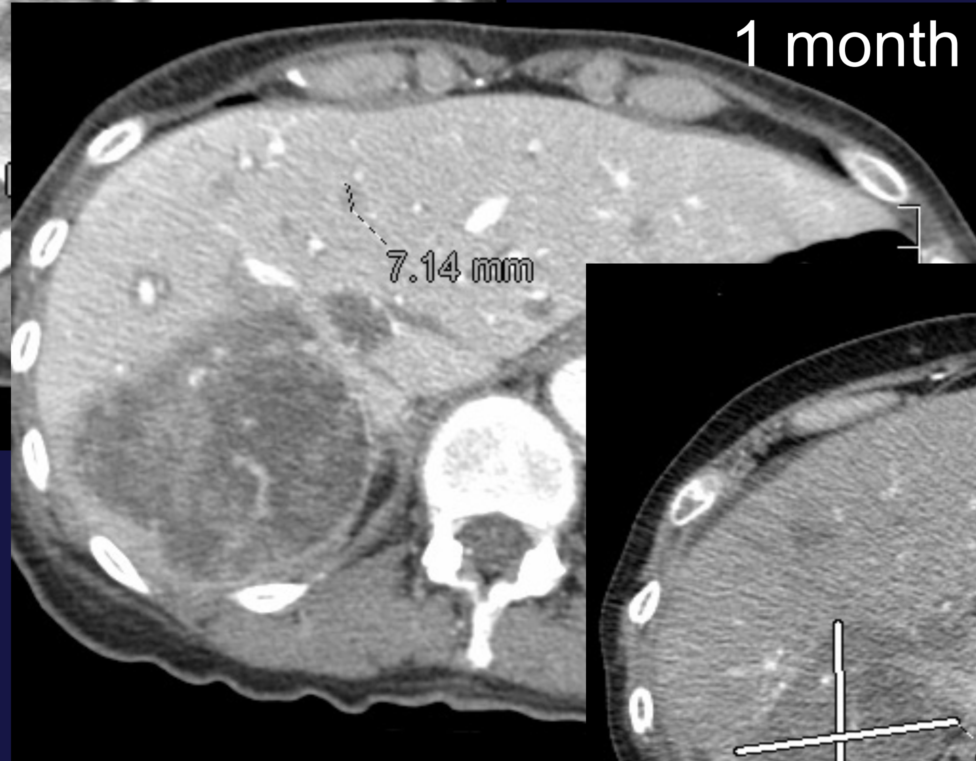
- ECOG 1
- CP A
- Portal vein tumor thrombus
- Large tumor w/ satellite lesions

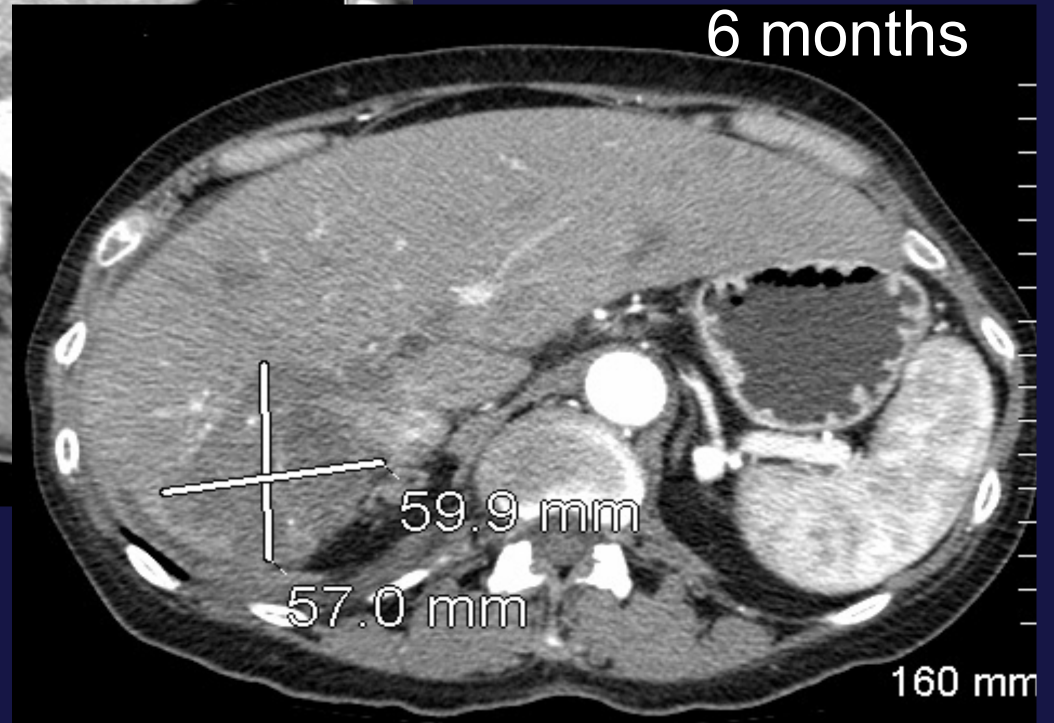
Plan:

Gem-Cis plus TARE

Penn IR



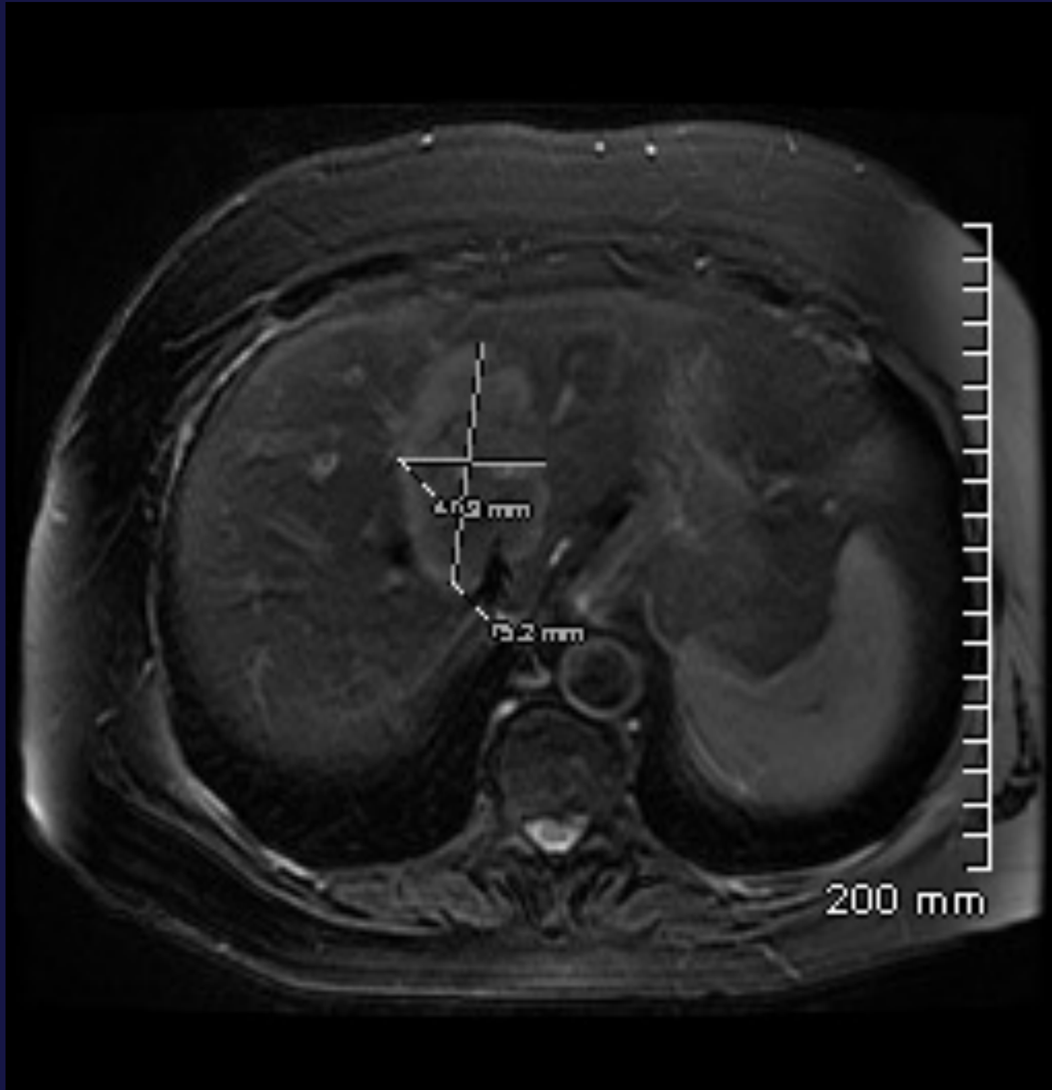




Penn IR

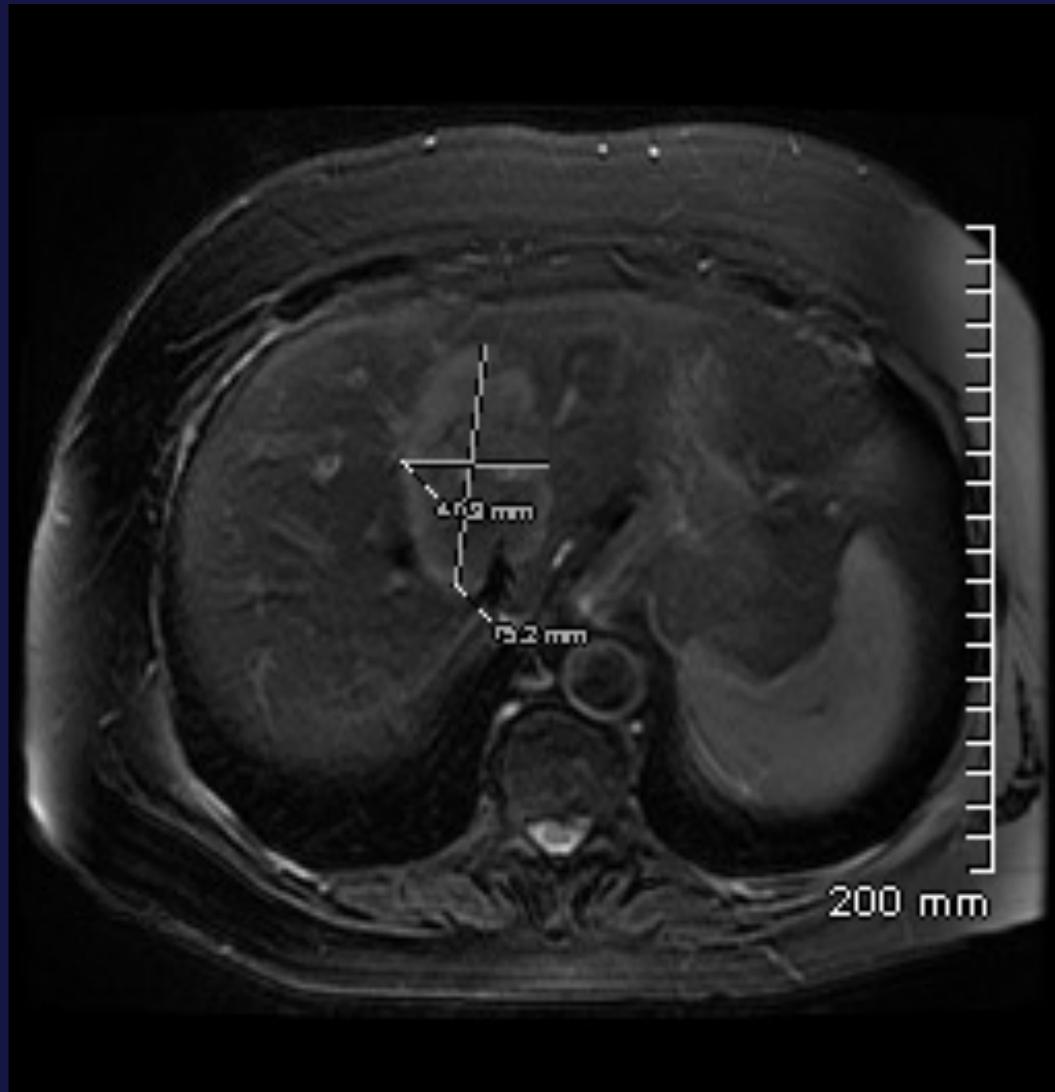
Case 2

60-y/o F with biopsy proven ICC now with mild PD on first-line systemic therapy



- MR findings:
  - 9.2 cm LHL mass
  - Patent portal vein
  - No intrahepatic or extrahepatic metastases
- CP A, ECOG 0
- Labs:
  - TB 0.1
  - Alb 3.2
  - INR 0.96
  - Plt 272
  - Cr 0.9
  - CA 19-9 204
  - AFP 4

Penn IR



Referred to IR for locoregional therapy

Penn IR

Transarterial Therapies

Limited data

- Variability in literature: efficacy, technique
- Most are retrospective studies or prospective series

Penn IR

Radioembolization

9-16 mo mOS

Prospective TARE studies

- 9.3 mo - *Saxena. Ann Surg Onc (25 pts)*
- 14.9 mo – *Ibrahim. Cancer 2008 (24 pts)*
- 11.5 mo – *Rafi. CVIR 2013 (19 pts)*
- 16.3 mo – *Camacho. JVIR 2014 (21 pts)*

Mouli, et al. *JVIR.* 2013. *(retrospective, 46 pts)*

prognostic factors

- ECOG: 14.3 mo (ECOG 0), 7.2 mo (ECOG 1), 9.9 mo (ECOG 2)
- Multifocality: 14.6 mo (solitary), 5.7 mo (multifocal)
- PVT: 14.4 mo (no PVT), 5.3 mo (PVT)
- Growth pattern: 15.6 mo (peripheral), 6.1 mo (infiltrative)
- Hepatic tumor burden: 14.4 mo (<25%), 5.3 mo (25-50%)

Penn IR

Chemoembolization

13-15 mo mOS (conventional TACE)

- 15 mo - *Kiefer et al. Cancer 2011* (multicenter prospective series, 62 pts)
  - Systemic chemo + cTACE→ median OS 28 mo
- 13 mo - *Vogl et al. Int j Cancer 2012 (retrospective)*
  - 8.7% PR, 57.4% SD, 33.9% PD (RECIST)
- 13.4 mo - *Ray et al. J Vasc Interv Radiol 2013* (meta analysis)

Similar median survival in DEB-TACE studies

- 13 mo - *Aliberti et al. Cardiovasc Intervent Radiol 2008*
- 11.7 mo - *Kuhlmann et al. Eur J gastroenterol Hepatol 2012*
- 17.5 mo from diagnosis - *Schiffman et al. Ann Surg Oncol 2011* diagnosis

Penn IR

TACE vs TARE

No Difference in Overall Survival

12.5 mo TARE v 13 mo TACE

- *Yang et al. J Gastrointest Oncol 2015* (systematic review, 929 pts)

13.9 mo TARE, 12.4 mo cTACE, 12.3 mo DEB-TACE

- *Boehm et al. J Surg Oncol 2015* (meta-analysis, 647 pts)

13.5 mo TARE, 14.2 mo TACE

- *Mosconi et al. CVIR 2021* (meta-analysis, 1695 pts)

14.1 mo TARE, 15.9 mo TACE, 18.9 mo EBRT, 21.3 mo HAI < 30.2 mo ablation

- *Edeline et al. Cancer Treatment Reviews 2021* (systematic review, 3990 pts)

Higher OS if TARE/TACE/HAI with concomitant systemic therapy as 1st line

- 25.2 v 15.7 mo
- *Edeline et al. Cancer Treatment Reviews 2021* (systematic review, 3990 pts)

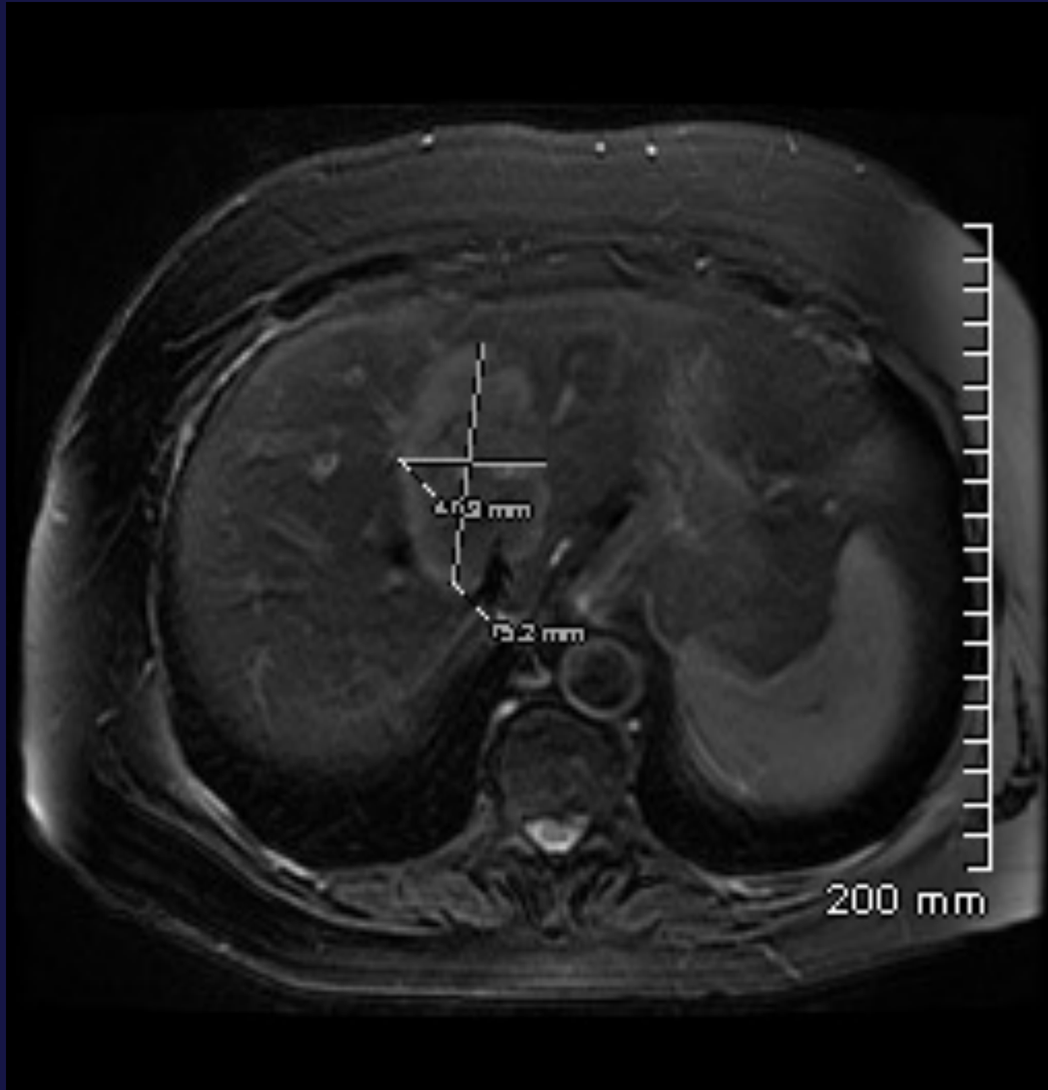
Penn IR

TACE vs TARE

- Similar OS
- Similar rates of adverse events

- Prior biliary intervention: TARE may have less risk of liver abscess
- Vascular invasion: ? TARE over TACE
- Short-term QOL goals: TACE→ higher rate of post embolic syndrome, QOL may be worse with concurrent systemic therapy
- Timing: Time to treatment and time to response assessment shorter with TACE
- Cisplatin is a radiosensitizer→ unknown synergy with TARE

Penn IR



- ECOG 1 post 1st line chemo
- CP A
- No prior biliary interventions

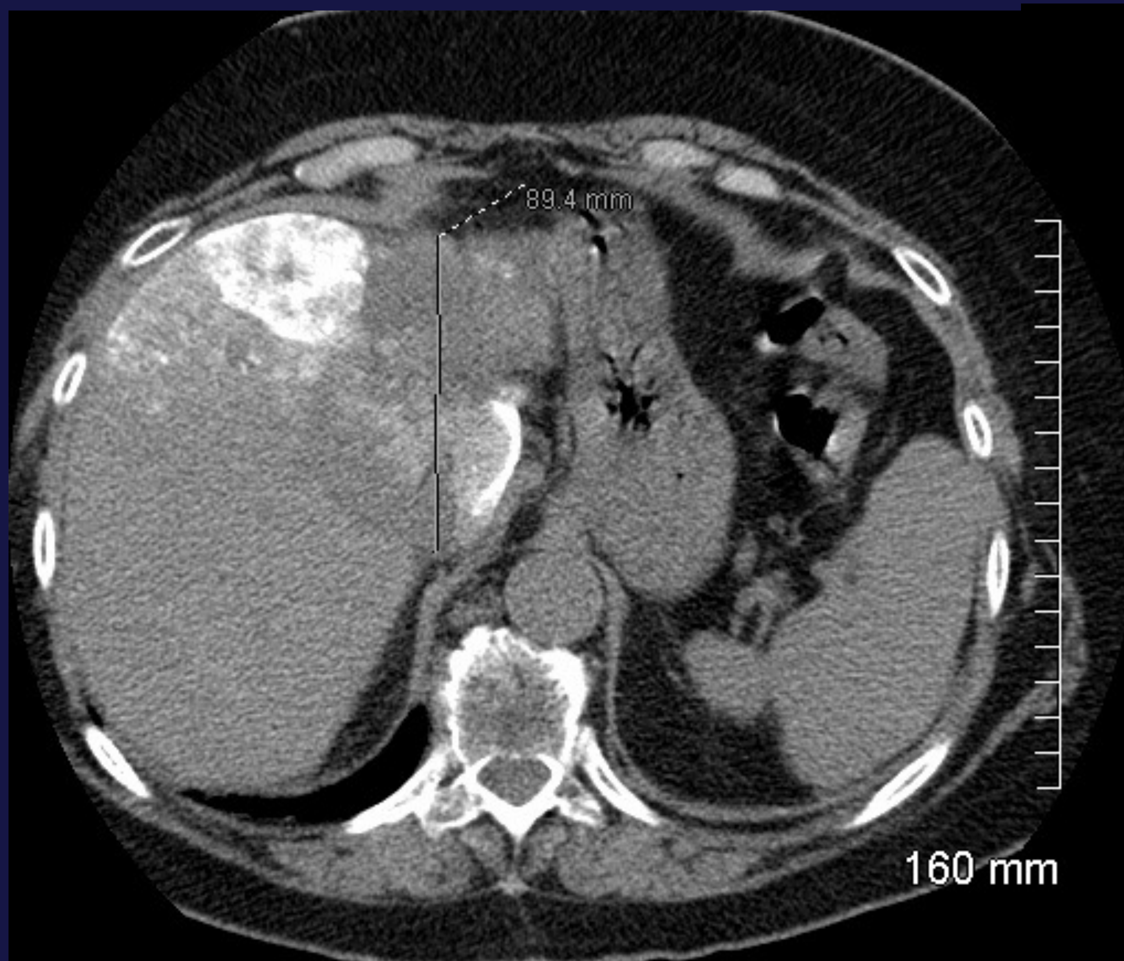
- Patient wanted treatment as soon as possible

Decision to treat with

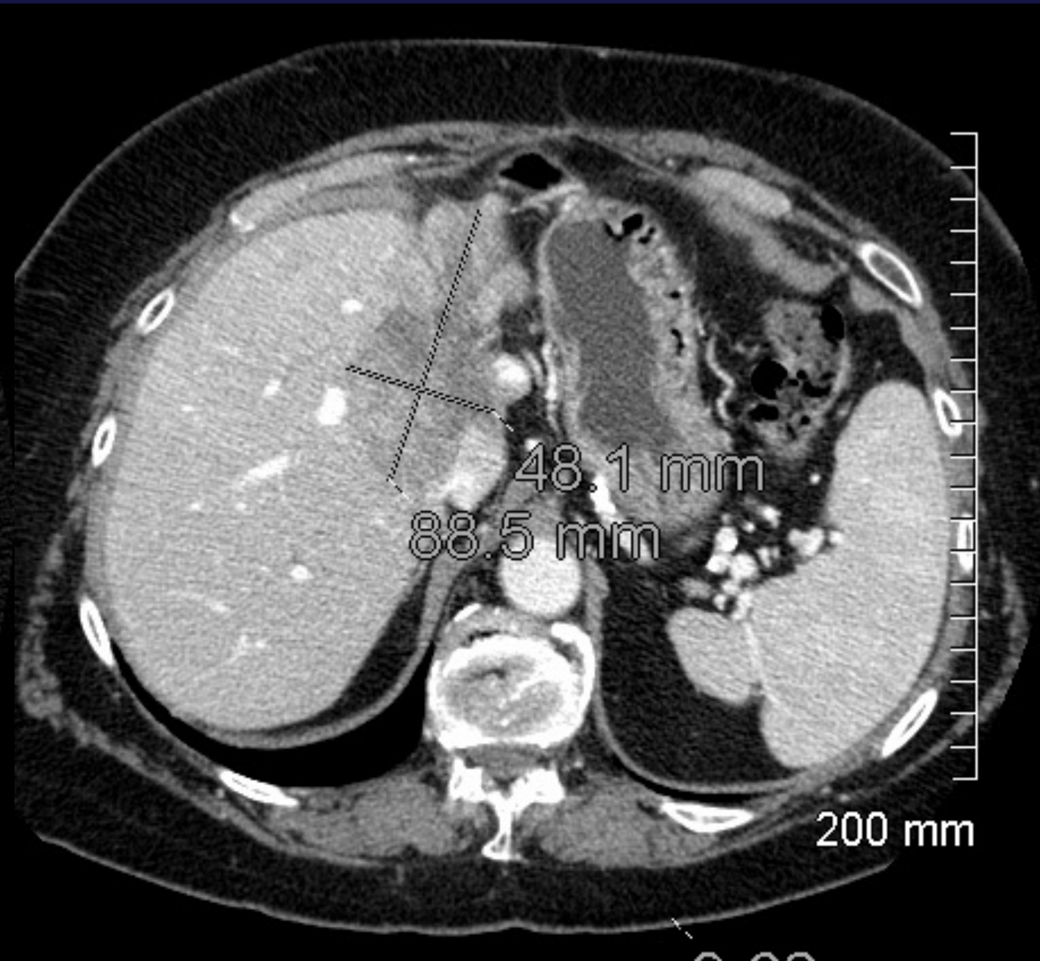
TACE

Penn IR

1 month post TACE

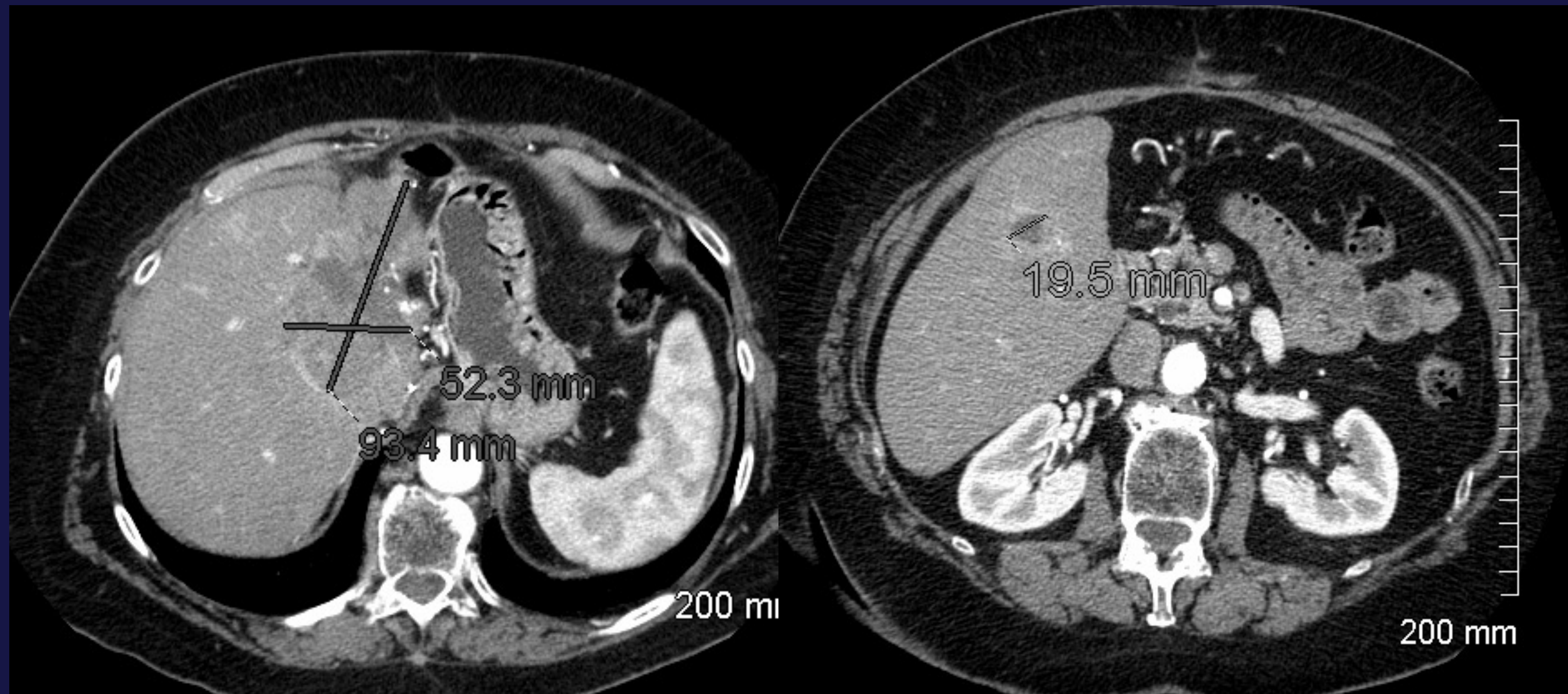


6 months post TACE



Penn IR

18 mos post TACE



Penn IR

2nd Line Systemic Therapy

Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial

Angela Lamarca, Daniel H Palmer, Harpreet Singh Wasan, Paul J Ross, Yuk Ting Ma, Arvind Arora, Stephen Falk, Roopinder Gillmore, Jonathan Wadsley, Kinnari Patel, Alan Anthoney, Anthony Maraveyas, Tim Iveson, Justin S Waters, Claire Hobbs, Safia Barber, W David Ryder, John Ramage, Linda M Davies, John A Bridgewater, Juan W Valle, on behalf of the Advanced Biliary Cancer Working Group

Lancet Oncol 2021; 22: 690–701

- FOLFOX + ASC vs ASC alone (RCT 162 pts)
- Documented progression on first line gem/cis

Survival

- Combo OS: 50.6% @ 6 mo, 25.9% @ 12 mo → mOS 6.2 mo
- ASC alone OS: 35.5% @ 6 mo, 11.4% @ 12 mo → mOS 5.3 mo *(p=0.031)*

ASC = Active Symptom Control

Penn IR

Take-Home Points

- ICC has a grim prognosis, but working with our oncologists, we add value

- Our approach
  1. Resect or ablate if possible
  2. 1st line Gem/Cis + TARE (D10 of 1st and 3rd cycle)
  3. 2nd line chemo + TARE or TACE

- No significant survival difference between TARE and TACE treatments

Thank you

Susan.Shamimi-Noori@pennmedicine.upenn.edu