My Approach to a Patient with Cholangiocarcinoma

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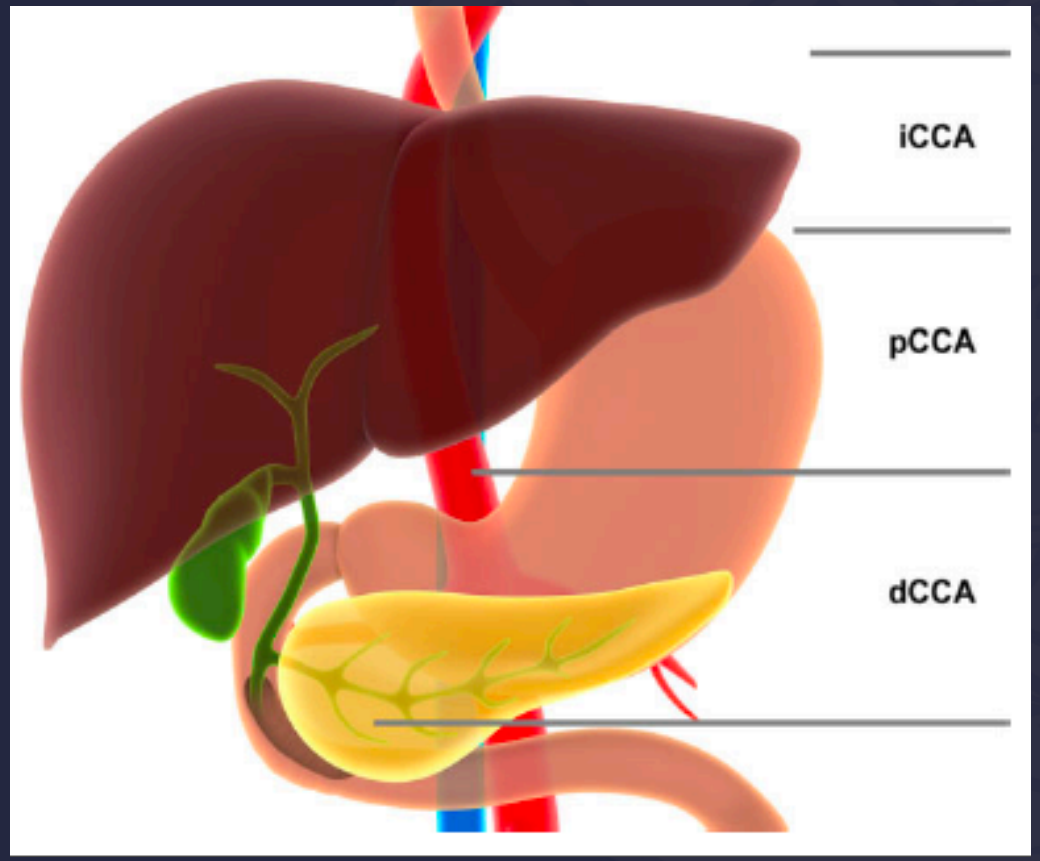
Disclosures

Consultant – BSC, Bard, ABK, Accurate Medical, BMS; Advisory Board – Varian

The use of radioembolization is off-label for cholangiocarcinoma.

Brand names are included in this presentation for participant clarification purposes only. No product promotion should be inferred.

Classification of Cholangiocarcinoma

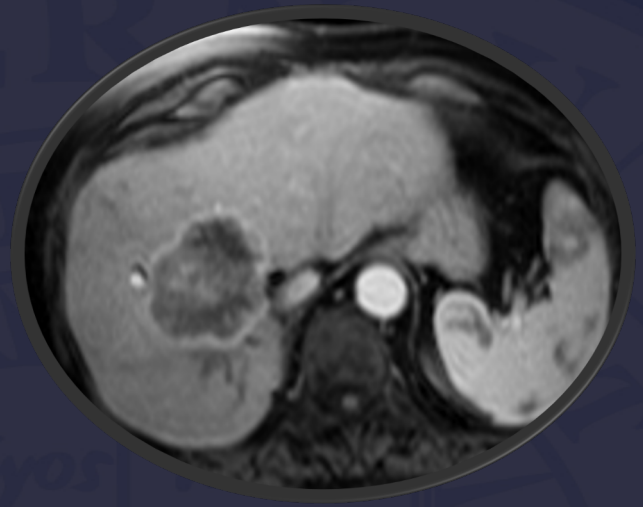


Intrahepatic CCA
< 20%

Rare hepatic malignancy: Incidence 1-2/100,000 persons in U.S.
10% of primary liver cancers

Massarweh NN, El-Serag HB. *Cancer Control*. 2017;24(3):1073274817729245.

EPIDEMIOLOGY



- Risk factors: often no clear predisposing condition
  - PSC, chronic cholangitis, choledochal cysts, hepatitis
- Dismal prognosis
  - Overall 5-year survival < 5%
  - Median survival 3-6 months without treatment
- Curative operative resection in < 30%
  - More feasible for extra-hepatic forms
  - 5-year survival post surgery 20-40%
  - Median OS after non curative resection is 3 months

Yang H. *J World J Gastroenterology.* 2008

Unresectable ICC

Treatment Options

- Systemic chemotherapy
  - Gemcitabine + cisplatin
  - FOLFOX
- Radiation therapy
  - Limited by RILD
- Ablation
  - Small cohorts
  - Peripheral tumors < 3 cm
- Brachytherapy/PDT
  - Limited data
  - Limited to small tumors
- Intra-arterial therapies
  - Chemo-infusion
  - Chemoembolization
  - Radioembolization

Liver-Directed Therapy

- Locally advanced disease (liver-dominant)
- Poor surgical candidates
- Convert to surgical candidate
- Progression/toxicities on chemotherapy
- Chemotherapy holiday
- Debulking for symptomatic relief

Valle J, et al. *NEJM* 2010;362(14):1273-81.

Intra-arterial Therapy for Advanced Intrahepatic Cholangiocarcinoma: A Multi-institutional Analysis

Omar Hyder, MD[1], J. Wallis Marsh, MD[2], Riad Salem, MD[3], Elena N. Petre, MD[4], Sanjeeva Kalva, MD[5], Eleni Liapi, MD[1], David Cosgrove, MD[1], Donielle Neal, MD[2], Ihab Kamel, MD[1], Andrew X. Zhu, MD[5], Constantinos T. Sofocleous, MD, PhD[4], Jean-Francois H. Geschwind, MD[1], and Timothy M. Pawlik, MD, MPH, PhD[1]

Retrospective review of 198 patients treated at 5 institutions over 20 years

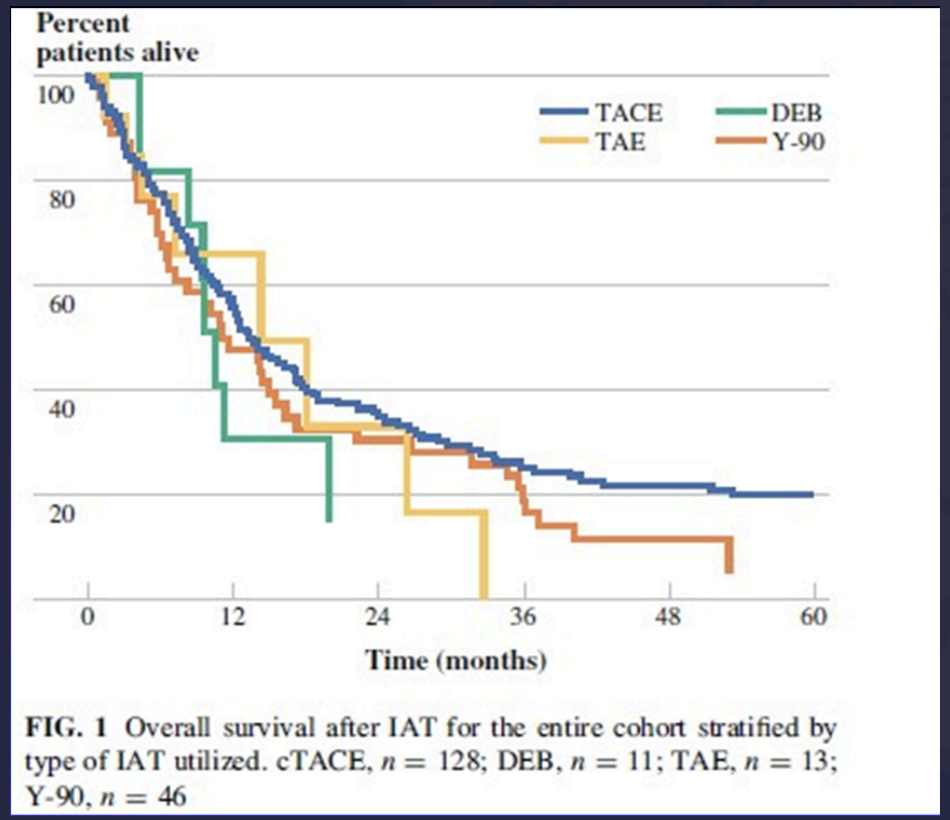


FIG. 1 Overall survival after IAT for the entire cohort stratified by type of IAT utilized. cTACE, $n = 128$; DEB, $n = 11$; TAE, $n = 13$; Y-90, $n = 46$

- CR/PR in 25%, SD 62%
- Median survival 13 months post-treatment

- Demonstrates feasibility, safety, and potential efficacy of IAT for ICC
- No significant difference between modalities

Hyder O, et al. *Ann Surg Oncol*. 2013;20(12):3779-86.

Safety of Yttrium-90 Microsphere Radioembolization in Patients with Biliary Obstruction

Ron C. Gaba, MD, Ahsun Riaz, MD, Robert J. Lewandowski, MD, Saad M. Ibrahim, MD, Robert K. Ryu, MD, Kent T. Sato, MD, Reed A. Omary, MD, MS, and Riad Salem, MD, MBA

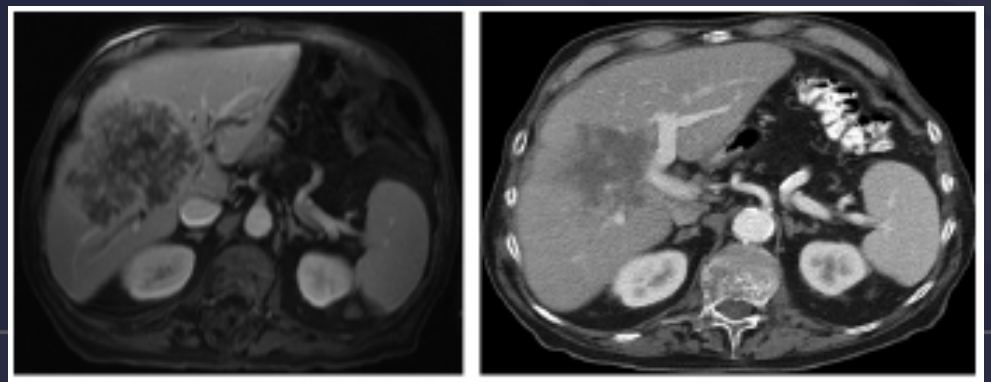
JVIR 2010

Radioembolization

- 12 pts/19 Tx - hilar malignancies
- No biliary complications
  - Median fu 22.9 mos.
- Pre/Post-Labs
  - WBC 5.3 vs. 5.3; P=0.490
  - Tbili 1.0 vs. 1.1; P=0.460
  - ALP 195 vs. 146; P=0.712

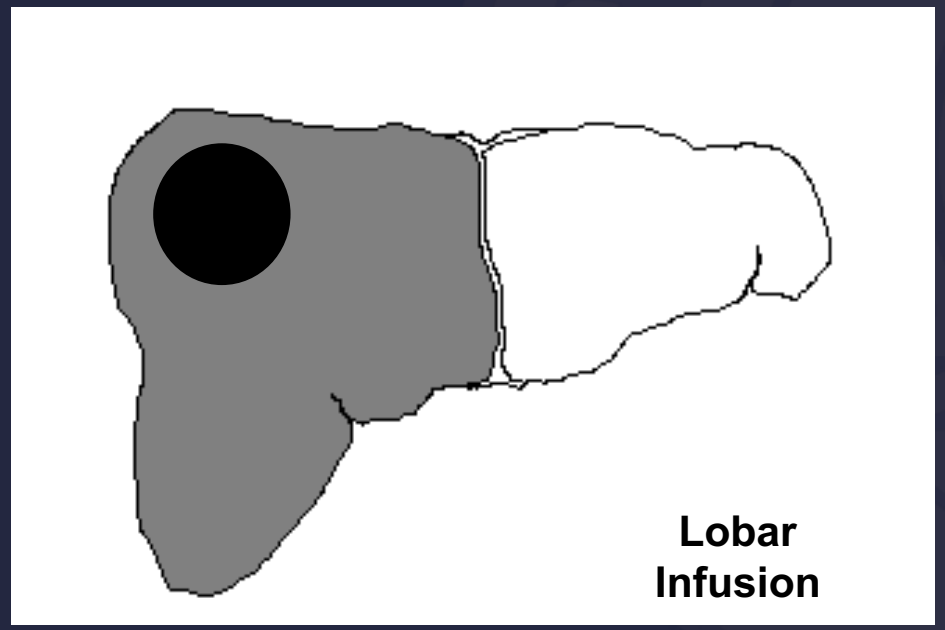
Chemoembolization

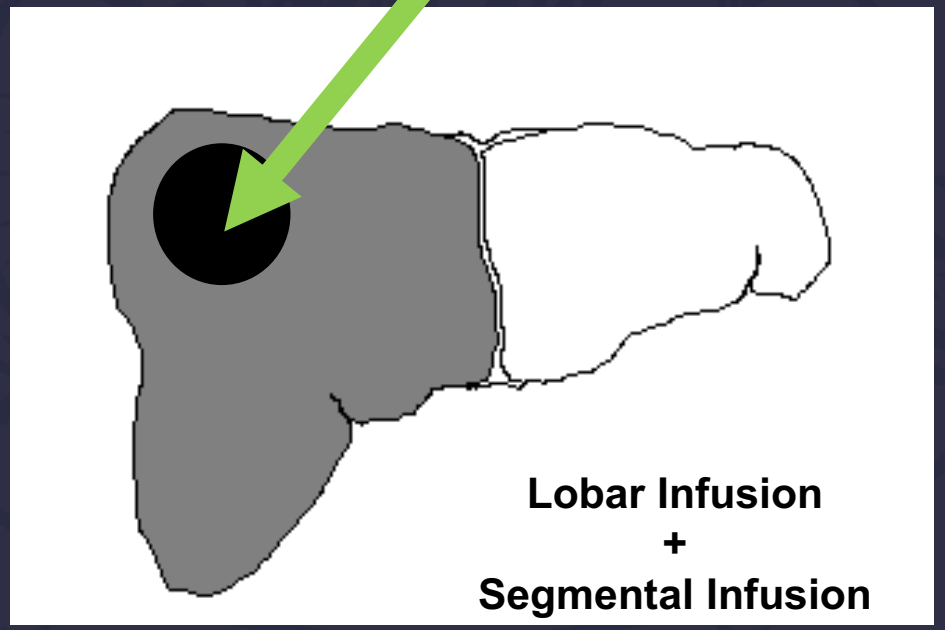
- Biloma incidence 3.6% (972 pts)
  - Higher risk in setting of intrahepatic biliary ductal dilation
- Liver abscess incidence 1.8% (2,439 pts/6,255 TACE)
  - Incidence 0.2% without preexisting biliary abnormalities



Sakamoto I, et al. *AJR Am J Roentgenol.* 2003; 181:79–87. Song SY, et al. *J Vasc Interv Radiol.* 2001; 12:131–320.

(Modified) Radiation Lobectomy



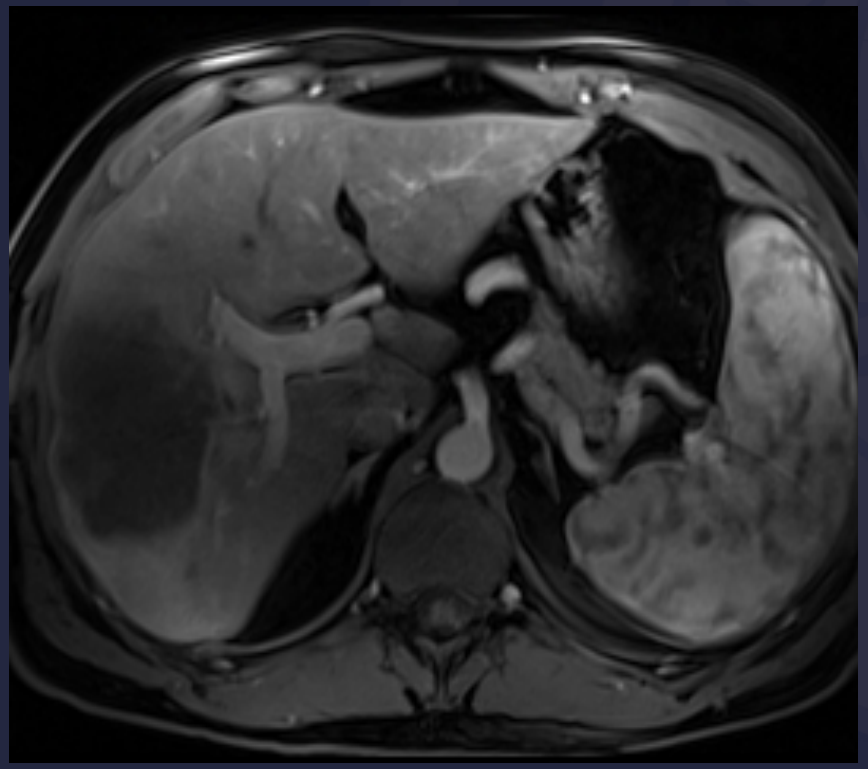


Grant number: R01CA2338878

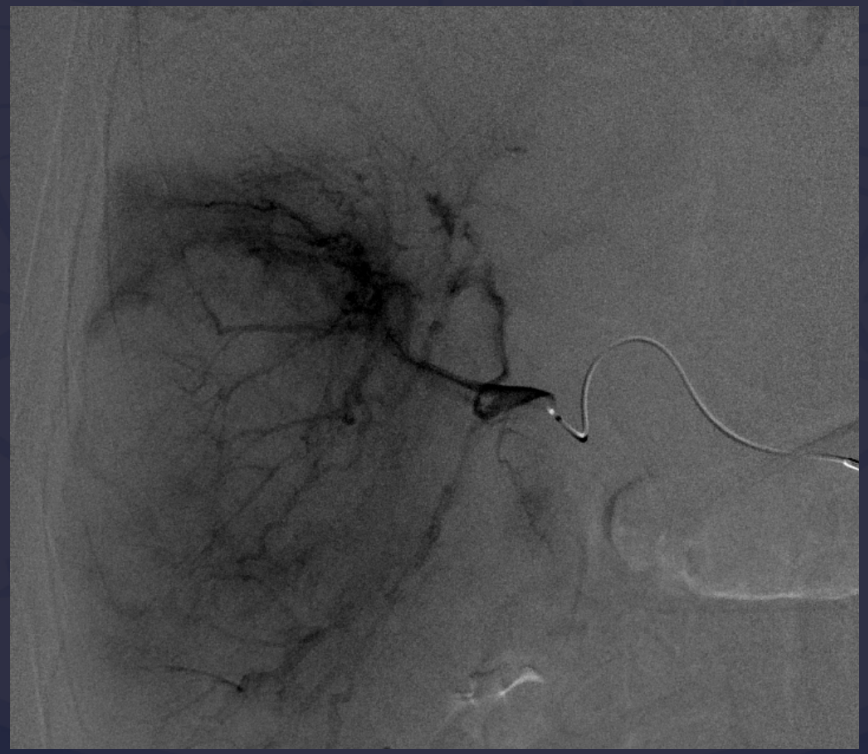
Y-90 radiation lobectomy: Dose optimization and prediction of FLR hypertrophy to enable resection of HCC

38-Year-Old Male with PSC

MRI

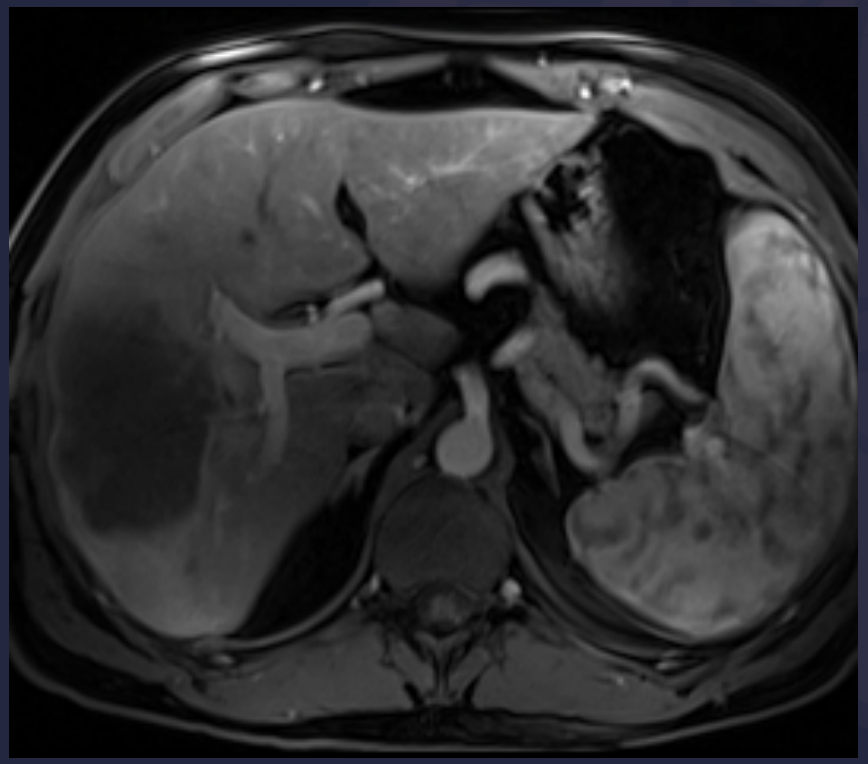


Angiography



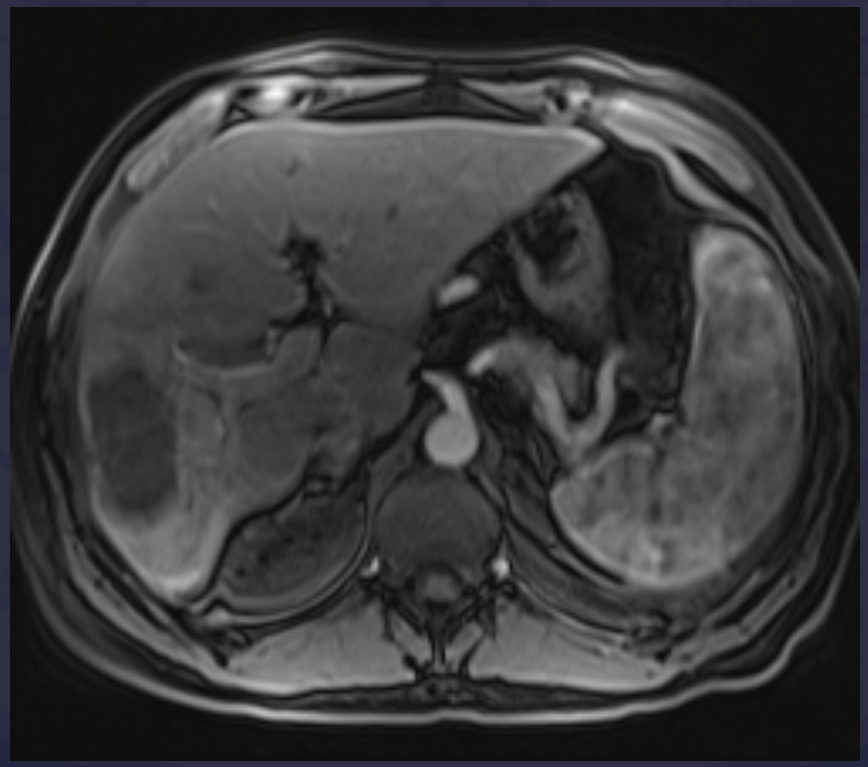
FOLLOW-UP

PRE-Y-90



FLR 34%

3-Month Follow-Up



FLR 55%

Radioembolization ICC Literature

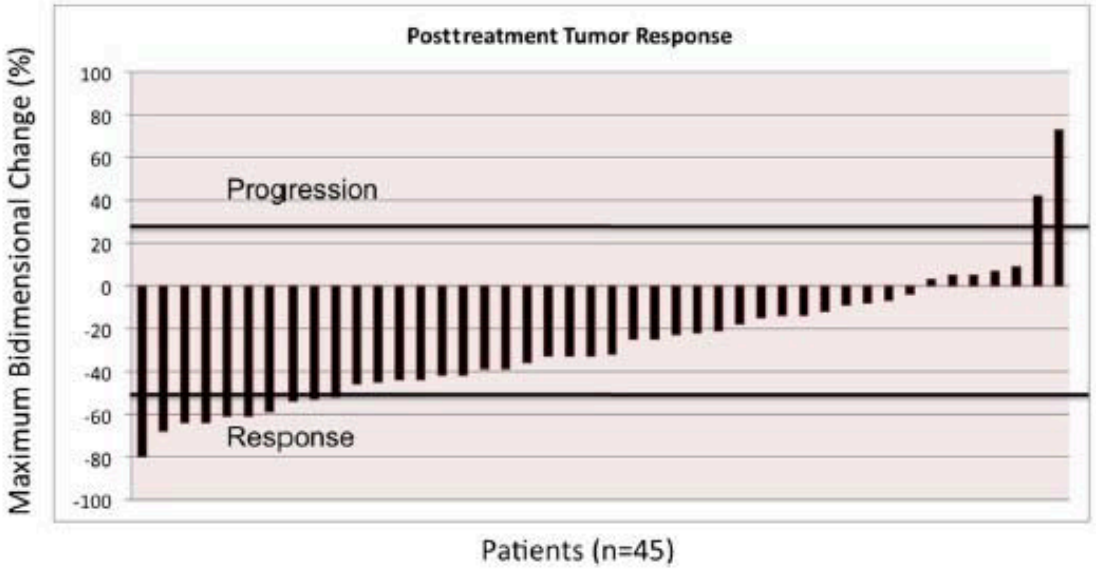
Year	Author	Group	Journal	Study Design	# of Pt	# down staged	Therapy
2008	Ibrahim et al.	NU	Cancer	Retrospective	24		Y90
2010	Saxena et al.	Australia	ASO	Retrospective	25		Y90
2012	Hoffman et al.	Germany	CVIR	Retrospective	33		Y90
2013	Mouli et al.	NU	JVIR	Retrospective	46	5	Y90
2013	Rafi et al.	Emory	CVIR	Retrospective	19		Y90
2013	Camacho et al.	Emory	JVIR	Retrospective	21		Y90
2015	Edeline et al.	France	Clin Nuc Med	Retrospective	24	11	Y90+CTx
2016	Mosconi et al.	Italy	British J Cancer	Retrospective	23		Y90
2016	Beuzit et al.	France	Eur J Radiology	Retrospective	45		Y90
2017	Swinburne et al.	Mount Sinai	Cancer Biotherapy and Radiopharm	Retrospective	29	1	Y90
2017	Jia et al.	China	J Cancer Research and Clin Onc	Retrospective	24		Y90
2018	Namal et al.	Turkey	J Imaging Interv Rad	Retrospective	14		Y90+CTx
2018	Reimer et al.	Germany	CVIR	Retrospective	21	0	Y90
2018	Shaker et al.	Michigan	American J Surgery	Retrospective	17		Y90
2018	Gangi et al.	Tampa	JVIR	Retrospective	85	0	Y90
2018	Bourien et al.	France	EJNNMI	Retrospective	64	12	Y90
2019	Kohler et al.	Multicenter	J Clinical Med	Retrospective	46	0	Y90
2019	Levillain et al.	Multicenter	EJNNMI	Retrospective	58	0	Y90
2019	White et al.	Multicenter	JVIR	Prospective	61	0	Y90
2020	Edeline et al.	France	JAMA Oncology	Prospective	41	9	Y90+CTx
2020	Buettner et al.	Multicenter	JVIR	Retrospective	115	5	Y90
2020	Bargellini et al.	Multicenter	CVIR	Retrospective	81	3	Y90

CLINICAL STUDY

Yttrium-90 Radioembolization for Intrahepatic Cholangiocarcinoma: Safety, Response, and Survival Analysis

Samdeep Mouli, MD, Khairuddin Memon, MD, Talia Baker, MD, Al B. Benson, III, MD, Mary F. Mulcahy, MD, Ramona Gupta, MD, Robert K. Ryu, MD, Riad Salem, MD, and Robert J. Lewandowski, MD

46 patients



PD 2%

Figure 1. Tumor response per WHO criteria presented as a waterfall plot. Bar values demonstrate the maximum change in tumor size from baseline in 45 patients after ^{90}Y radioembolization. Thresholds for disease progression and response are marked. (Available in color online at *www.jvir.org*.)

Significant prognostic factors: multifocal disease (5.7 vs. 14.6 months), infiltrative tumor (6.1 vs. 15.6 months), bi-lobar disease (10.9 vs. 11.7 months)

JVIR 2013

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Yttrium-90 Radioembolization for Intrahepatic Cholangiocarcinoma: Safety, Response, and Survival Analysis

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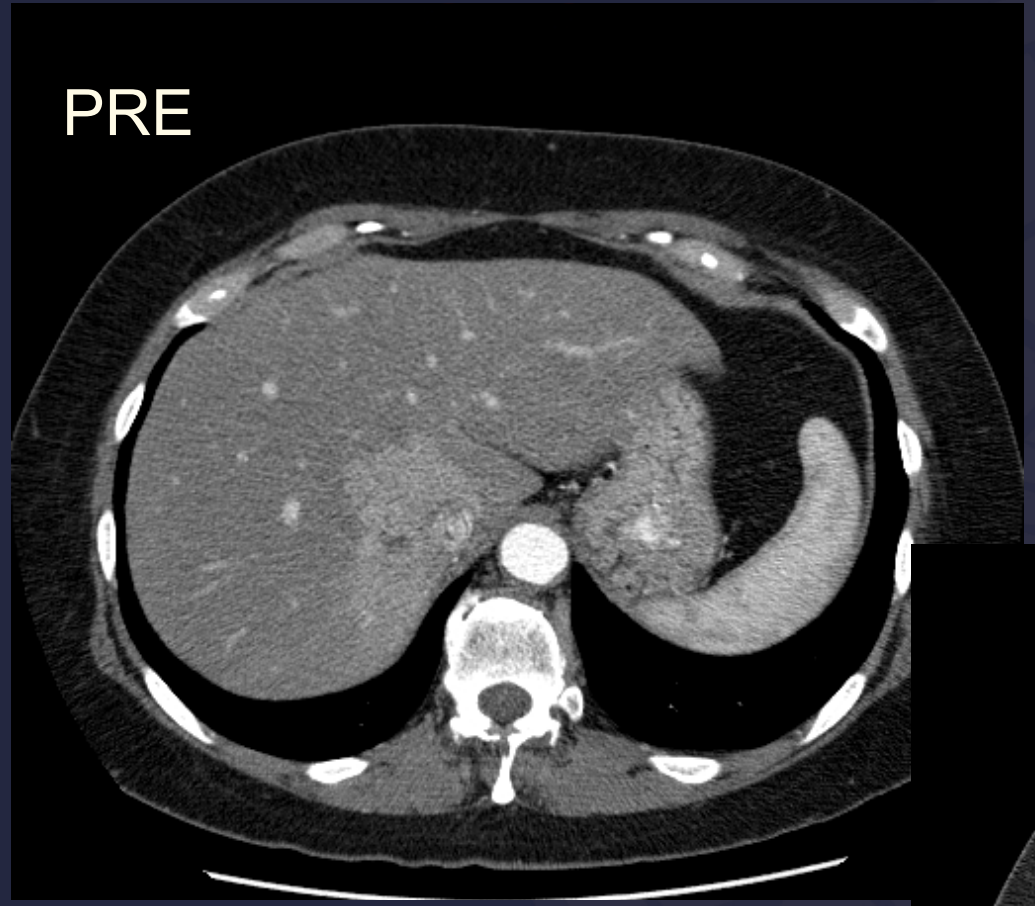
Y-90 Resection Cohort (≈ 10%)

Patient	Resection Type	Time Y90 to resection (days)	Survival (days)
1	Right Lobectomy	155	979
2	Trisegmentectomy	78	1412
3	Right Lobectomy	77	1344
4	Trisegmentectomy	113	169
5	Right Lobectomy	262	905

JVIR 2013


PRE


POST

Northwestern Updated Data

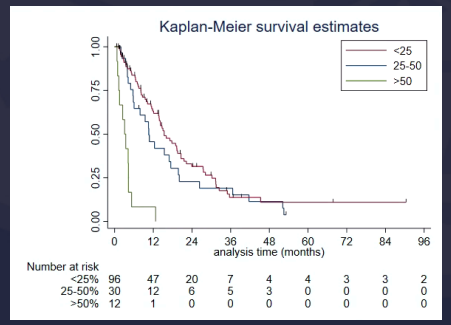
- Single-institution, retrospective analysis from 2004-2020
  - Cohort of 138 patients with unresectable ICC
  - Treated with glass microspheres
- Target lesion WHO response
  - CR: 3 (2.3%)
  - PR: 46 (34.9%)
  - SD: 74 (56.1%)
  - PD: 9 (6.8%)
- Time to Progression
  - Target lesion: median not reached
  - Intrahepatic: 5.9 months
  - Extrahepatic: 13.1 months

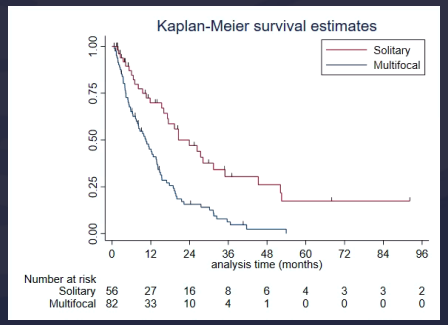
Characteristic	Incidence
Solitary	56 (40.6%)
Unilobar	59 (42.8%)
Tumor burden <25%	96 (69.6%)
Central location	66 (47.8%)
Infiltrative morphology	100 (72.5%)
Extrahepatic disease	48 (34.8%)
Prior chemotherapy	56 (40.6%)
Prior liver-directed therapy	19 (13.8%)
Tumor thrombus	14 (10.1%)

Manuscript in Preparation

Northwestern Updated Data

- Median OS: 13.8 mos. (95% CI, 10.5-16.0)
  - Censored to resection/transplantation
- Significant baseline prognosticators (multivariate analysis)
  - Solitary tumor (P < 0.001)
  - Tumor burden < 50% (P = 0.03)
  - No prior chemotherapy (P = 0.02)
  - No tumor thrombus (P = 0.004)
  - Higher serum albumin (P = 0.01)





Manuscript in Preparation

Northwestern Updated Data

- Downstaging
  - Resection: 11 patients (8.0%)
    - Right lobectomy (n = 6)
    - Tri-segmentectomy (n = 4)
    - Left lobectomy (n = 1)
  - Median OS: 41.8 months

  - Transplant (bridge): 3 patients (2.2%)
    - All patients had primary sclerosing cholangitis

Manuscript in Preparation

Research

JAMA Oncology | Original Investigation

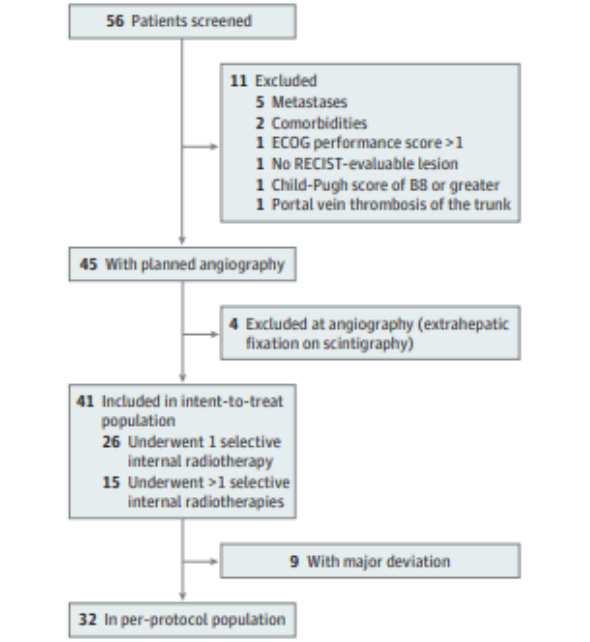
Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma
A Phase 2 Clinical Trial

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

Phase 2 (MISPHEC) clinical trial; multi-center (experienced with Y90)

- Chemotherapy naïve unresectable ICC
- November 12, 2013–June 21, 2016
- Concomitant first-line chemotherapy with cisplatin and gemcitabine

Figure 1. Flowchart



ECOG indicates Easter Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors.

Edeline J, et al. *JAMA Oncol.* 2019;6(1):51-59.

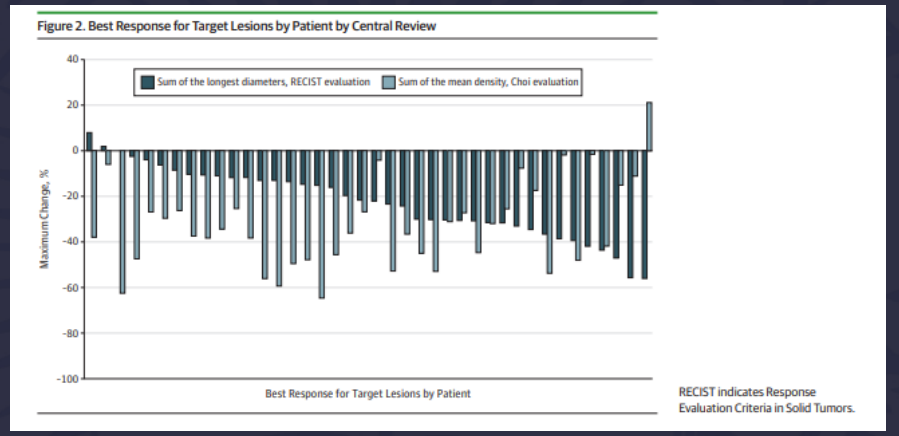
Research

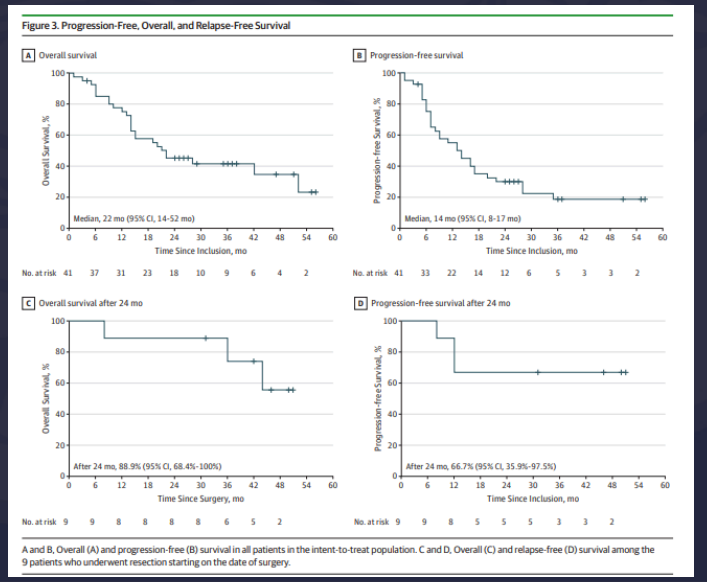
JAMA Oncology | Original Investigation

Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma

A Phase 2 Clinical Trial

- RECIST response 41%
- Choi response 93%
- Disease control rate 98%
- Median OS 22 months
- Median PFS 14 months
- Downstage to surgery 22%
- R0 resection in 8/9 patients



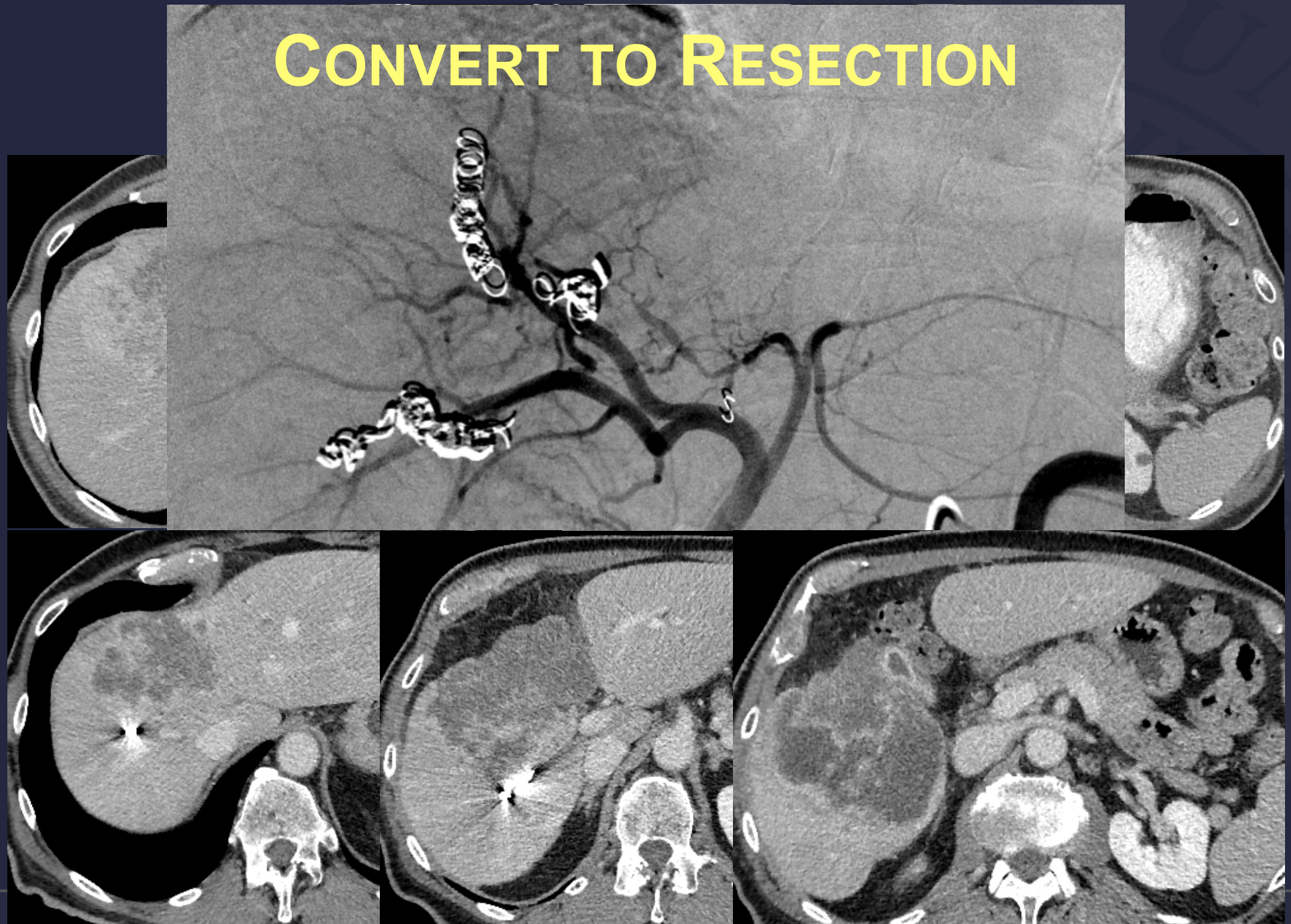


Edeline J, et al. *JAMA Oncol.* 2019;6(1):51-59.

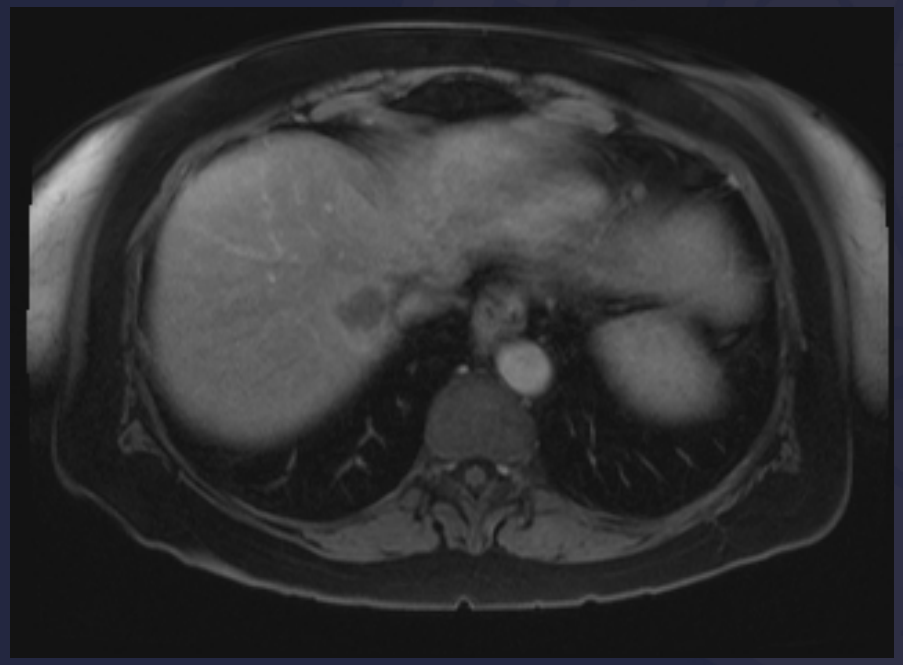
My Approach to ICC Patients

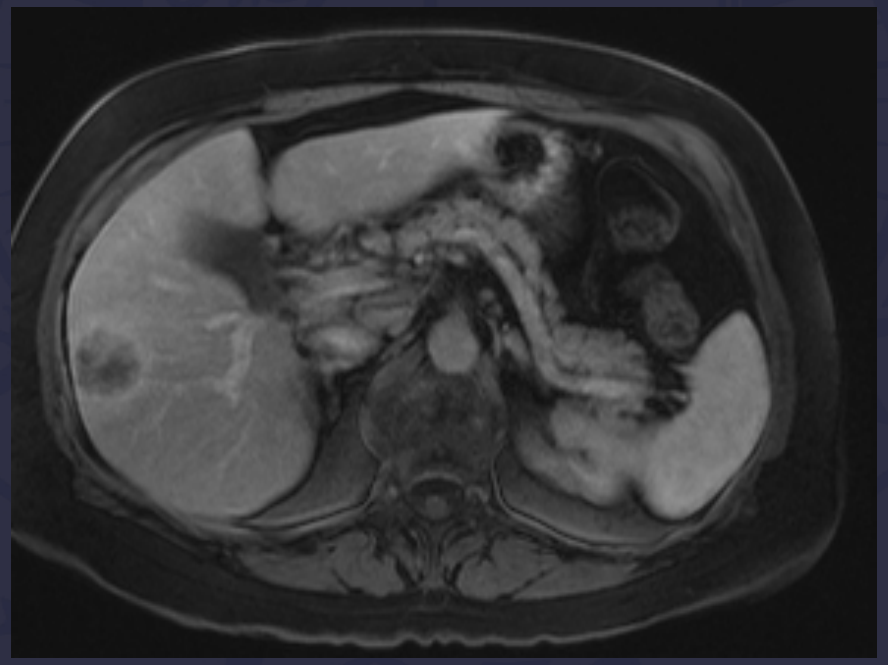
- Consider best approach to get to surgery
  - Radiation lobectomy
  - Combined systemic + Y-90
- Solitary and/or peripheral tumors
  - Ablative radiation segmentectomy
- Central tumors
  - Difficult to target
  - Selective vs. Lobar vs. Lobar + Selective

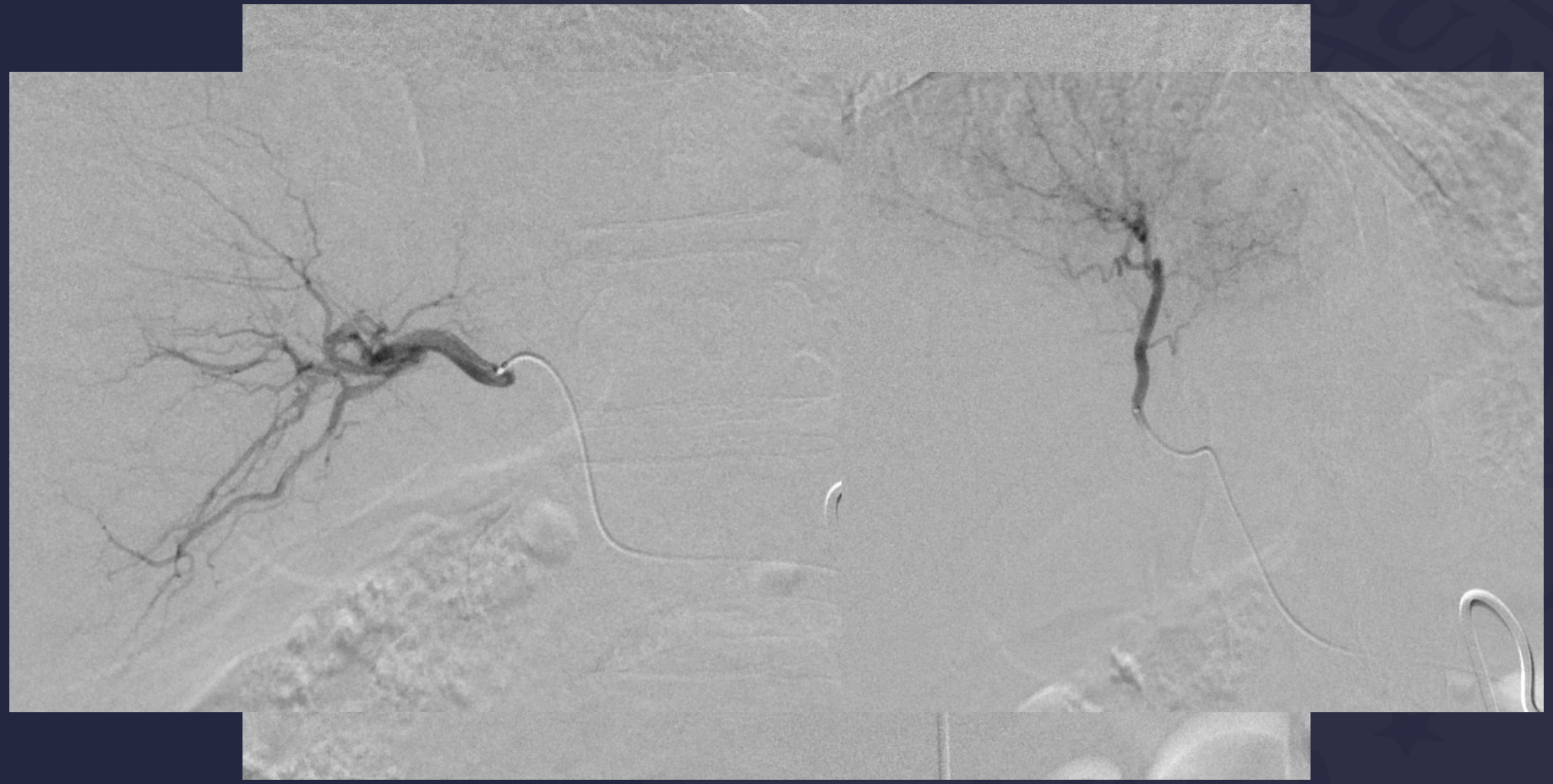
Convert to Resection



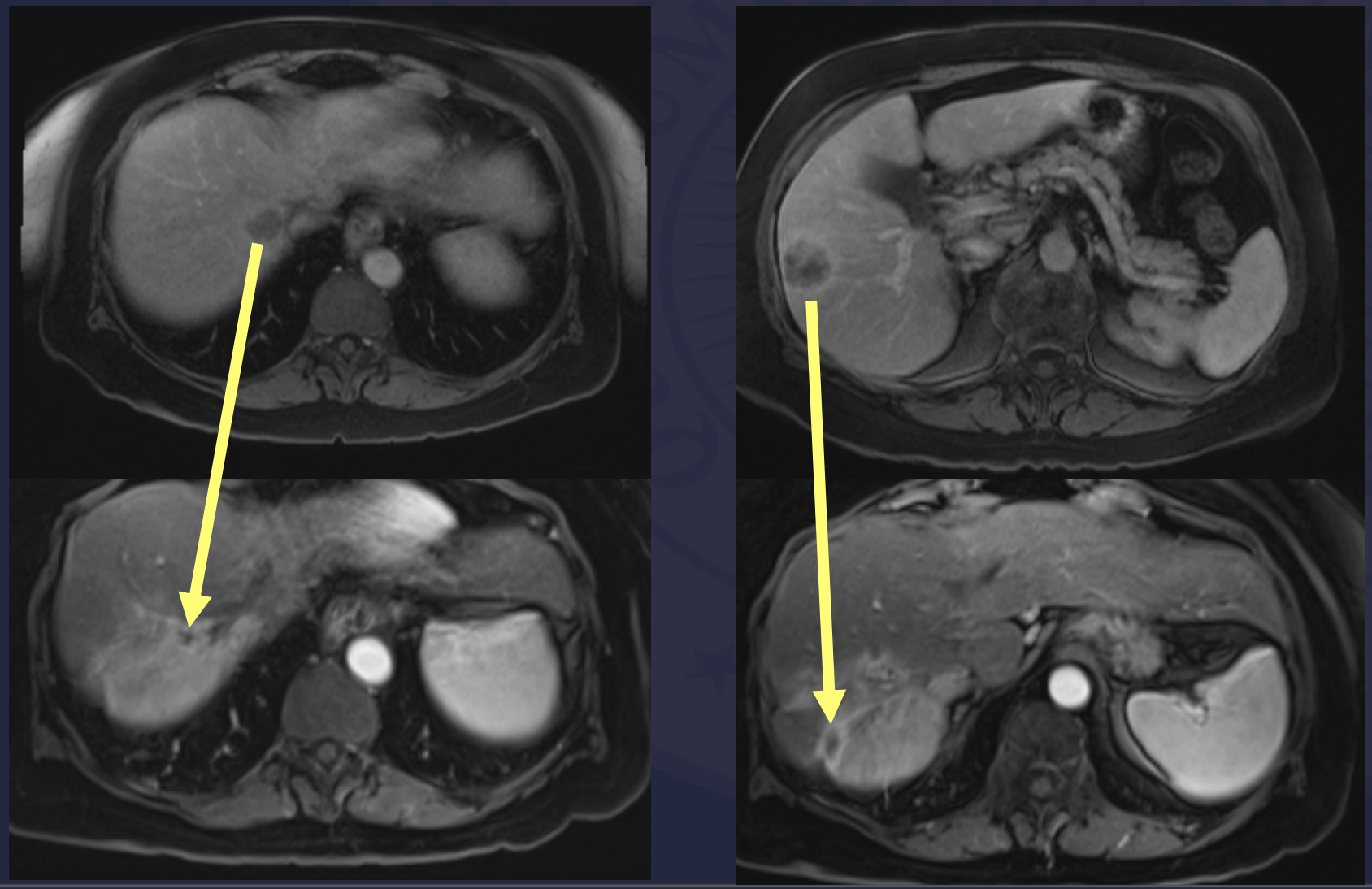
Segmental Treatment





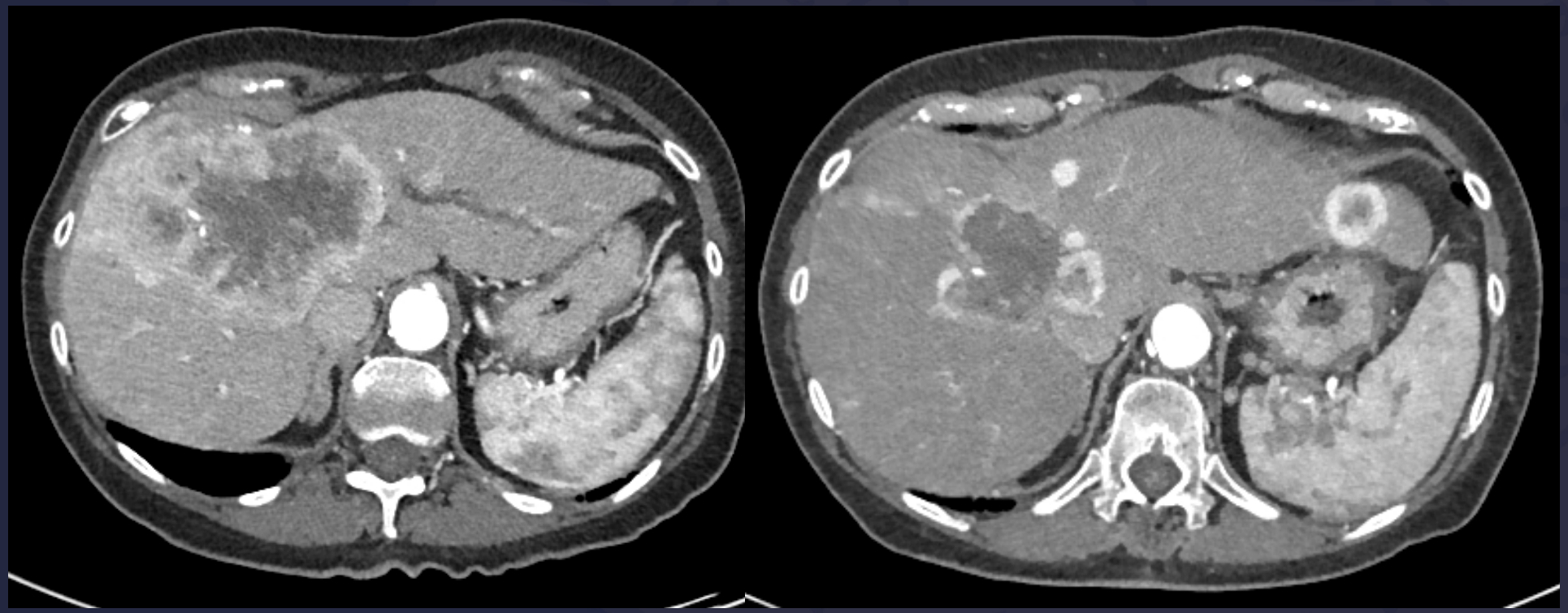


6-Month Follow-up



Central Tumors

One-Year Follow-up



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NORTHWESTERN RADIOLOGY