Introduction to Tools, Imaging, and Procedural Set-Up

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How Is Radioembolization Performed?

Two parts to the procedure

First part: “Mapping” Angiogram

Hepatic vasculature is evaluated, and target vessels for treatment are identified

- Similar to TACE

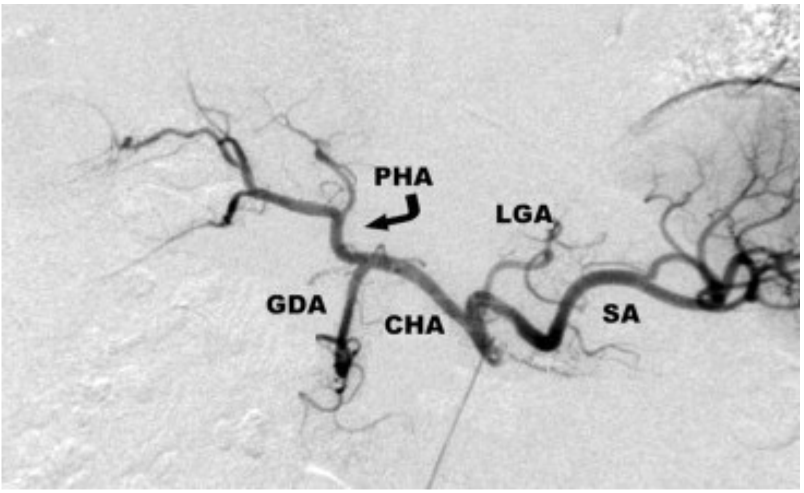
Any evidence of non-target embolization from the point of anticipated delivery are embolized

- Most commonly, this includes aberrant hepatico-enteric collaterals
- The GDA used to be always embolized, historically, but this is now recognized as no longer routinely needed (<1% of time)

Once treatment site is determined, Tc99-MAA particles are administered

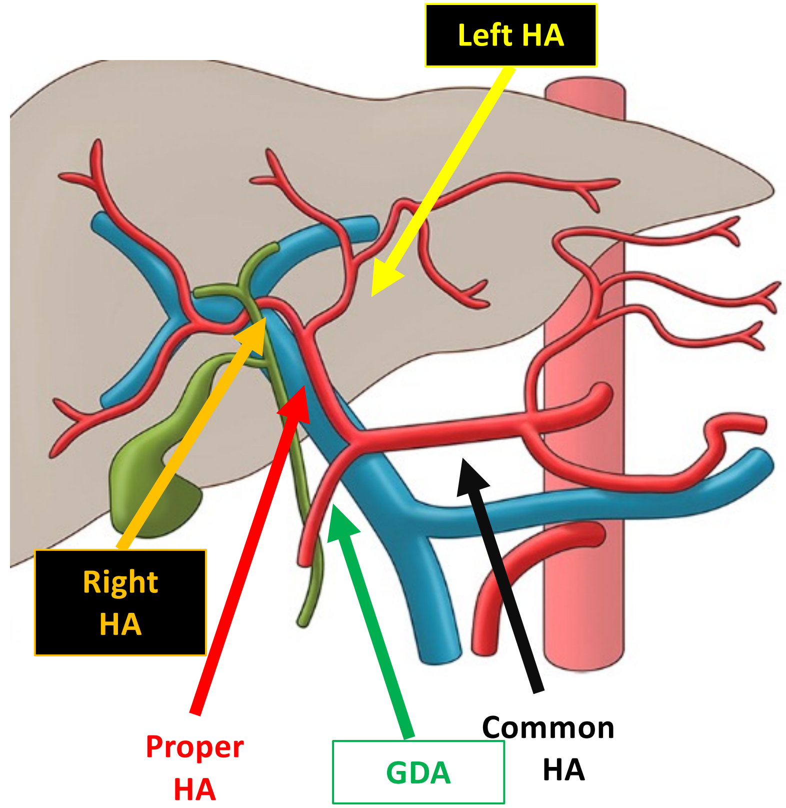
- Procedure is completed, and patient is transported to Nuclear Medicine
- Planar and SPECT images are obtained to determine lung shunt fraction and also assess for possible unrecognized non-target embolization sources


Let’s start with the basics
of angiography…

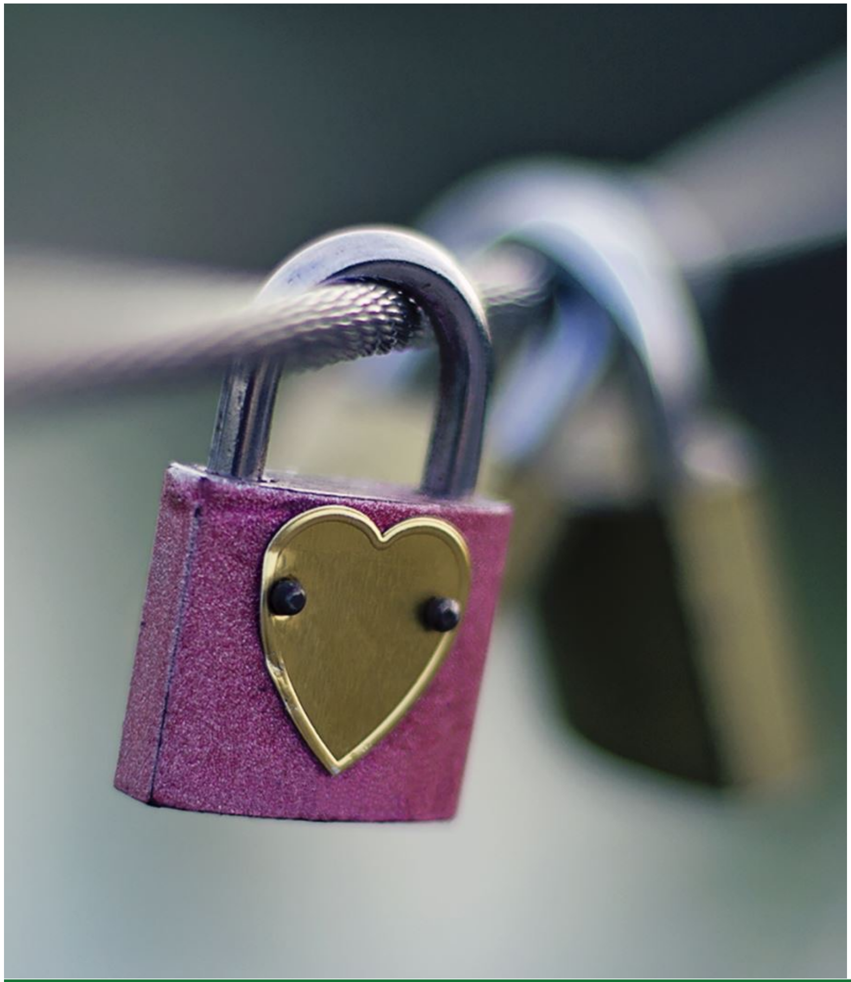


Conventional hepatic anatomy:

- Proper hepatic artery → Right and left hepatic artery
- Segment 4 can arise from left or separately (ie, middle hepatic artery)



Favelier S, et al. Anatomy of liver arteries for interventional radiology. *Diagn Interv Imaging*. 2015 Jun;96(6):537-46.



Fundamental Angiography

- AP View is the standard view
- Obliques will help identify vessels that are anterior or posterior
- RAO → Anterior objects will move to the right of the screen, posterior objects will move to the left

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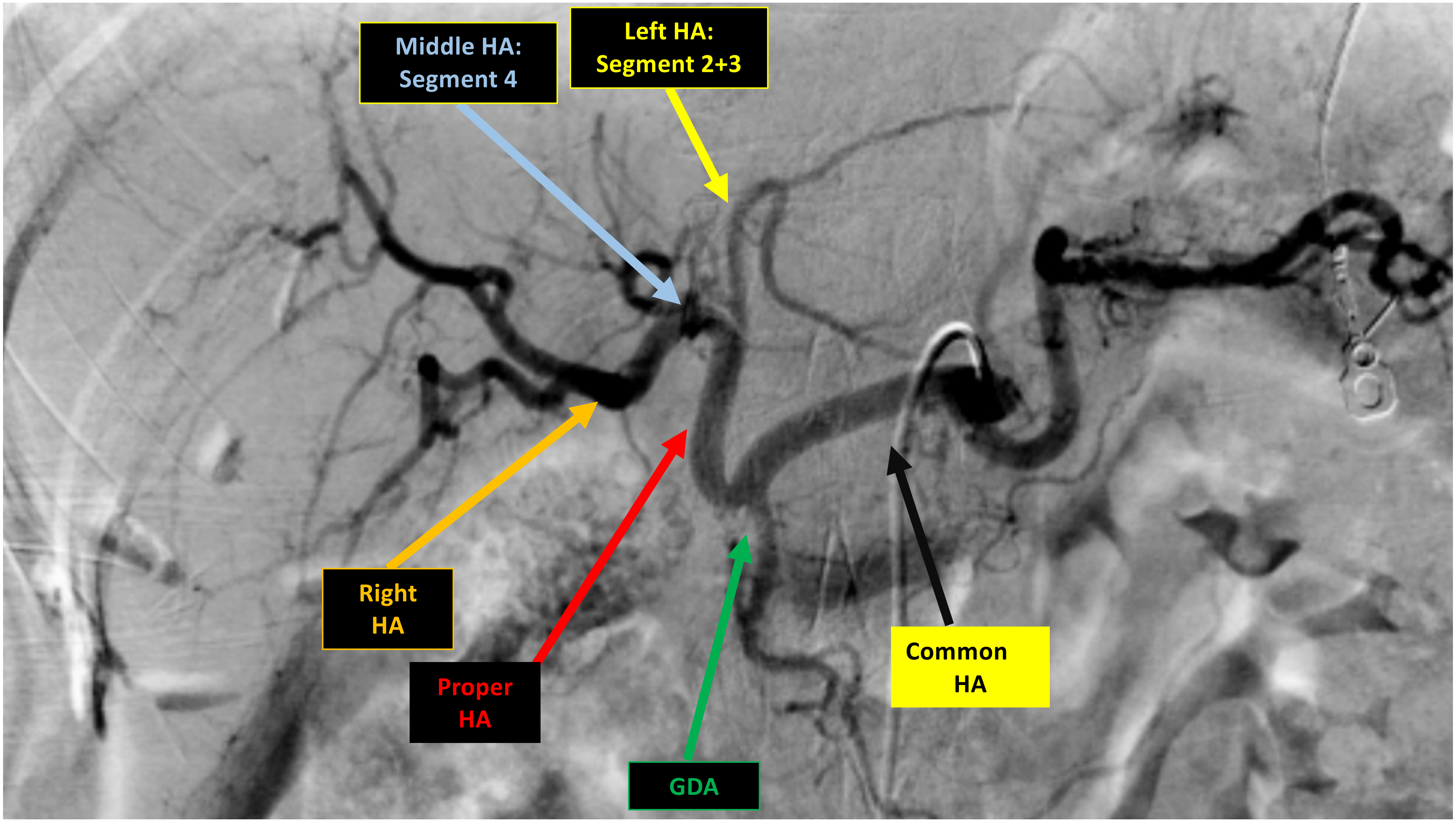
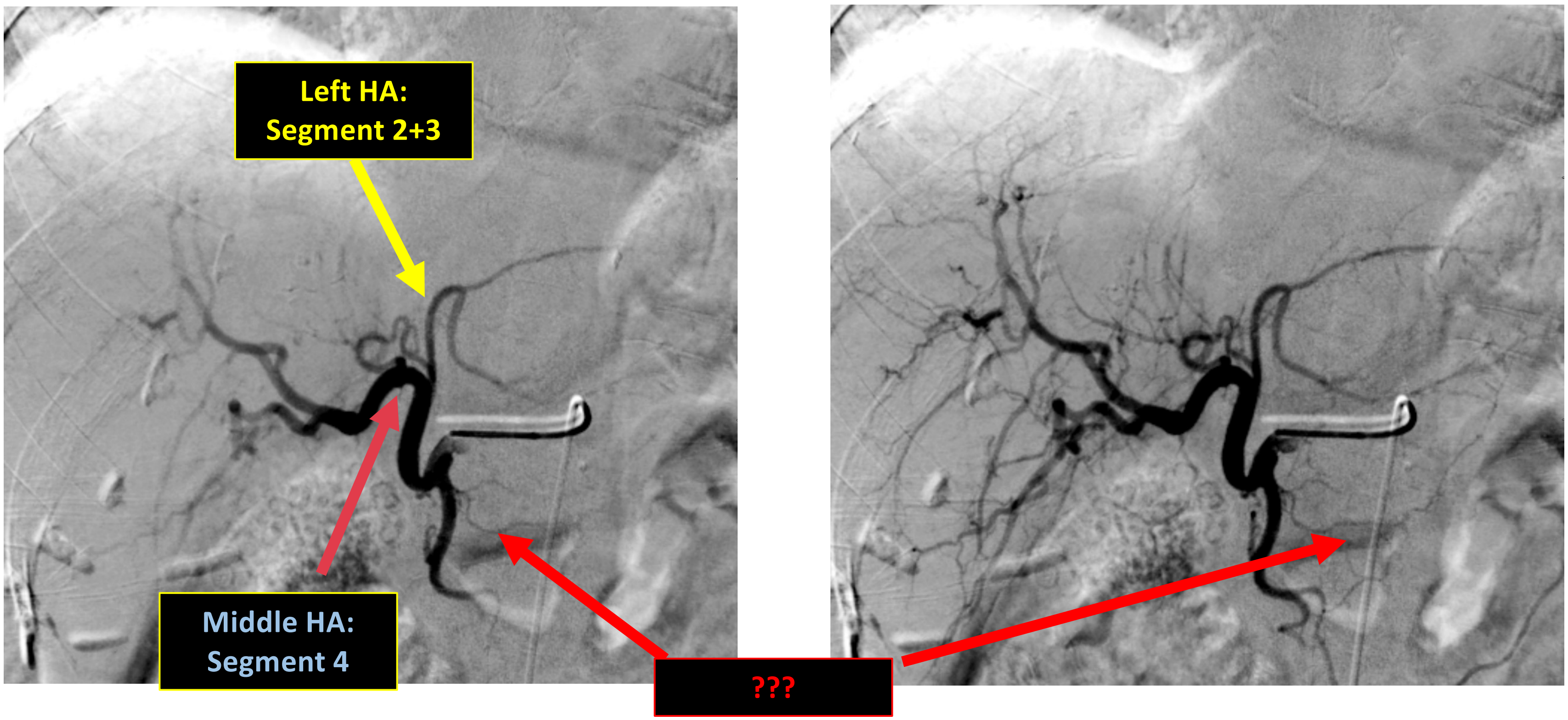

Middle HA:
Segment 4
Left HA:
Segment 2+3
Right
HA
Proper
HA
GDA
Common
HA

Same Angiogram



Right Gastric Artery (RGA)

Must always identify RGA

“Snake in the grass”

Treatment → Radiation-induced ulcer

A lot of variation in its origin

Most often from the proper hepatic artery (51%)

- Base of left hepatic artery (23%)
- Common hepatic artery (9%)
- GDA (3%)

Runs along lesser curvature of stomach

- Anastomosis with left gastric artery

Catheterization can be difficult

- Angled microcatheters (J shape)
- Retrograde access via the left gastric artery

Importance of Imaging

Important to use intra-procedural cross-sectional imaging

Cone beam CT or Angio-CT allows one to assess for sources of non-target administration

- Also allows one to confirm on-target therapy

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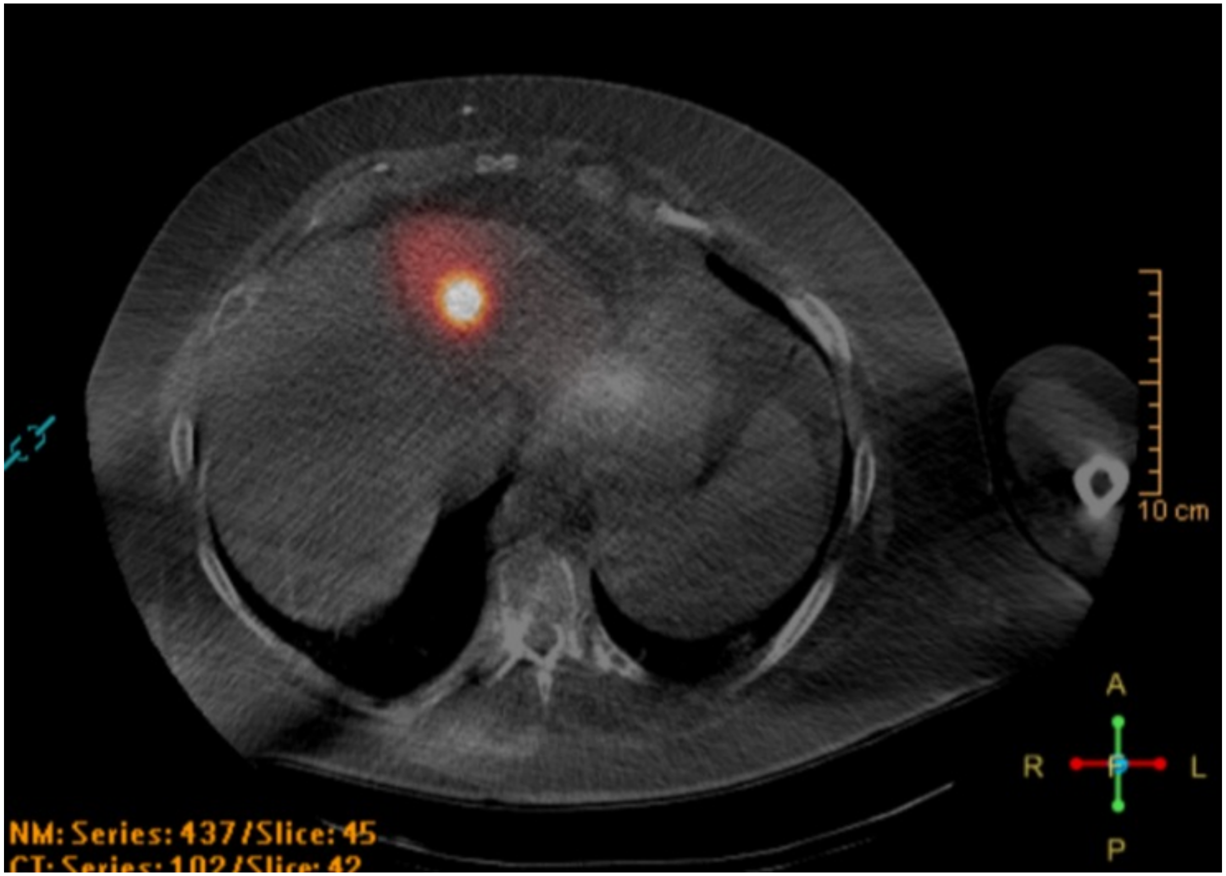
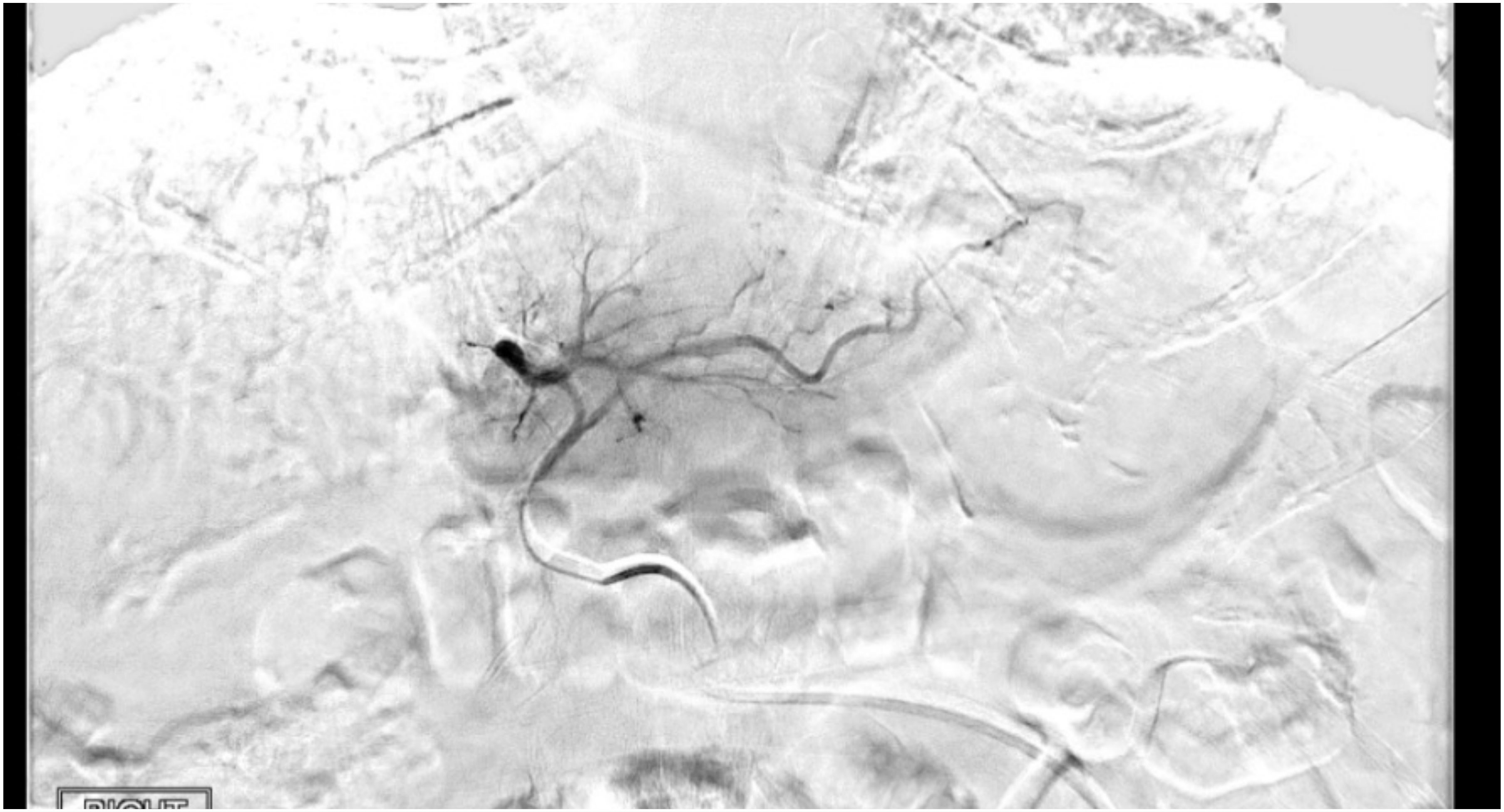
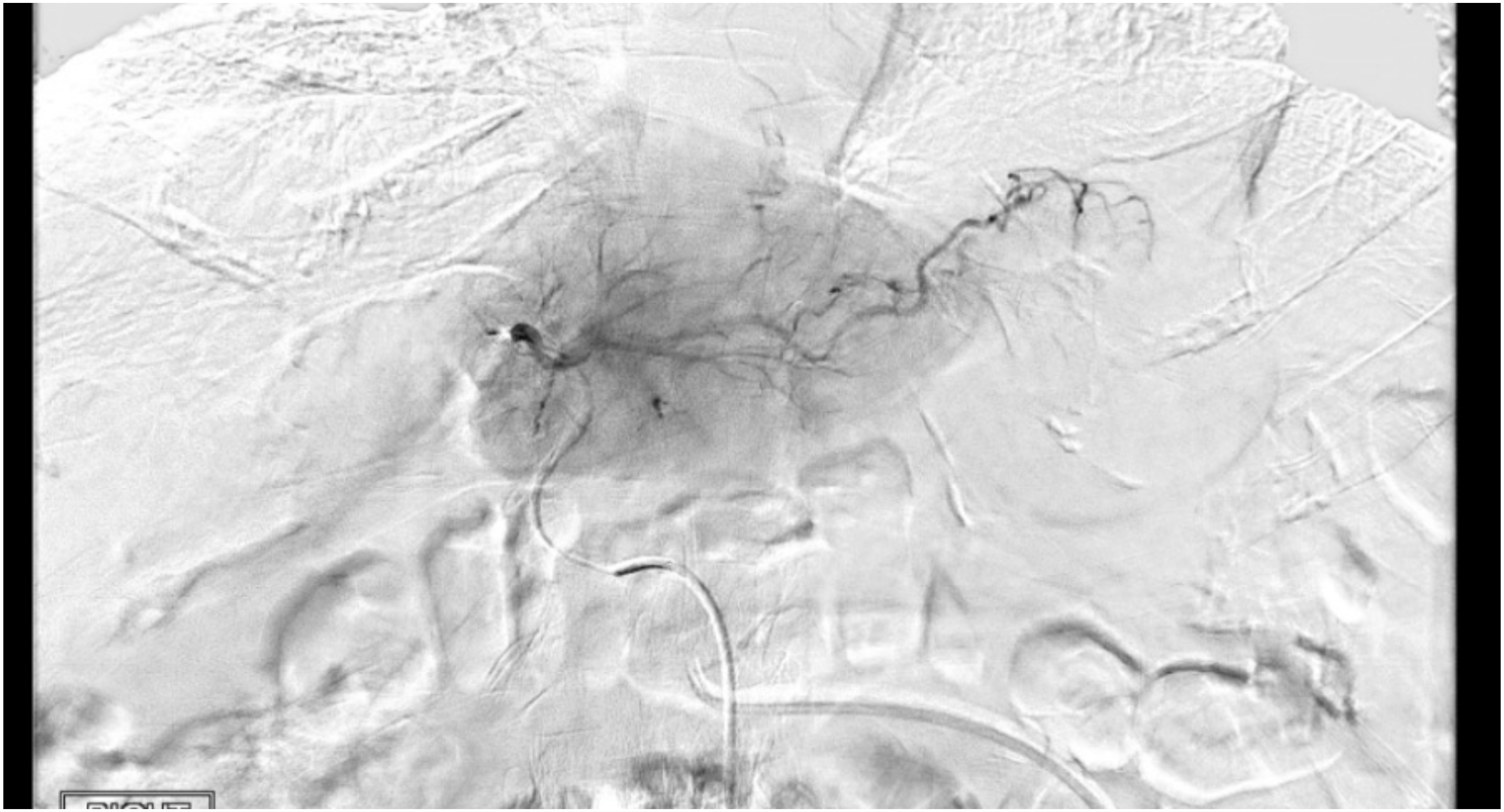
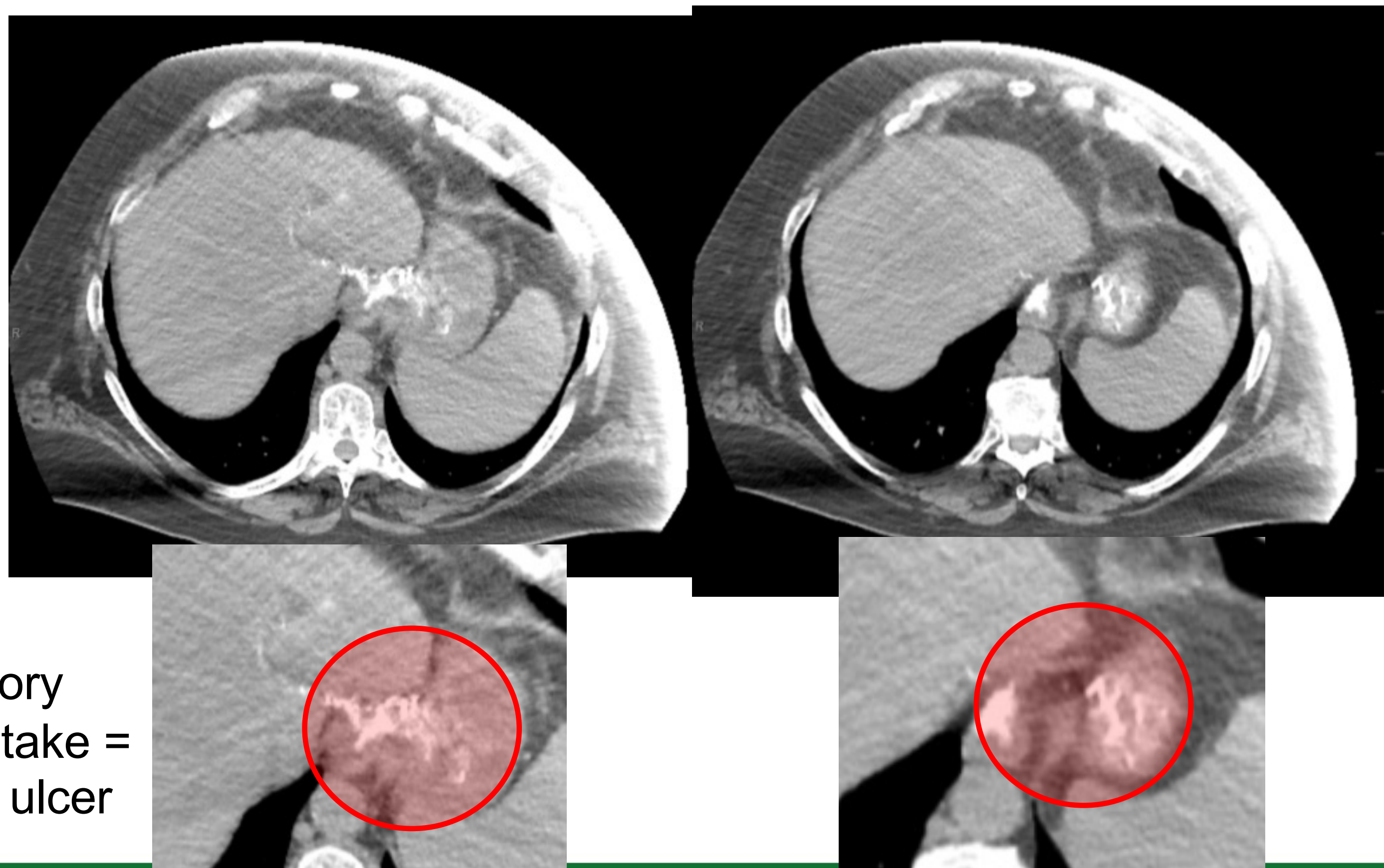

10 cm
A
R
L
P
NM: Series: 437 / Slice: 45
CT: Series: 102 / Slice: 42



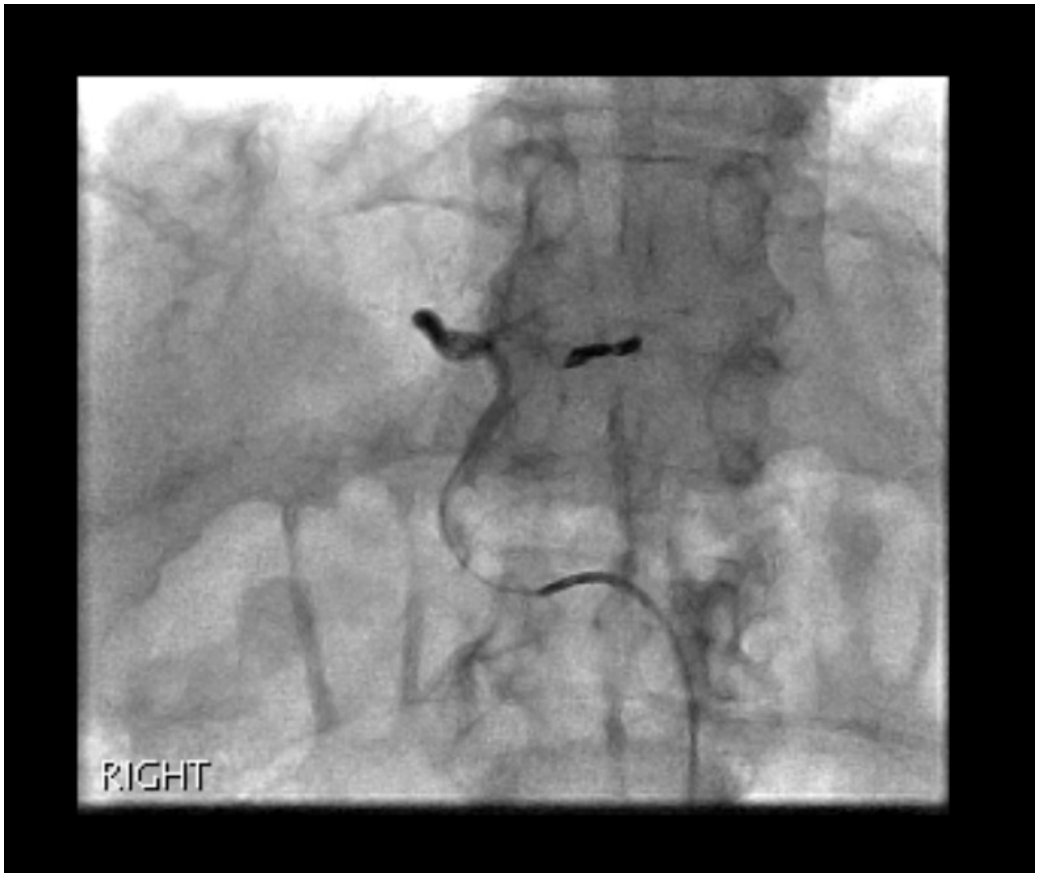



RIGHT

Intra-Procedural CT

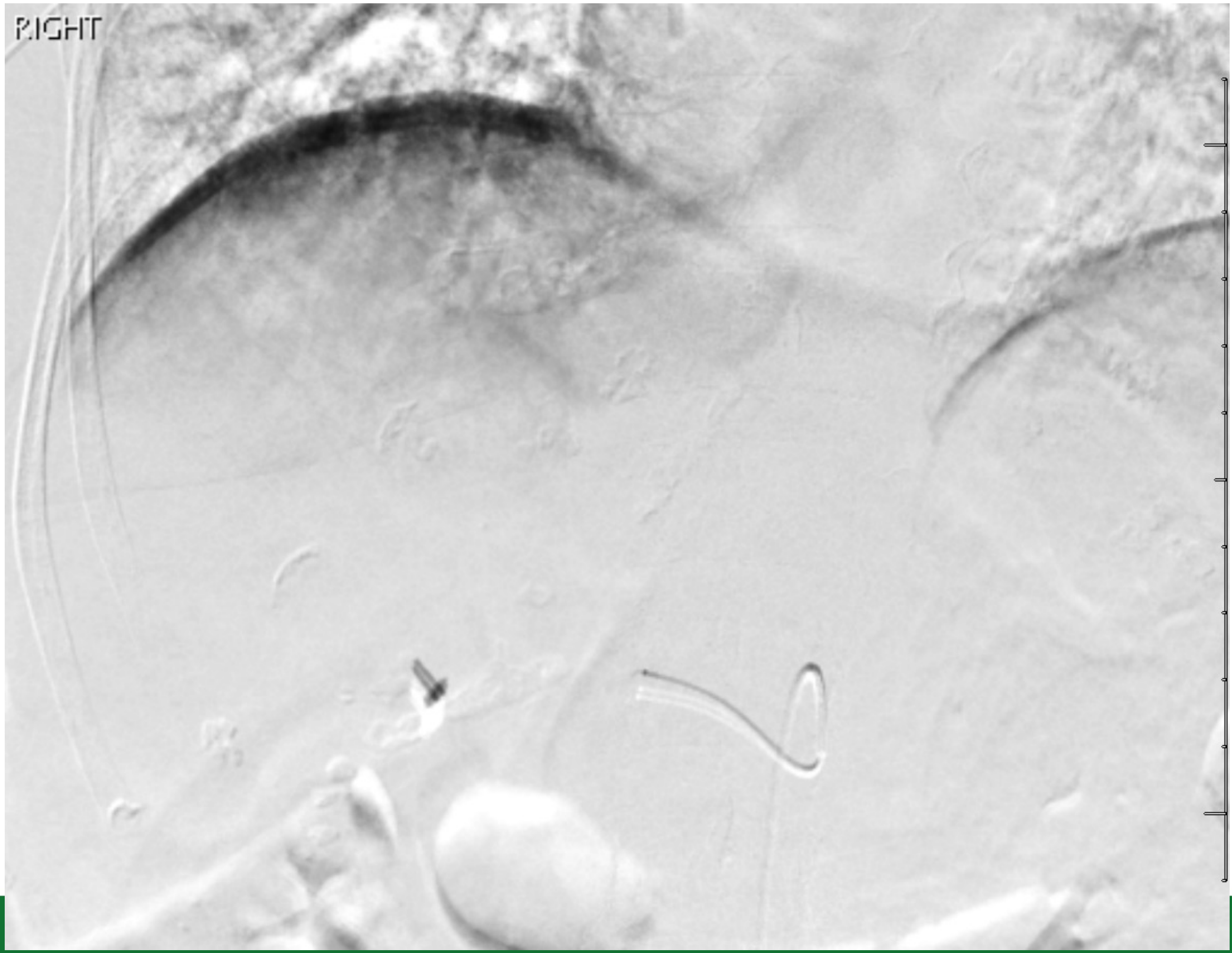


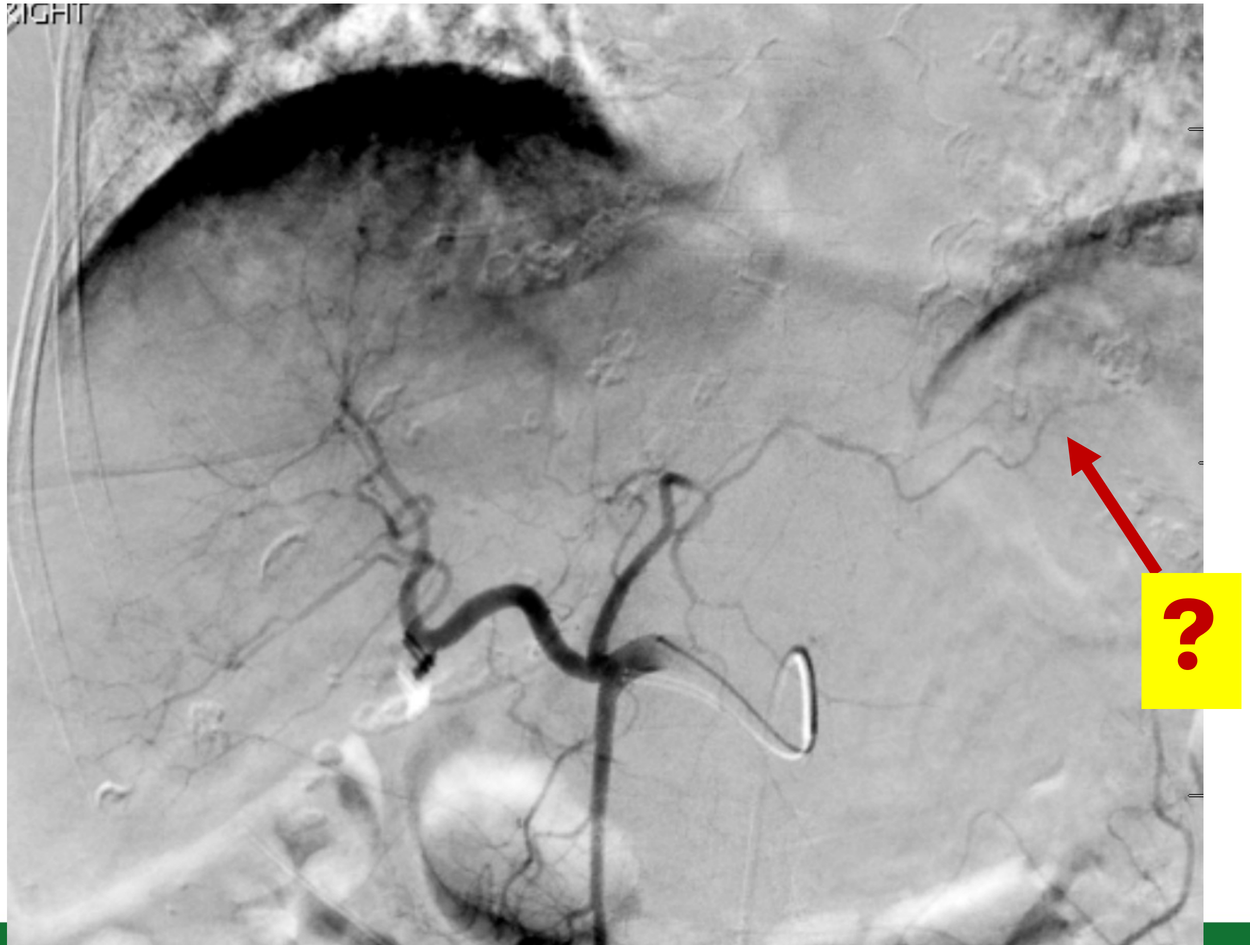
Accessory
Gastric Uptake =
Radiation ulcer

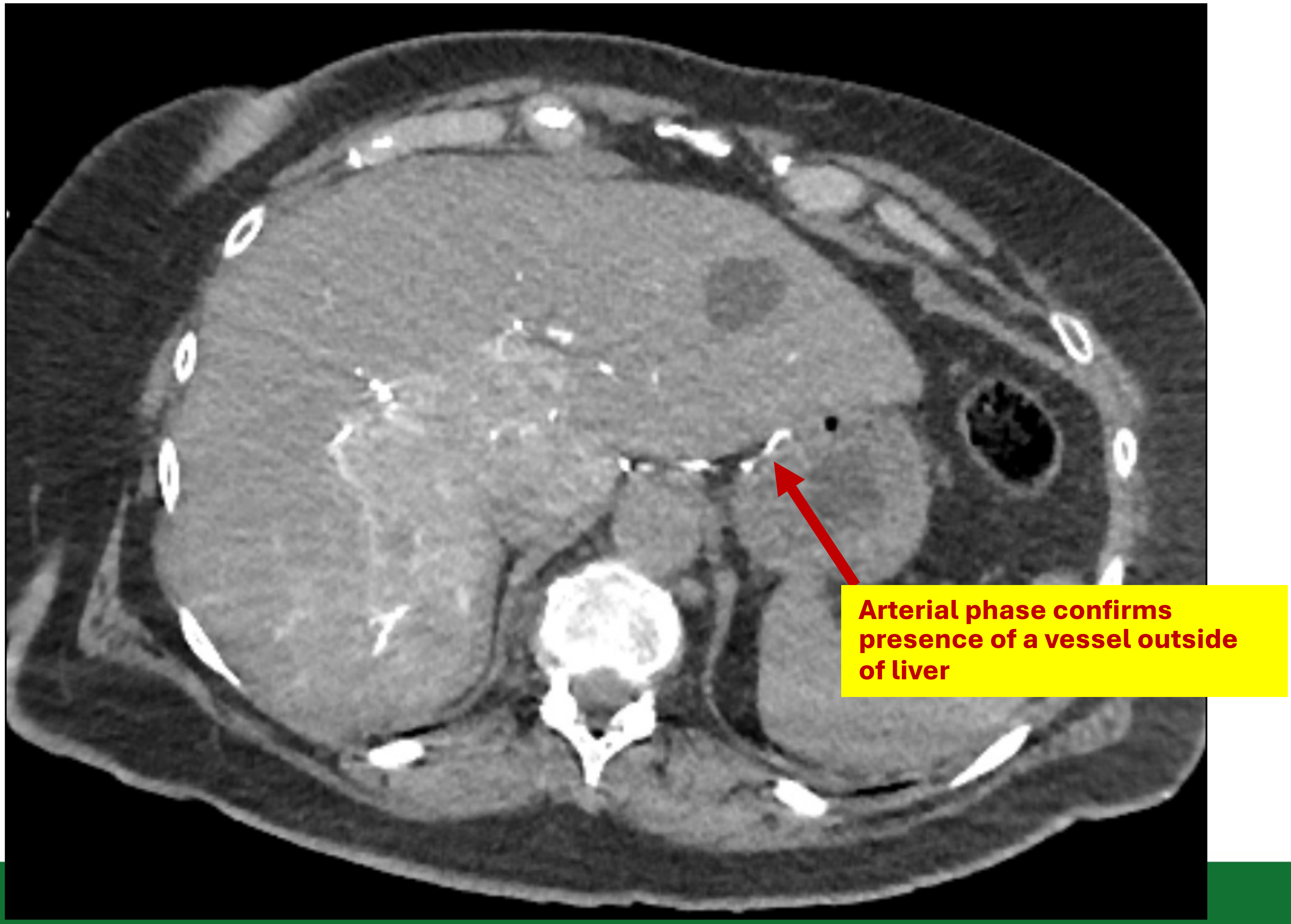

RIGHT

Companion Case

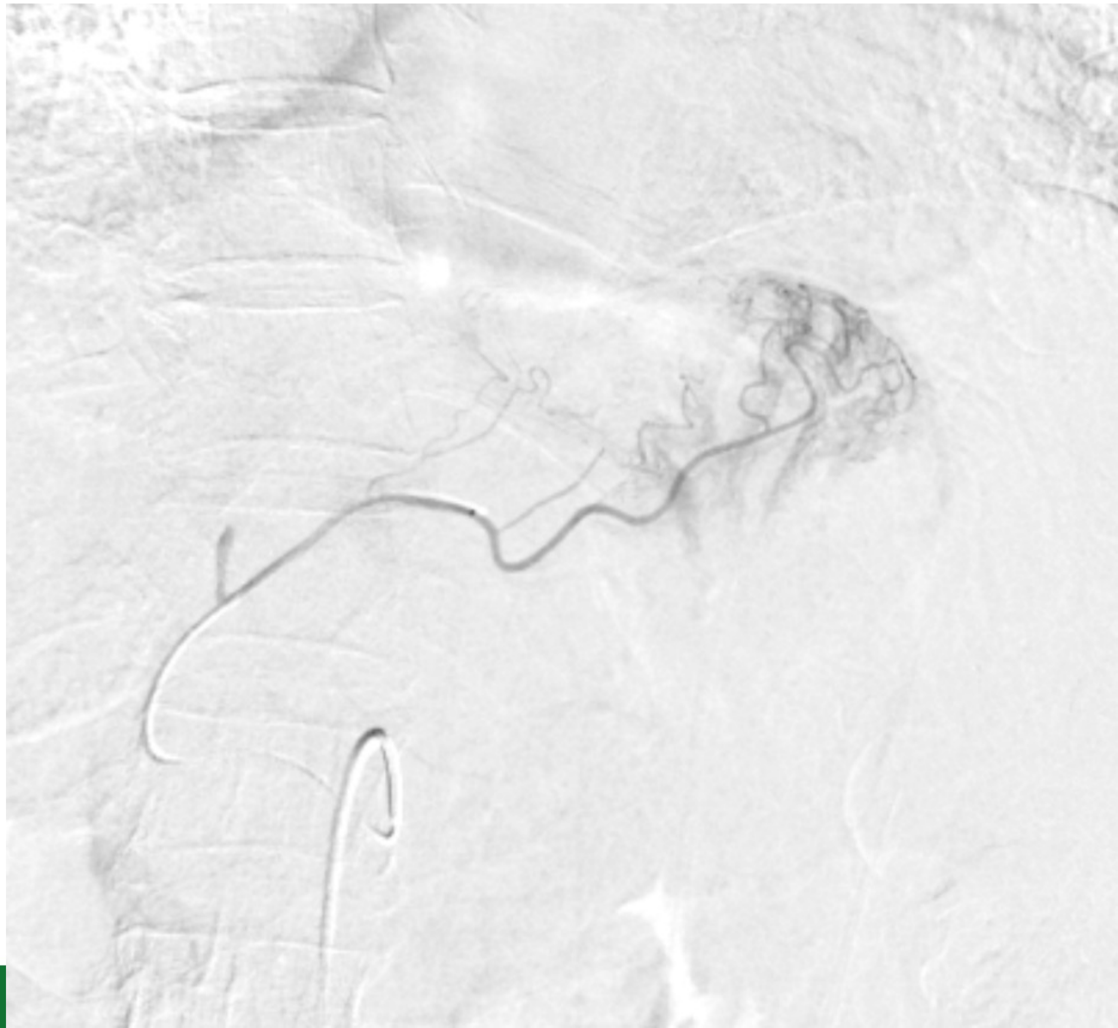
75-yr-old Female with intrahepatic cholangiocarcinoma – referred for Y-90


RIGHT

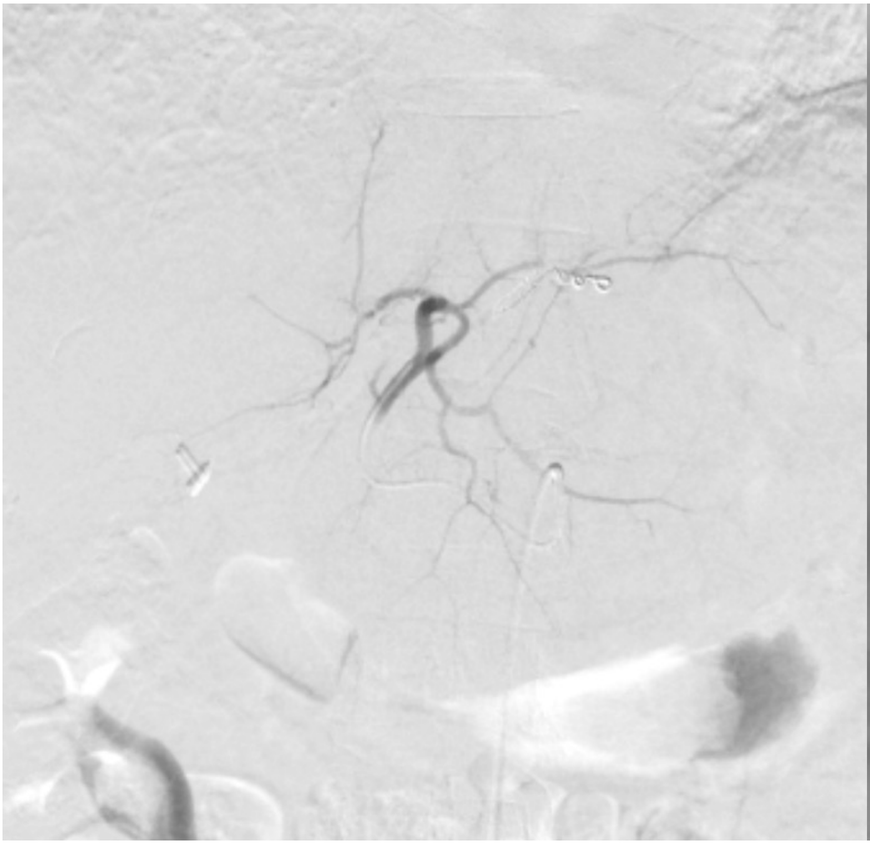


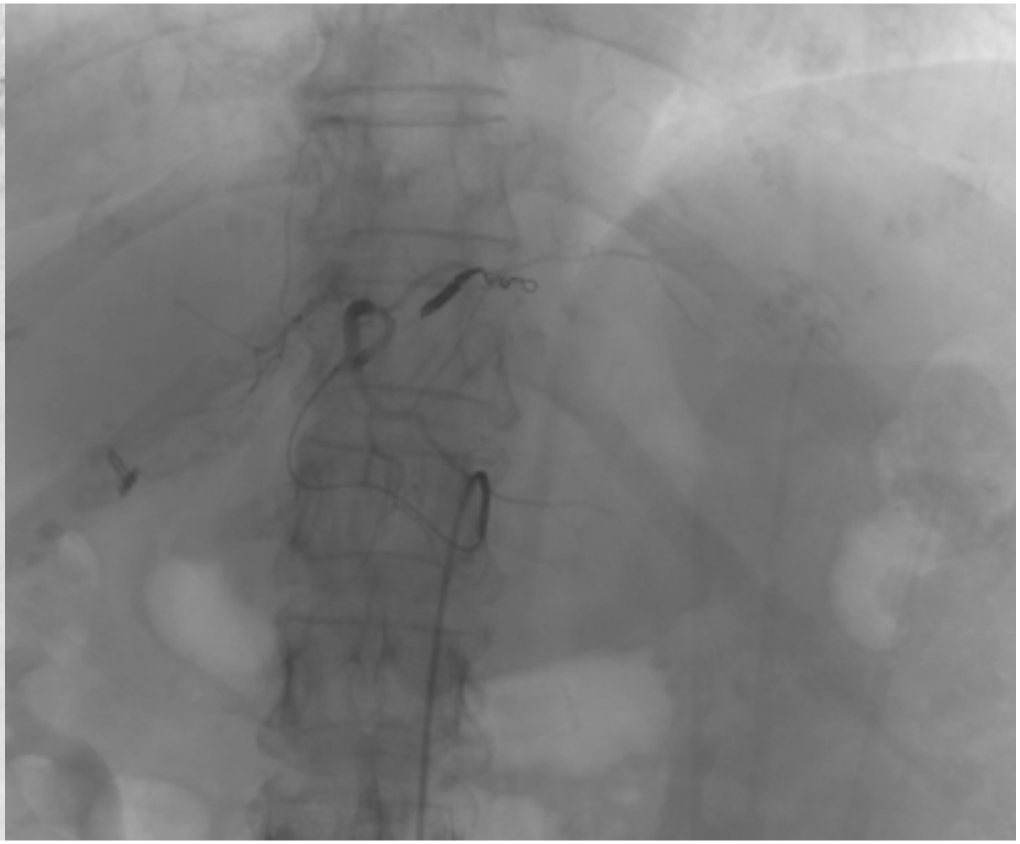

Arterial phase confirms presence of a vessel outside of liver


Venous phase clearly delineates that fundus of stomach is enhancing, consistent with accessory left gastric



Post coil embolization





Procedural Set-Up

Authorized User and Radiation Safety Officer (RSO) Coordination for procedure

Proper shielding

- **Arcylic shields, syringe shields, and spill trays**
- **Designate "hot zones" for handling and disposal of radioactive waste**

Properly cover floor where Y90 will be performed

Procedural Set-Up

Ensure all connections are properly hooked up

- To this day, we still read instructions for administration out loud to avoid accidents/spills

Perform time-out prior to administration

- Especially important for multi-vial cases
- Confirm prescribed activity (and residual)

Summary

Radioembolization requires both fluoroscopy and intra-procedure cross-sectional imaging to be performed safely and effectively

Recognition of basic anatomy and sources of non-target treatment is essential

Make sure to follow protocols on procedure day!

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Ideal Patient Selection / Considerations (and Patients to Avoid)

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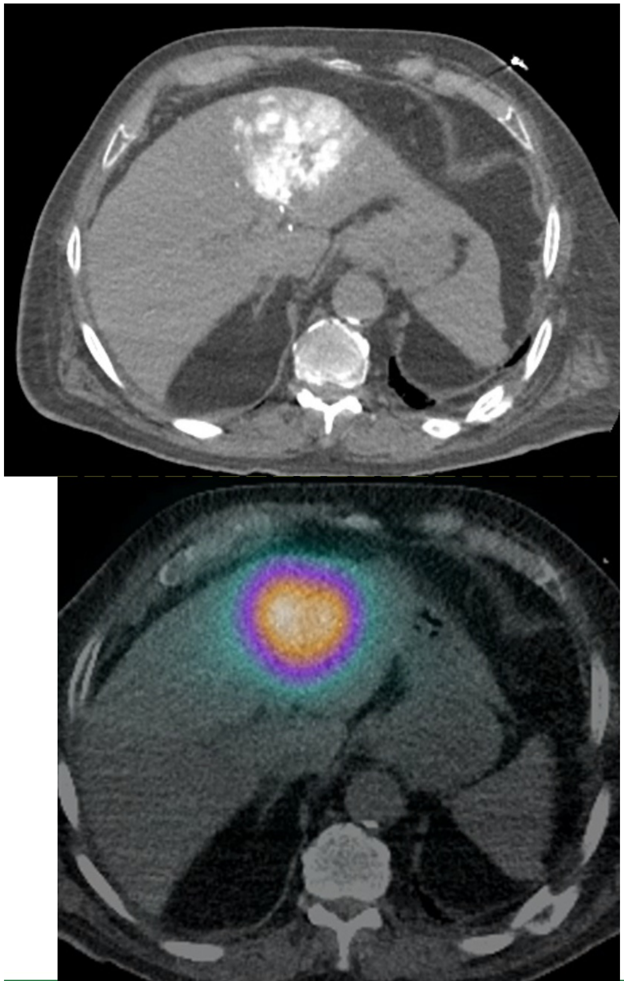
Patient Selection for Y90

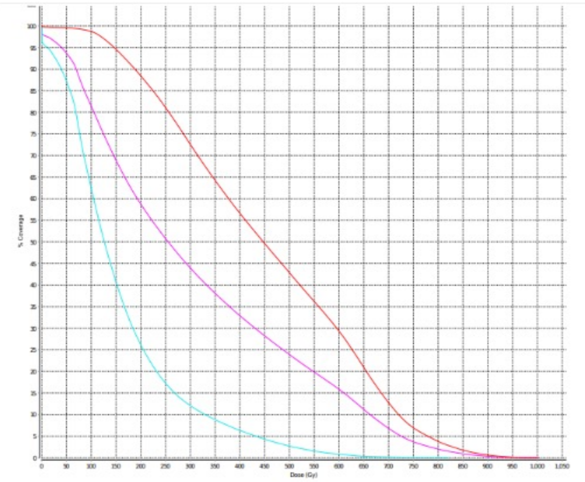
- Patient and disease
- Careful assessment of
  - Liver function
  - Tumor burden
  - Performance status
  - Presence (or absence) of extrahepatic disease
- IR clinic visit
  - Review imaging
  - Review labs
  - Discuss procedure
  - Potential adverse effects
  - Alternatives

Major Selection (Inclusion) Criteria

- **Disease Type:** Unresectable primary (eg, hepatocellular carcinoma, intrahepatic cholangiocarcinoma) or metastatic liver tumors with liver-dominant disease (eg, colon cancer, breast cancer).
- **Performance Status:** ECOG 0–2
- **Liver Function:** Adequate hepatic reserve (bilirubin <3.0 mg/dL, Child-Pugh A or B—not severe hepatic impairment), albumin levels >2.5 g/dL, and low transaminases (AST/ALT <5 X ULN).
- **Hematologic Function:** Granulocyte count >1.5 x 10^9/L, platelet count >50 x 10^9/L
- **Renal function:** Serum creatinine <2.0 mg/dL
- **Tumor Burden:** Preferably ≤50%–70% liver involvement, and measurable disease on cross-sectional imaging

Lewandowski RJ, et al. *Semin Intervent Radiol.* 2006;23(1):64-72. Wehrenberg-Klee E, et al. *Tech Vasc Interv Radiol.* 2019;22(2):70-73. Dendy MS, et al. *OncotargeT*. 2017;8:37912-37922. González-Flores E, et al. *Clin Transl Oncol.* 2024;26(4):851-863.





Dose ID	Dose Details
D1	LDM with Known Activity Dose (Restricted to Liver Segment)

Contour	Line Style	Max Dose	Min Dose	Mean Dose	SD
	D1	D1	D1	D1	D1
GTV_left	—	1007.54	0.00	455.28	203.11
Normal_Liver_left	—	822.34	0.00	159.45	124.69

Ideal patient for radiation segmentectomy:

- Unresectable HCC
- Unablatable
- Solitary tumor (≤2 Couinaud segments 1-8 cm)
- Child-Pugh A cirrhosis
- No macrovascular invasion
- ECOG 0-1
- Adequate pulmonary function
- No extrahepatic disease
- No uncorrectable GI tract blood flow
- No shunting resulting in a single dose of >30 Gy or a cumulative dose of >50 Gy to the lung (glass microspheres), >25 Gy (resin microspheres)

Salem R, et al. *Hepatol.* 2025;82(6):1125-1132. Sarwar A, et al. *Radiology.* 2024;311(2):e231386.

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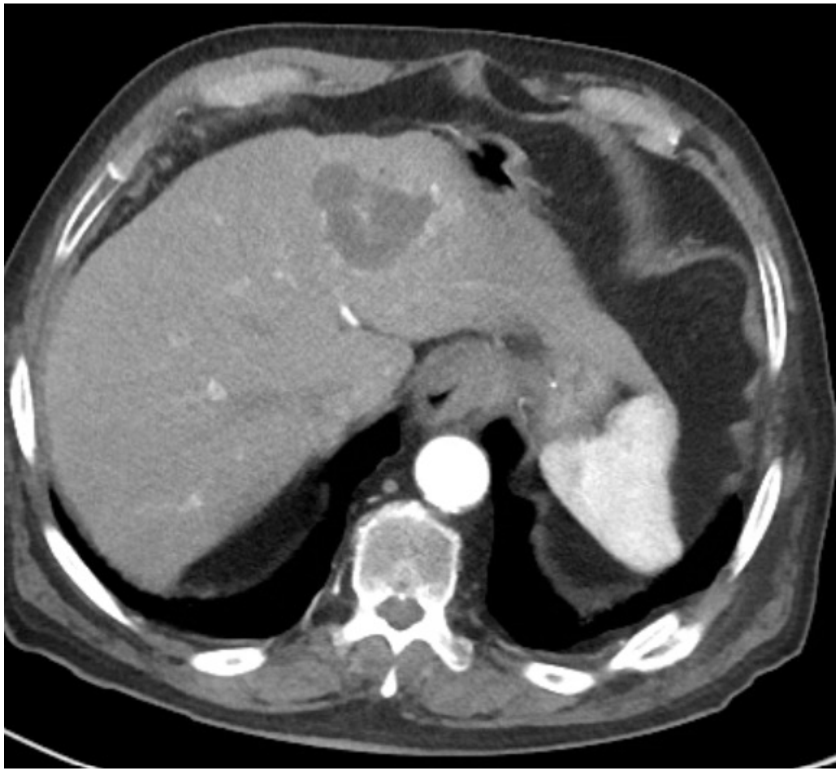
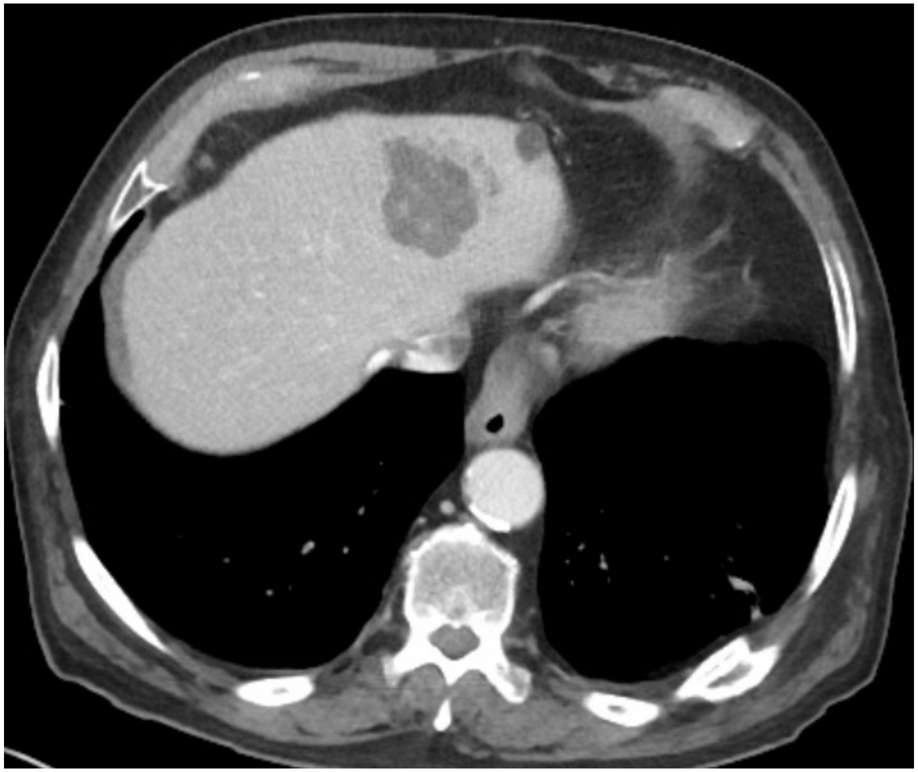
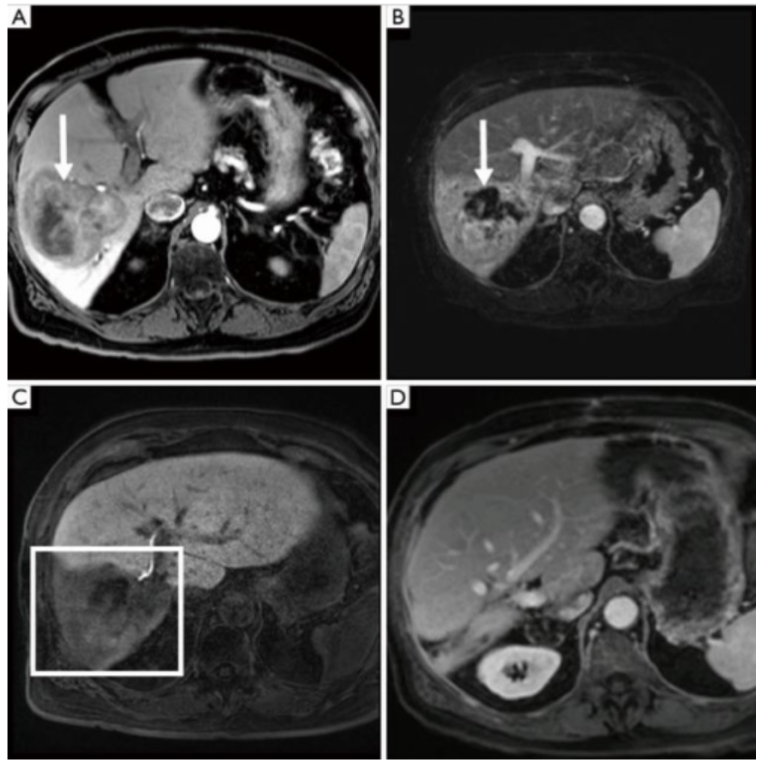
6-Month Follow-Up





Bridge to Resection HCC



Ahmed A, et al. *J Gastrointest Oncol*. 2021;12(2):751-761.

Special Considerations

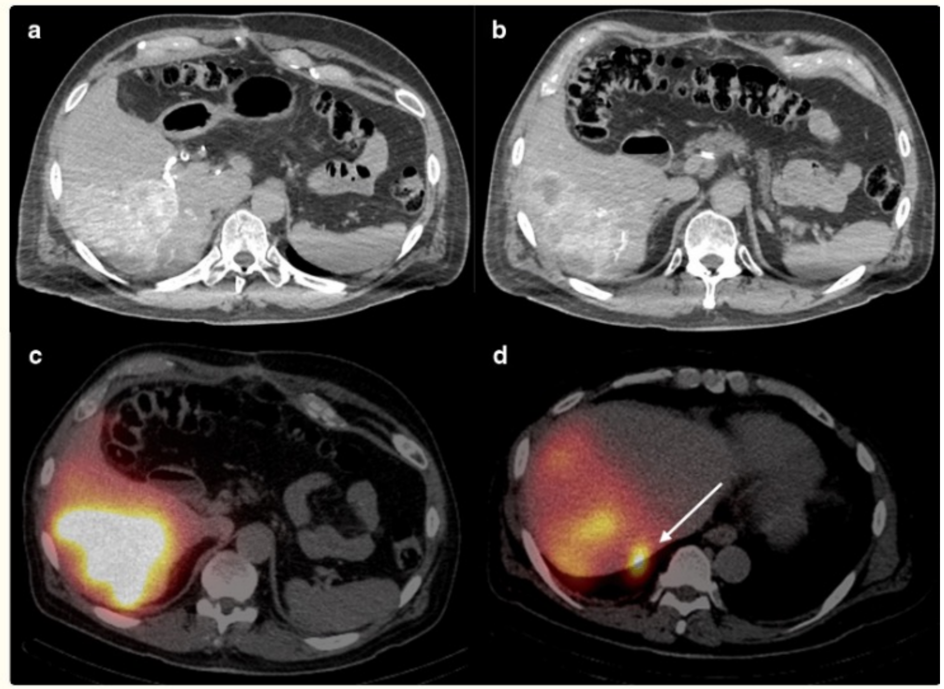
- Personalized dosimetry (partition model, MIRD)
- Radiation segmentectomy/lobectomy for curative intent in select cases
- Preventing reflux/improving tumor perfusion: pressure-enabled delivery systems
- Flow redistribution
- Integration with systemic therapy: timing and compatibility with immunotherapy/chemotherapy
- Retreatment possible with reassessment of liver function and vascular anatomy

Salem R, et al. *Hepatol.* 2025;82(6):1125-1132. Sarwar A, et al. *Radiology*. 2024;311(2):e231386.

58-yr-old Male with metastatic ACC treated with ^{90}Y resin microsphere (SIR-spheres) for local control of liver metastases leading to surgically proven negative pathology after partial hepatectomy 7 months after SIRT

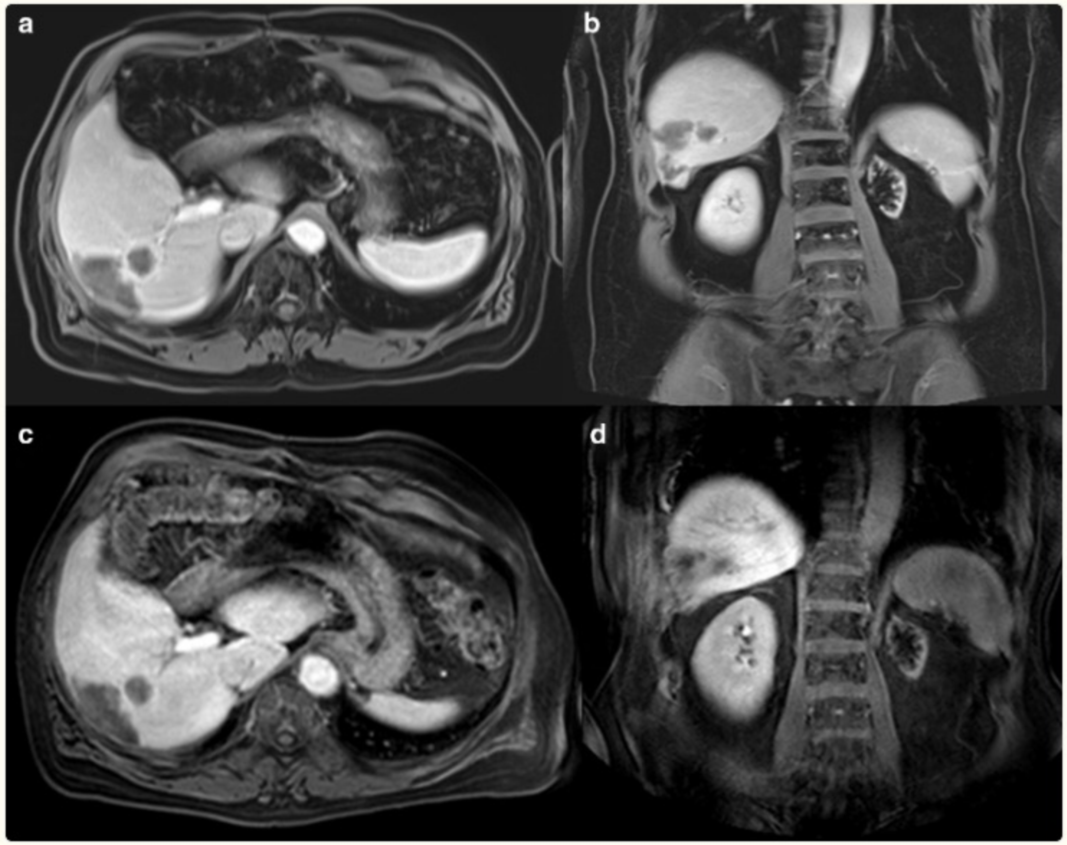
Fig. 2.

Fig. 4.



Lu S, Dhillon J, et al. *EJNMMI Res*. 2021;11(1):17.

Fig. 8.



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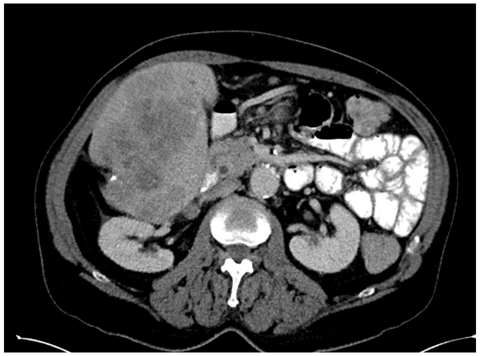
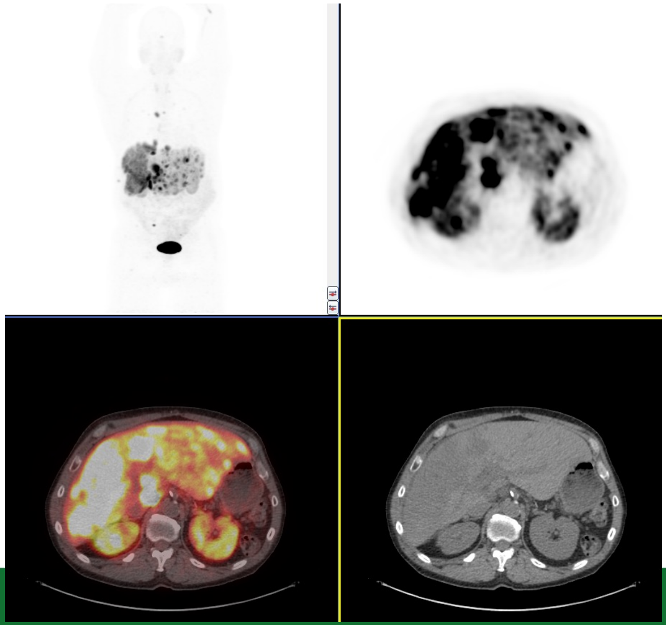
Metastatic NET Pain Palliation

- 50-yr-old Male with pancreatic NET well-differentiated grade 2
- Liver dominant SSTR+ bulky metastases
- Progression 3 months after bland embolization
- Right abdominal pain

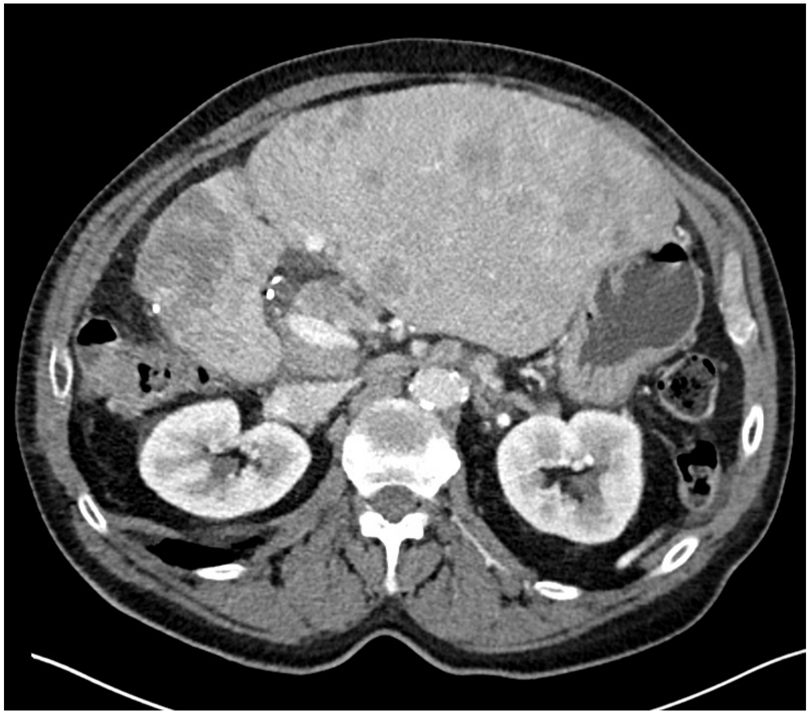




NET = neuroendocrine tumor; SSTR = somatostatin receptor positive; PRRT = peptide receptor radionuclide therapy.

Post radioembolization to right lobe and medial segment left

Y90 resin microspheres:
January: 2.81 GBQ right lobe
February: Medial seg left 0.31 GBq
April: Medial seg 0.83 GBQ, right lobe 1.69 GBQ



2 yrs post radioembolization

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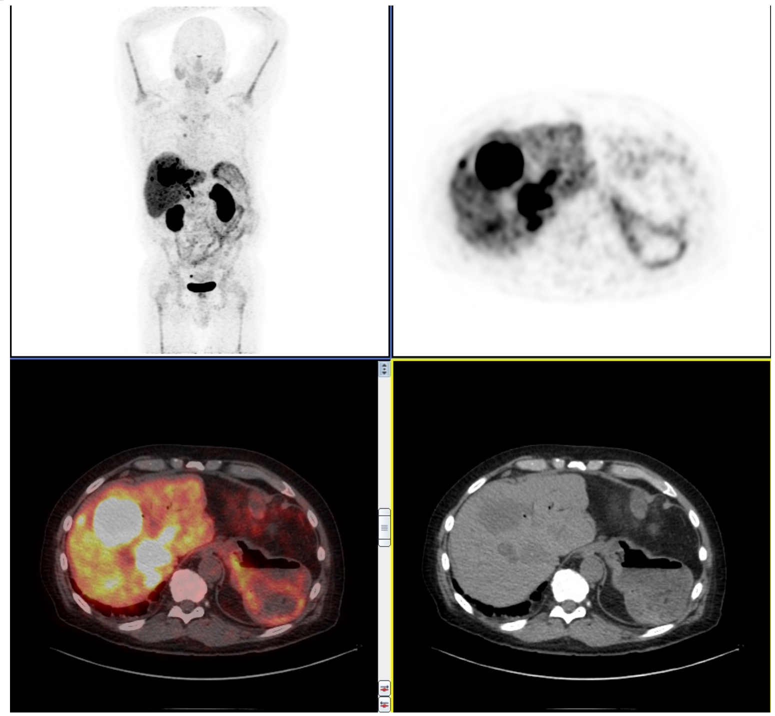
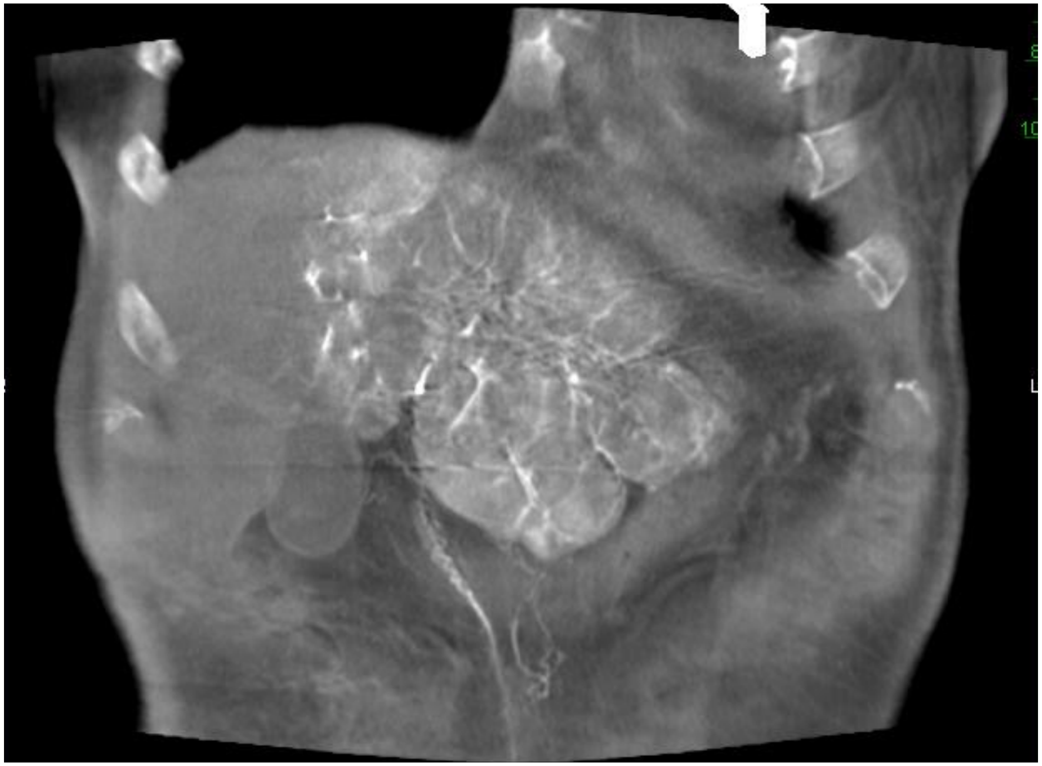
Previous Biliary Instrumentation/Surgery Risk of Hepatic Infection

- Metastatic neuroendocrine tumor
  - TARE (about 8%) <TAE/TACE (about 20%) despite broad-spectrum antibiotic coverage
  - Y90 glass microspheres appear to carry 6.9 times the risk of resin microspheres



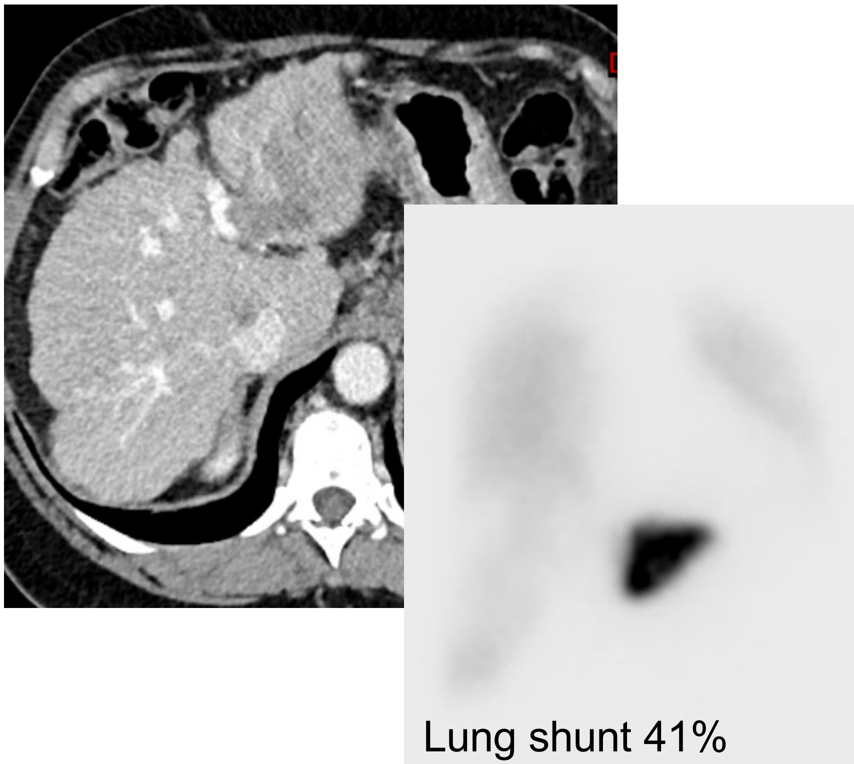
Cholapranee A, et al. *Cardiovasc Intervent Radiol.* 2015;38(2):397-400. Devulapalli KK, et al. *Radiology.* 2018;288(3):774-781.

Patent Hepatic Falciform Artery



Schelhorn J, et al. *SpringerPlus*. 2014;3:595.

Contraindications/Patients to Avoid



- Absolute
  - Significant lung shunting
  - Uncorrectable GI deposition
  - Severe liver dysfunction
  - Pulmonary insufficiency
  - Bleeding diathesis
  - Pregnancy
  - Life expectancy less than 3 months
- Relative
  - Poor performance status (ECOG >2)
  - Extensive tumor burden (>70%), infiltrative tumor type
  - Relative: multiple tumor nodules too numerous to count, portal vein thrombosis without Tc-99m MAA deposition

Lewandowski RJ, et al. *Semin Intervent Radiol.* 2006;23(1):64-72. Wehrenberg-Klee E, et al. *Tech Vasc Interv Radiol.* 2019;22(2):70-73. Dendy MS, et al. *Oncotarget.* 2017;8:37912-37922. González-Flores E, et al. *Clin Transl Oncol.* 2024;26(4):851-863. Kis B, et al. *J Vasc Interv Radiol.* 2025;36(2):207-218.

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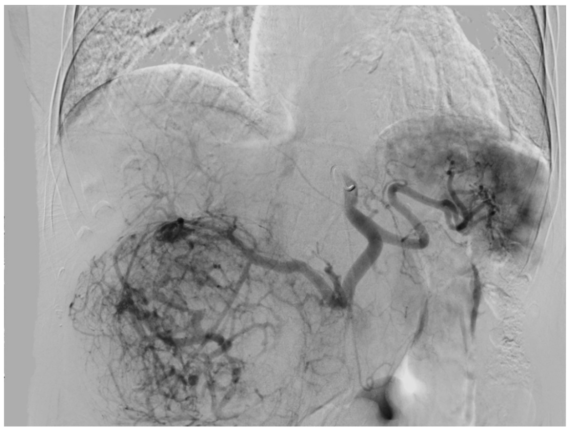
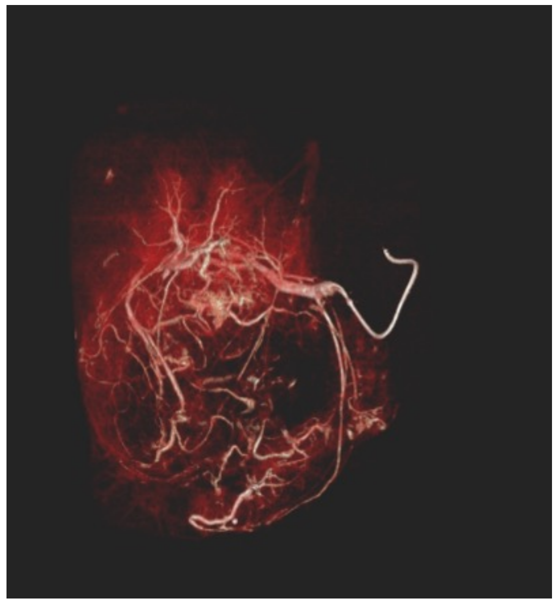
IGHT
F

High Hepato-Pulmonary Shunt

Pre-embolization





Post-embolization, persistent shunt

2 ml vial 500-700 micron microspheres, 3 vials 2ml 900 micron, 2 vials 300-500 micron

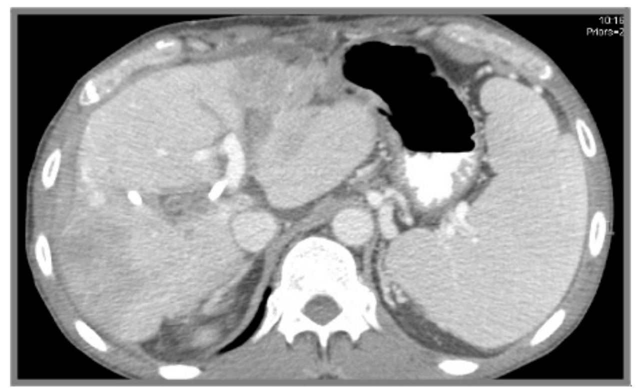
Special consideration for low tumor burden hypovascular bilobar mNET

- 40-yr-old Male diagnosed in 2005 with Grade 1 ileal carcinoid
- 2% tumor involvement
- Liver metastases, no systemic chemotherapy

- 2/24/2011 (128 Gy, 2.4 GBq right) and 5/5/2011 (130 Gy, 1.68 GBq left)

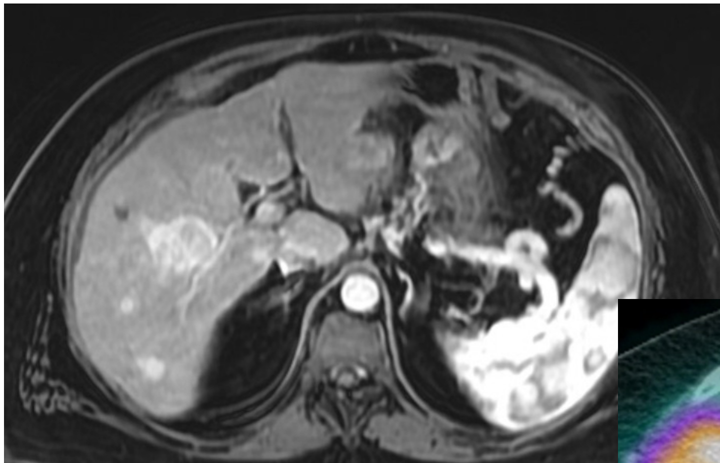
- Survived 40 mo post TARE

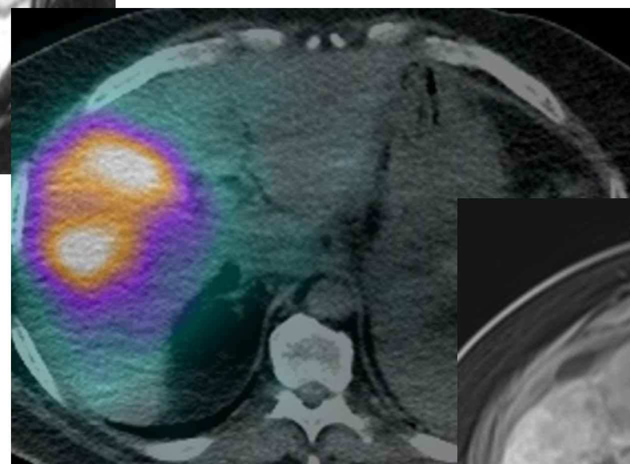
2/2011

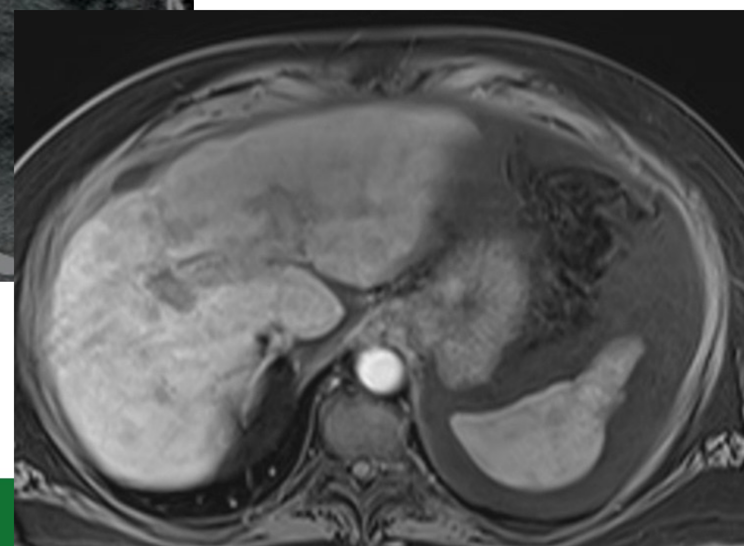


2/2014

Su YK, et al. *J Vasc Interv Radiol*. 2017;28:1520-1526. Tomozawa Y, et al. *J Vasc Interv Radiol*. 2018;29(6):858-865. Currie BM, et al. *J Vasc Interv Radiol.* 2019;30:1915-1923.







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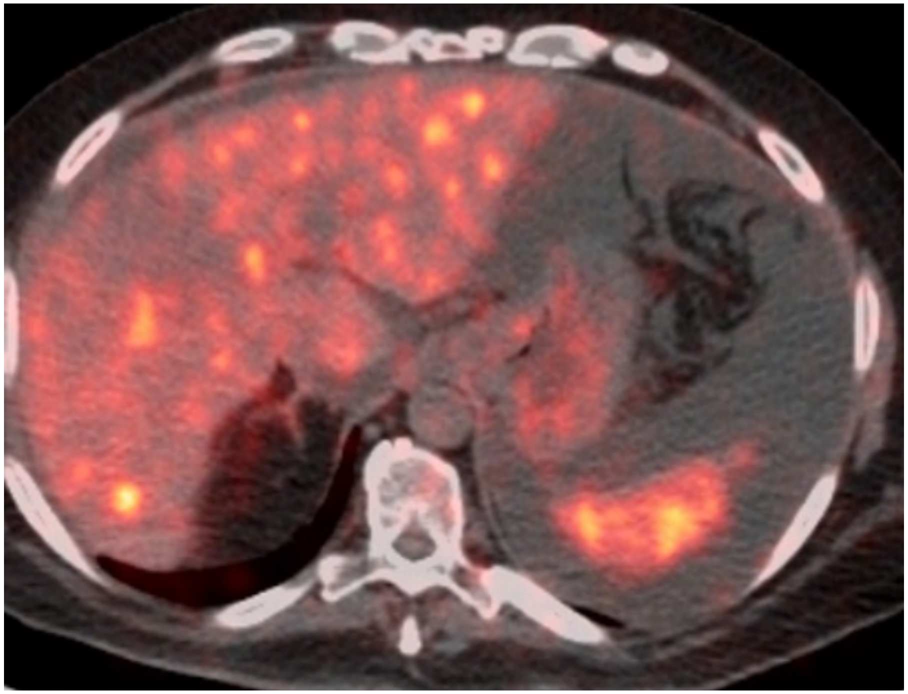

Liver, left, biopsy:

- Fragments of liver with degenerated hepatocytes, rare ballooned hepatocyte, rare acidophilic body, bile ductular reaction, portal fibrosis, and minimal steatosis (approx. 3%). See comment.
- Negative for acute or chronic hepatitis, cirrhosis, or malignancy/neuroendocrine tumor.

COMMENT: **Although the histopathological changes in this biopsy are nonspecific, the possibility of drug-induced liver injury cannot be excluded.** No acute or chronic hepatitis, cirrhosis, or malignancy/neuroendocrine tumor is seen.

Summary

- Best candidates have good liver function, ECOG performance status 0-2, and manageable tumor burden (≤70% liver involvement)
- Exclusion criteria include severe hepatic dysfunction, extensive extrahepatic disease, uncorrectable vascular shunting, and life expectancy less than 3 months
- Adequate metabolic function and careful angiographic assessment are needed to minimize risks and optimize safety
- Stringent patient selection directly improves efficacy, reduces complications, and ensures appropriate use of Y-90 radioembolization

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Prevention and Management of Complications

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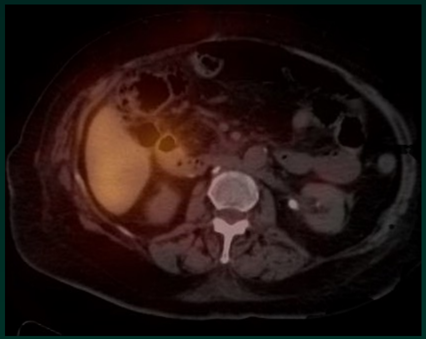
Faculty Disclosures

- **Ripal T. Gandhi, MD, FSIR, FSVM**
  Advisory Board: Trisalus Life Sciences
  Consultant: ABK Biomedical; Argon; BD Life Sciences; Cook Medical; Medtronic; Quantum Surgical; RenovoRx; Sirtex; Telix
  Speakers Bureau: Genentech; Quantum Surgical; Sirtex; Trisalus Life Sciences

Repercussions of Nontarget Radioembolization

- GI ulceration
  (gastric, duodenal ulcer, perforation)
- Esophageal injury
- Pancreatitis
- Skin ulceration
- Cholecystitis and biliary complications
- Radiation pneumonitis



Naymagon, et al. *Dig Dis Sci*. 2010;55:2450-58.

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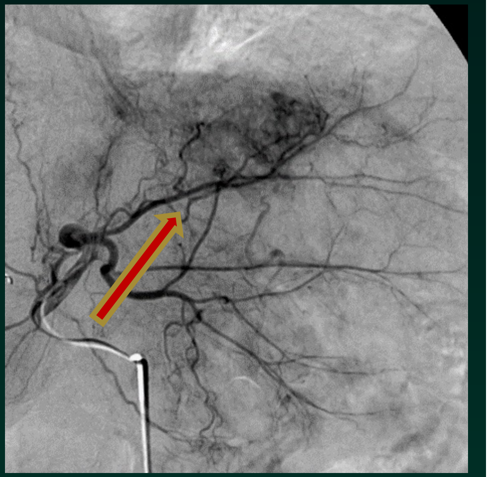
Miami Cardiac & Vascular Institute
BAPTIST HEALTH SOUTH FLORIDA

Gastrointestinal Ulcers

- Occurs secondary to inadvertent delivery of Y90 to hepaticoenteric communications, such the GDA, right gastric artery, left gastric or accessory left gastric artery, supraduodenal artery

- Incidence in the literature 0-29% (the latter from proper hepatic artery Y90); Modern day <5% incidence

- Can be prevented with understanding of anatomy and variants, meticulous angiography, and cone beam CT



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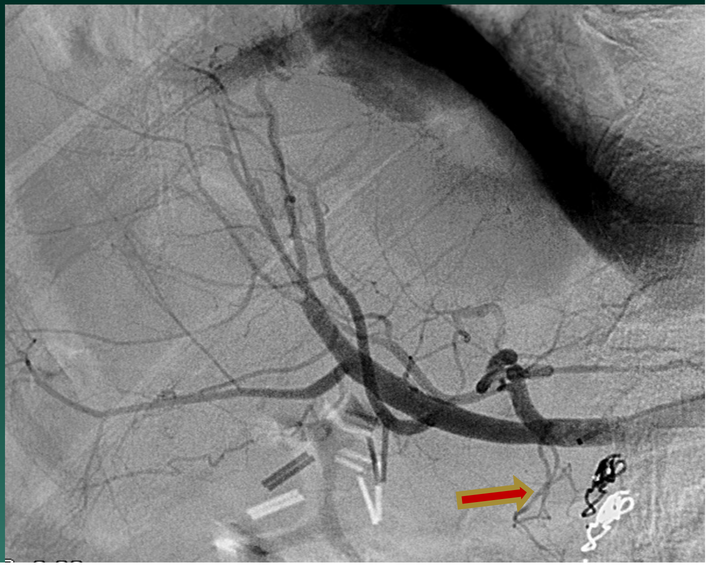
Gastrointestinal Ulcers: Risk Factors

- One study demonstrated that the following increase the risk of ulcer:
  1. Stasis during administration
  2. Distal origin of the GDA
  3. Proximal administration of Y90 (even in setting of coil embolization)
  4. Young age

- GDA Embolization



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GI Ulcers: Should GDA and Gastric Arteries Be Routinely Embolized?

- Old dogma: Prophylactic embolization of GDA and gastric arteries is mandatory (esp. Resin)
- Stanford paper here shows 34% of patients required 31% adjunctive embolization before Y90 administration secondary to formation of collaterals (despite embolization of all hepaticoenteric vessels at mapping angiography)
- 19.7% of vessels were new collateral vessels not seen on initial mapping angiography
- Despite re-embolization, 7.1% of patients developed GI ulceration (vs 1.3% who did not have visible collateral vessels)

Development of New Hepaticoenteric Collateral Pathways after Hepatic Arterial Skeletonization in Preparation for Yttrium-90 Radioembolization

Mohamed H.K. Abdelmaksoud, MD, MS, Gloria L. Hwang, MD, John D. Louie, MD, Nishita Kothary, MD, Lawrence V. Hofmann, MD, William T. Kuo, MD, David M. Hovsepian, MD, and Daniel Y. Sze, MD, PhD

PURPOSE: Development of new hepaticoenteric anastomotic vessels may occur after endovascular skeletonization of the hepatic artery. Left untreated, they can serve as pathways for nontarget radioembolization. The authors reviewed the incidence, anatomy, management, and significance of collateral vessel formation in patients undergoing radioembolization.

MATERIALS AND METHODS: One hundred thirty-eight treatments performed on 122 patients were reviewed. Each patient underwent a preparatory digital subtraction angiogram (DSA) and embolization of all hepaticoenteric vessels in preparation for yttrium-90 (^{90}Y) administration. Successful skeletonization was verified by C-arm computed tomography (CACT) and technetium-99m macroaggregated albumin ($^{99m}TcMAA$) scintigraphy. During the subsequent treatment session, DSA and CACT were repeated before administration of ^{90}Y, and the detection of extrahepatic perfusion prompted additional embolization.

RESULTS: Forty-two patients (34.4%) undergoing 43 treatments (31.2%) required adjunctive embolization of hepaticoenteric vessels immediately before ^{90}Y administration. Previous scintigraphy findings showed extrahepatic perfusion in only three cases (7.1%). Vessels were identified by DSA in 54.1%, by CACT in 4.9%, or required both in 41.0%. The time interval between angiograms did not correlate with risk of requiring reembolization ($P = .297$). A total of 19.7% of vessels were new collateral vessels not visible during the initial angiography. Despite reembolization, three patients (7.1%) had gastric or duodenal ulceration, compared with 1.3% who never had visible collateral vessels, all of whom underwent whole-liver treatment with resin microspheres ($P = .038$).

CONCLUSIONS: Development of collateral hepaticoenteric anastomoses occurs after endovascular skeletonization of the hepatic artery. Identified vessels may be managed by adjunctive embolization, but patients appear to remain at increased risk for gastrointestinal complications.

J Vasc Interv Radiol 2010; 21:1385–1395

GI Ulcers: Should GDA and Gastric Arteries Be Routinely Embolized?

- Radioembolization with resin performed in 62 patients undergoing 69 deliveries
- Prophylactic embolization of GDA only performed in 2 patients (3%)
- No GI ulceration

CrossMark

Yttrium-90 Radioembolization with Resin Microspheres without Routine Embolization of the Gastroduodenal Artery

Thomas J. Ward, MD, John D. Louie, MD, and Daniel Y. Sze, MD, PhD

ABSTRACT

Purpose: To evaluate safety of resin microsphere radioembolization (RE) without prophylactic embolization of the gastroduodenal artery (GDA).

Materials and Methods: Between July 2013 and April 2015, all patients undergoing RE with resin microspheres for liver-dominant metastatic disease were treated without routine embolization of the GDA. Selective embolization of distal hepaticoenteric vessels was performed if identified by digital subtraction angiography, cone-beam computed tomography, or technetium-99m macroaggregated albumin scintigraphy. Resin microspheres were administered using 5% dextrose flush distal to the origin of the GDA in lobar or segmental fashion, with judicious use of an antireflux microcatheter in recognized high-risk situations. Gastrointestinal toxicity was evaluated by the performing physician for at least 3 months.

Results: RE with resin microspheres was performed in 62 patients undergoing 69 treatments. During planning angiography, embolization of 0 or 1 vessel (median, 1; range, 0–4) was performed in 86% of patients, most commonly the right gastric and supraduodenal arteries. Prophylactic embolization of the GDA was performed in only 2 patients (3%). In 6 treatments (9%), adjunctive embolization was required immediately before RE, and an antireflux microcatheter was used in 14% of treatments. Clinical follow-up was available in 60 of 62 patients (median, 134 d; range, 15–582 d). No signs or symptoms of gastric or duodenal ulceration were observed.

Conclusions: RE using resin microspheres without embolization of the GDA can be performed safely.

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J Vasc Interv Radiol. 2017;28(2):246-25

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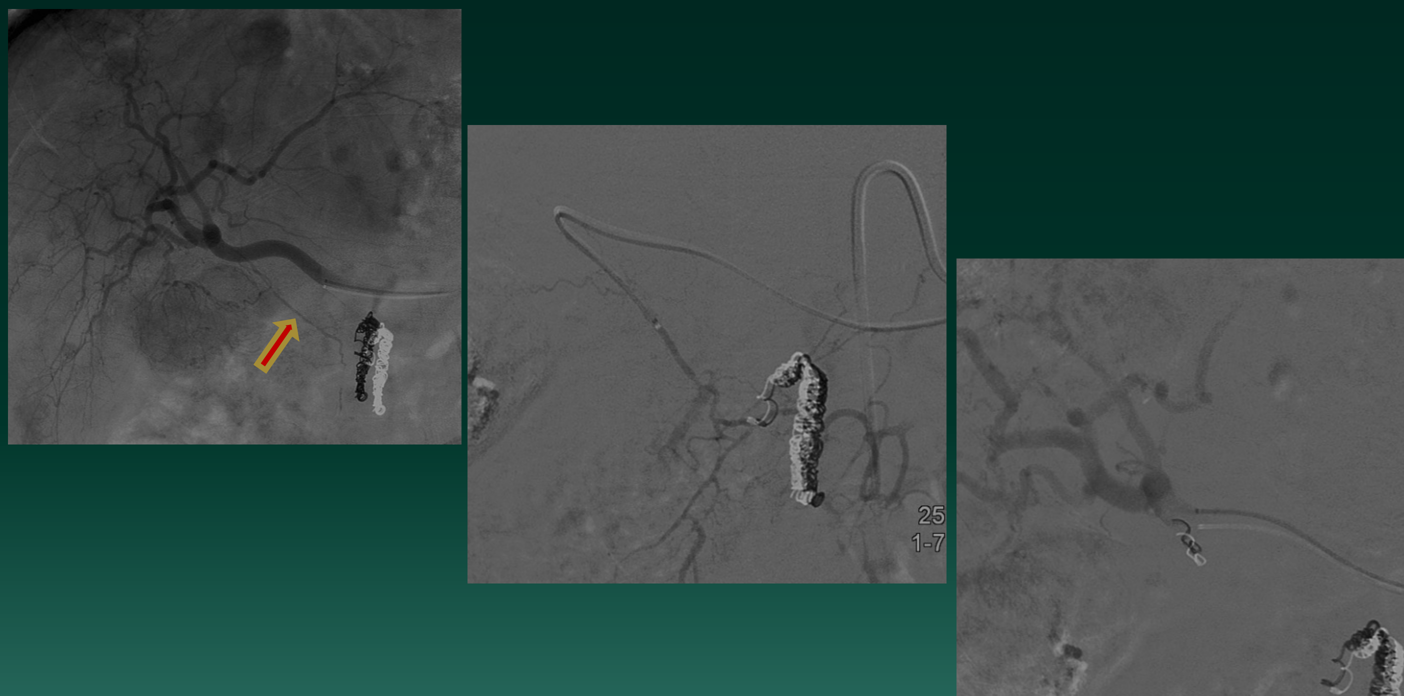
Supraduodenal Artery

- Supraduodenal artery was not present at time of mapping angiography
- Added an additional hr to the procedure



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Clinical Presentation of Gastrointestinal Ulcers

- Patients typically present with abdominal pain with associated anorexia, nausea and vomiting, GI bleeding
- Time to Diagnosis
  - In review by Naymagon et al, diagnosis occurred between 3 wks and 7 mo
  - Mean time to diagnosis 3.2 months
  - Symptoms can occur hours to days after Y90, allowing for early treatment
- Suspicion of ulcer should be confirmed by endoscopy
- Ulcer can be difficult to heal because it originates from serosal surface

Dig Dis Sci (2010) 55:2450–2458
DOI 10.1007/s10620-010-1156-y

REVIEW

Gastroduodenal Ulceration Associated with Radioembolization for the Treatment of Hepatic Tumors: An Institutional Experience and Review of the Literature

Steven Naymagon · Richard R. P. Warner · Kalpesh Patel · Noam Harpaz · Josef Machac · Joshua L. Weintraub · Michelle K. Kim

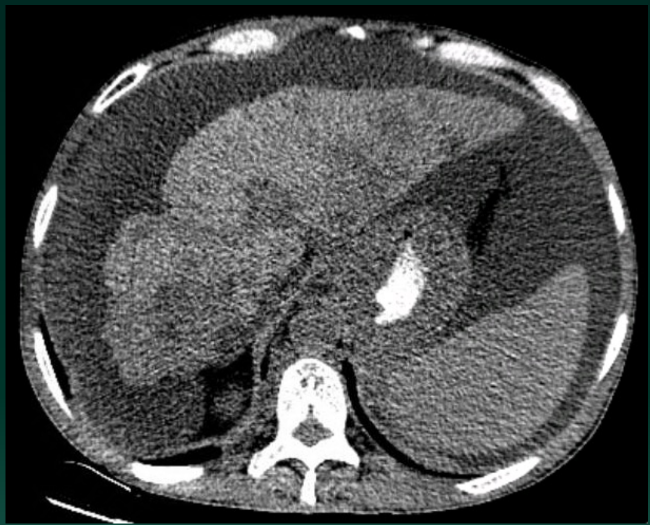
lar Institute

Management of Gastrointestinal Ulcers

- Prophylactic use of proton pump inhibitors is recommended
- **Treatment of Ulcer**
  - Proton pump inhibitor
  - Sucralfate covers and protects ulcer site
  - Sodium bismuth
  - Motility agents
  - Potential benefit of pentoxifylline and alpha-tocopherol (Vitamin E)
- Use of biologic agents and other systemic agents may have to be withheld to allow for healing
- Ulcers refractory to medical management may require surgery

Radioembolization-Induced Liver Disease (REILD)

- Incidence: <6%
- Typically occurs 1-2 months after Y90 administration (usually within 3 months of Y90)
- Presents with jaundice and ascites with elevated bilirubin and alk phos (AST/ALT may be normal) in the absence of tumor progression or biliary obstruction



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Radioembolization-induced liver disease: a systematic review

Manon N.G.J.A. Braat[a], Karel J. van Erpecum[b], Bernard A. Zonnenberg[a], Maurice A.J. van den Bosch[a] and Marnix G.E.H. Lam[a]

Eur J Gastroenterol Hepatol. 2017 Feb;29(2):144-152

- 26 studies were included in review
- The incidence of symptomatic REILD varied between 0 and 31%, although in most reports, the incidence was 0-8%, with a lethal outcome in 0-5%
- Presentation of hepatotoxicity and REILD was similar for cirrhotic and noncirrhotic patients

Radioembolization-induced liver disease: a systematic review

Manon N.G.J.A. Braat[a], Karel J. van Erpecum[b], Bernard A. Zonnenberg[a], Maurice A.J. van den Bosch[a] and Marnix G.E.H. Lam[a]

Eur J Gastroenterol Hepatol. 2017 Feb;29(2):144-152

Table 4. Studies on yttrium-90 radioembolization for primary and secondary malignancies

References	*n*	Tumor type	Microspheres	Dosimetric calculation	Delivery	REILD (%)[a]	Remarks
Sangro *et al.* [14]	45	Various metastases, HCC (27%)	Resin	BSA and partition model	73% WLD	20 (6.6)	No cirrhosis
Jakobs *et al.* [20]	30	Breast cancer metastases	Resin	Empiric	100% WLD	3.3 (3.3)	–
Kennedy *et al.* [21]	148	NET metastases	Resin	BSA	37% WLD	0	–
Kennedy *et al.* [22]	515	Various, HCC (12%)	Resin	74% BSA; 19% empiric	32% WLD	5.4 (5.4)	–
Van Hazel *et al.* [33]	25	CRC metastases	Resin	BSA	100% WLD	0	Phase 1 dose escalation study with irinotecan. RE on day 2 or 3 of cycle 1
Kosmider *et al.* [5]	19	CRC metastases	Resin	Empiric or BSA	100% WLD	26 (5)	RE combined with systemic chemotherapy as first-line treatment
Piana *et al.* [28]	81	Various metastases, HCC (9%)	Resin	BSA 25% dose reduction if previous chemo or TACE	5% WLD; 9% SD; 86% LD	1 (1)	–
Klingenstein *et al.* [23]	13	Uveal melanoma metastases	Resin	Empiric or BSA	85% WLD	7.8 (7.8)	–
Paprottka *et al.* [27]	42	NET metastases	Resin	BSA	57% WLD	0	–
Seidensticker *et al.* [30]	34	Various metastasis	Resin	BSA	50% WLD	8.8 (NR)	Comparison of WLD and SD
Gil-Alzugaray *et al.* [17][b]	172	HCC (16%), CCC, various metastases	Resin	BSA for WLD, partition model if > 2 segments were spared	63% WLD	8 (1.9)[b]	Comparison of standard protocol and modified protocol[c]
Lam *et al.* [25]	247	HCC (26%), CCC (11%), various metastases	Glass (*n* = 66); resin (*n* = 181)	Glass: –; resin: BSA	64% WLD; 9% SD; 27% LSD	4.0 (0.8)	20.6% cirrhosis
Peterson *et al.* [6]	112	Various metastases and HCC (4%)	Resin	BSA	77% WLD; 23% LD	1.8 (0)	–
Smits *et al.* [31]	59	Various metastases	Resin	BSA	64% WLD; 17% SD; 19% LD	0	CPB 10%
Sofocleous *et al.* [35]	14	CRC metastases	Resin	BSA	NR	0	Phase 1 study with delivery of 70, 85, or 100% of the calculated dose
Zarva *et al.* [36]	21	CRC (24%), HCC (38%), CCC (5%)	Resin	BSA	No WLD	0	Study of repeated RE
Lewandowski *et al.* [26]	214	CRC metastases	Glass	NR	83% SD; 17% LD	0	
Bester *et al.* [15]	427	Various metastases, HCC (6.8%), CCC (7.7%)	Resin	BSA	NR	2.3 (0)	Comparison of toxicity in patients with and without previous hepatectomy
Saxena *et al.* [34]	302	CRC metastases	Resin	BSA	In principle WLD	0.3 (0.3)	CPB 1%

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Radioembolization-Induced Liver Disease (REILD)

Risk Factors:

1. Abnormal liver function (high bili, low alb)
2. Cirrhosis (esp Child C, ascites)
3. Multiple lines of chemotherapy (oxaliplatin is also toxic to sinusoidal epithelium, irinotecan causes steatohepatitis, gemcitabine)
4. Prior radioembolization
5. Single session whole liver Y90 delivery
6. SBRT
7. Low-grade neuroendocrine disease with low disease burden or after Lutathera® (Lutetium Lu 177 dotatate) (PRRT)

Radioembolization-Induced Liver Disease (REILD)

- Histologic hallmark of REILD is venous occlusive disease
- Biopsy of the normal liver may help confirm diagnosis
- Repeat liver function tests weekly in patients with suspected REILD; if the problem persists or worsens within 2 wks, liver biopsy should be considered

[1]Gil-Alzugaray, et al. *Hepatology*. 2013;57:1078-1087.
[2]Sangro, et al. *Hepatology*. 2017.

Radioembolization-Induced Liver Disease (REILD)

- **Treatment**
  1. Steroids
  2. Diuretics (for mild cases)
  3. Defibrotide
     - Enhances plasmin activity
     - May help for hepatic venous occlusive disease
  4. Anticoagulation (given venous occlusive disease)
  5. Radioprotectants (ie, ursodeoxycholic acid, pentoxifylline)

[1]Gil-Alzugaray, et al. *Hepatology.* 2013;57:1078-1087.

Radioembolization-Induced Liver Disease (REILD)

Treatment

Treat initially with diuretics (spironolactone 100 mg and/or furosemide 40 mg daily) and adjust the dose based on weight loss and renal function.

If liver function starts to decline (e.g., total bilirubin ≥6 mg/dL and prothrombin activity ≤60% or international normalized ratio ≥1.4), consider defibrotide intravenously at a starting dose of 10 mg/kg.

If liver failure develops despite medical treatment, consider transjugular intrahepatic portosystemic stent-shunt placement.

Sangro, et al. *Hepatology*. 2017.

Radioembolization-Induced Liver Disease (REILD)

Prevention of REILD

- In one study[1], incidence of REILD was reduced from 22.7% to 5.4% and incidence of severe REILD from 13.3% to 2.2% seen with both modification of activity calculation, as well as
  1. Ursodeoxycholic acid 300 mg PO BID for 2 months post Y90
  2. Methylprednisolone 8 mg PO QD for 1st month, 4 mg PO QD for 2nd month post Y90
- Confounding factor in above study is that treatment design and activity (dose) was adjusted, as well as addition of medications
- Recommend sparing liver segments without disease if technically feasible

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Prognostic Factors and Prevention of Radioembolization-Induced Liver Disease

Belen Gil-Alzugaray,[1,2] Ana Chopitea,[2,3] Mercedes Iñarrairaegui,[1,2,4] Jose I. Bilbao,[2,5] Macarena Rodriguez-Fraile,[2,6] Javier Rodriguez,[2,3] Alberto Benito,[2,7] Inés Dominguez,[2,6] Delia D'Avola,[1,2,4] Jose I. Herrero,[1,4] Jorge Quiroga,[1,4] Jesus Prieto,[1,4] and Bruno Sangro[1,2,4]

Radioembolization (RE)-induced liver disease (REILD) has been defined as jaundice and ascites appearing 1 to 2 months after RE in the absence of tumor progression or bile duct occlusion. Our aims were to study the incidence of REILD in a large cohort of patients and the impact of a series of changes introduced in the processes of treatment design, activity calculation, and the routine use of ursodeoxycholic acid and low-dose steroids (modified protocol). Between 2003 and 2011, 260 patients with liver tumors treated by RE were studied (standard protocol: 75, modified protocol: 185). REILD appeared only in patients with cirrhosis or in noncirrhosis patients exposed to systemic chemotherapy prior to RE. Globally, the incidence of REILD was reduced in the modified protocol group from 22.7% to 5.4% and the incidence of severe REILD from 13.3% to 2.2% ($P < 0.0001$). Treatment efficacy was not jeopardized since 3-month disease control rates were virtually identical in both groups (66.7% and 67.2%, $P = 0.93$). Exposure to chemotherapy in the 2-month period following RE and being treated by the standard protocol were independent predictors of REILD among noncirrhosis patients. In cirrhosis, the presence of a small liver (total volume <1.5 L), an abnormal bilirubin (>1.2 mg/dL), and treatment in a selective fashion were independently associated with REILD. *Conclusion:* REILD is an uncommon but relevant complication that appears when liver tissue primed by cirrhosis or prior and subsequent chemotherapy is exposed to the radiation delivered by radioactive microspheres. We designed a comprehensive treatment protocol that reduces the frequency and the severity of REILD. (Hepatology 2013;57:1078-1087)

[1]Gil-Alzugaray, et al. *Hepatology.* 2013;57:1078-1087.

Radiation Pneumonitis

- Incidence: Extremely rare (far less than 1%)
- Dose to the lungs >30 Gy in a single administration or cumulative dose >50 Gy increase risk of pneumonitis and should be avoided
- Be conservative with pulmonary compromise (ie, COPD, lung rsxn)
- Systemic chemotherapy may predispose patients to developing radiation pneumonitis

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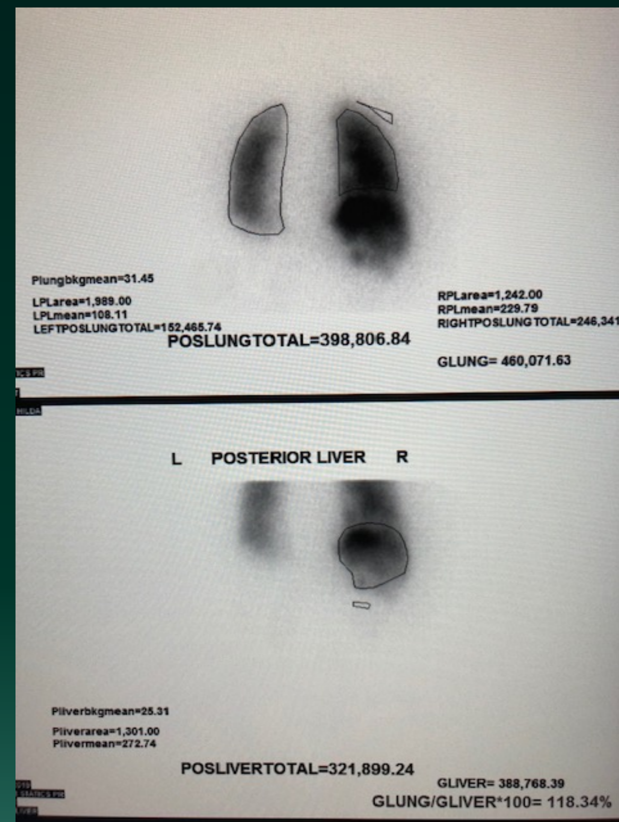
Radiation Pneumonitis

High Lung Shunts – Risk Factors

1. Vascular invasion (portal vein and hepatic vein tumor thrombus, arterioportal shunts)
2. Large tumor burden
3. Infiltrative disease
   - Large infiltrative HCC with >50% tumor burden



Radiation Pneumonitis

Restrictive Ventilatory Dysfunction

- Symptoms: Dry non-productive cough, low-grade fever, progressive exertional dyspnea 1-6 months after Y90

  (classically 1-2 months after Y90)

- Imaging: Early: Chest X-ray and chest CT demonstrate patchy consolidation with sparing of periphery and fissures (aka bat-wing appearance), atelectasis, pleural effusion

  Later Stages: Fibrosis, traction bronchiectasis, and localized honeycombing

Wright CL, et al. *JVIR*. 2012;23(5): 669-674.

Radiation Pneumonitis

Treatment

1. Steroids improve symptoms and lung function
2. Bronchodilators
3. Pentoxifylline – radioprotective; prevents early and late lung toxicity
4. Supplement O2

Radiation-Induced Cholecystitis

- Incidence: Rare (<2%)
- Abnormal imaging findings with regard to the gallbladder must be correlated with clinical symptoms

- Technical Considerations
  1. When feasible, deliver Y90 distal to cystic artery
  2. Prophylactic coil/gelfoam embolization of the cystic artery is controversial and is generally not necessary given low incidence of cholecystitis
  3. If particularly large cystic artery and distal delivery not possible, distal split dosing may be considered

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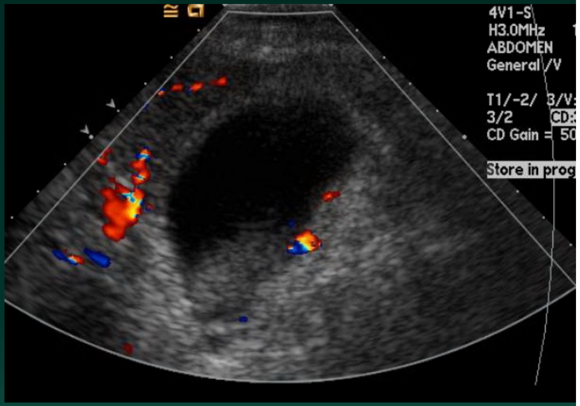
Radiation-Induced Cholecystitis

- Most cases can be managed conservatively with the following:
  1. Antibiotics
  2. Pain management
  3. Hydration

- Surgery or cholecystostomy may be needed in rare cases, but should be reserved as last resort

- Consider post radioembolization antibiotics if gallbladder is within the radiation field



Hepatobiliary Infection Post Y90

- With TACE, the risk of liver abscess increases 800-fold in patients with a violated sphincter

- Incidence less well defined with Y90, but according to a retrospective multicenter study[1] on 126 patients, abscess or cholangitis occurred in 8.7% of patients (6.7% of Y90 procedures); infectious complications can be morbid and difficult to manage

- Risk Factors for Hepatobiliary Infection
  1. Biliary-enteric anastomosis (ie, Whipple)
  2. Sphincterotomy
  3. Biliary stent or biliary drain across ampulla

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[1]Devulapalli K, et al. Safety of Yttrium-90 Radioembolization for Patients with History of Biliary Tract Instrumentation: Final Results of a Multicenter Study. Presentation at SIR 2016.

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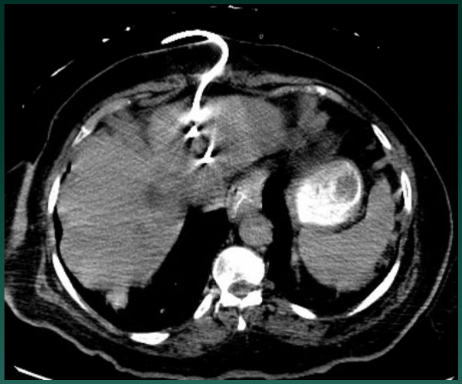
Hepatobiliary Infection Post Y90

- Prevention
  1. **Penn Protocol:** No liver abscess seen in 24 Y90 procedures in 16 patients with ABX and bowel prep[1]
     - Levofloxacin 500 mg PO QD and metronidazole 500 mg PO BID starting 48 hrs before procedure and continued 2 wks after discharge (IV dose on day of Y90)
     - Bowel prep: 1 gram neomycin and 1 gram erythromycin at 1, 2, and 11 pm on day before procedure
  2. **Moxifloxacin Protocol:** No liver abscess in 25 TACE procedures in 10 patients)[2]
     - Moxifloxacin 400 mg PO QD beginning 3 days before and continued for 17 days after the procedure

[1]Cholapranee A, et al. *Cardiovasc Intervent Radiol.* 2015; 38: 397-400. [2]Khan W, et al. *AJR.* 2011;197:W343-345

Hepatobiliary Infection Post Y90

- Management
  1. Antibiotics
  2. Percutaneous drainage
  3. ERCP or biliary drain (for obstruction)



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Cholapranee A, et al. *Cardiovasc Intervent Radiol.* 2015; 38: 397-400. Khan W, et al. *AJR*. 2011;197:W343-345

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Other Biliary Complications

1. Biliary Strictures
   - Resultant obstructive jaundice
   - May require ERCP or PTC with dilation of strictures and placement of biliary stents

2. Bilomas
   - Due to bile duct leak from Y90 injury to biliary tree
   - May require drainage

3. Biliary Necrosis
   - Forms multiple small, cystic lesions on imaging
   - Not usually drained

Biliary-Caval Fistula following Y90 Radioembolization

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[1] Division of Vascular and Interventional Radiology, Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin

Semin Intervent Radiol 2021;38:488–491

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Biliary-caval fistula in patient who developed recurrent cholangitis and sepsis

Cholapranee A, et al. *Cardiovasc Intervent Radiol.* 2015; 38: 397-400. Khan W, et al. *AJR*. 2011;197:W343-345

Radiation Dermatitis

1. Etiology: May occur due to nontarget delivery of Y90 radiomicrospheres
   - Periumbilical area – falciform artery
   - Abdomen/flank – inferior phrenic artery
2. Prevention
   - Embolize the falciform artery (or use icepack on abdomen)
   - Take caution when Y90 delivery in inferior phrenic artery (may be safe in hypervascular tumors with selective delivery)
3. Treatment
   - Supportive care
   - If severe, could require skin graft

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Cholapranee A, et al. *Cardiovasc Intervent Radiol.* 2015; 38: 397-400. Khan W, et al. *AJR.* 2011;197:W343-345

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Hematologic Toxicity

1. Lymphopenia
   - Commonly seen after Y90
   - Rarely results in infection

2. Thrombocytopenia
   - Y90 may result in splenomegaly with resultant thrombocytopenia
   - Y90 may exacerbate chemotherapy-related thrombocytopenia

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Carr BI. *LiverTranspl.* 2004;**10**(2 Suppl1):S107–10.
Lam MG, et al. *CVIR*. 2014; **37**(4):1009–17

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Review Papers on Y90 Complications

- Riaz A, Lewandowski RJ, Kulik LM, et al. Complications Following Radioembolization with Yttrium-90 Microspheres: A Comprehensive Literature Review. *J Vasc Interv Radiol.* 2009;20:1121-30.
- Riaz A, Awais R, Salem R. Side effects of yttrium-90 radioembolization. *Front Oncol.* 2014;4:1-11.
- Liu DM, Cade D, Klass D, et al. Interventional Oncology: Avoiding Common Pitfalls to Reduce Toxicity in Hepatic Radioembolization. *J Nucl Med Radiat Ther.* 2011;2: 2155-9619.

Conclusions

Most Y90 related toxicities can be prevented with appropriate measures.

Complications can be mitigated by:

- Appropriate patient selection
- Careful pretreatment planning and meticulous procedural

Most adverse events can be medically managed (surgery reserved for

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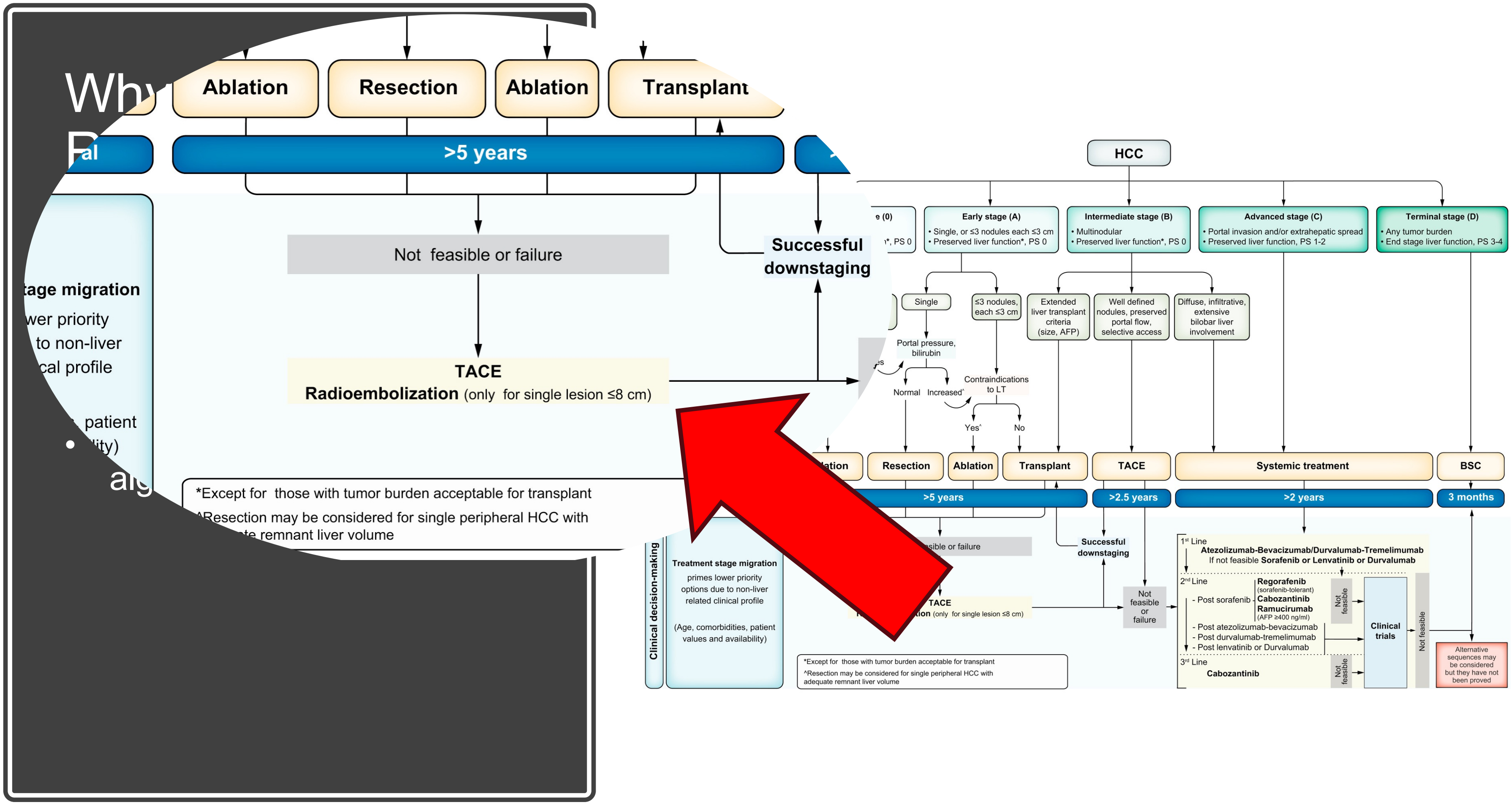
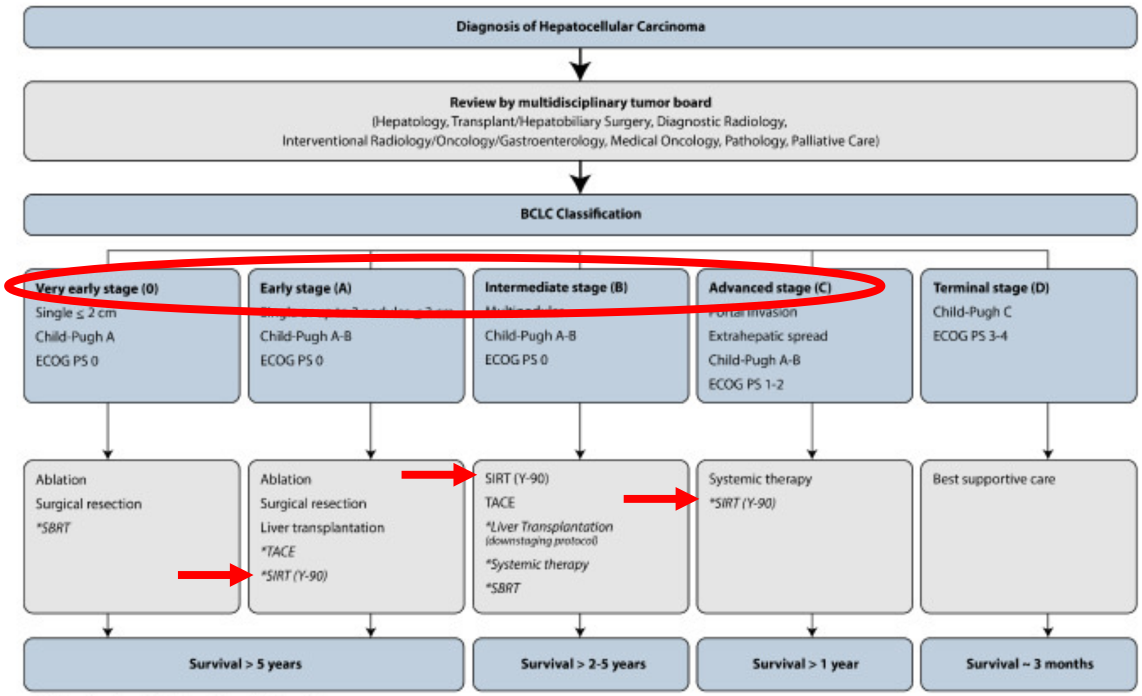
Competitive Treatments – Y90 Benefits vs Other LDT Therapies

Osman Ahmed, MD
Professor of Radiology
University of Utah

CIO



Salem R, et al. *Hepatology*. 2021;74(5):2342–2352. Reig M, et al. *J Hepatol*. 2022 Mar;76(3):681-693.



*addtional treatment options in select patients (see text)

BCLC - Barcelona Clinic Liver Cancer, ECOG - Eastern Cooperative Oncology Group, SBRT - Stereotactic Body Radiation, TACE - Transarterial Chemoembolization, SIRT - Selective Internal Radiation Therapy, Y-90 - Yttrium 90

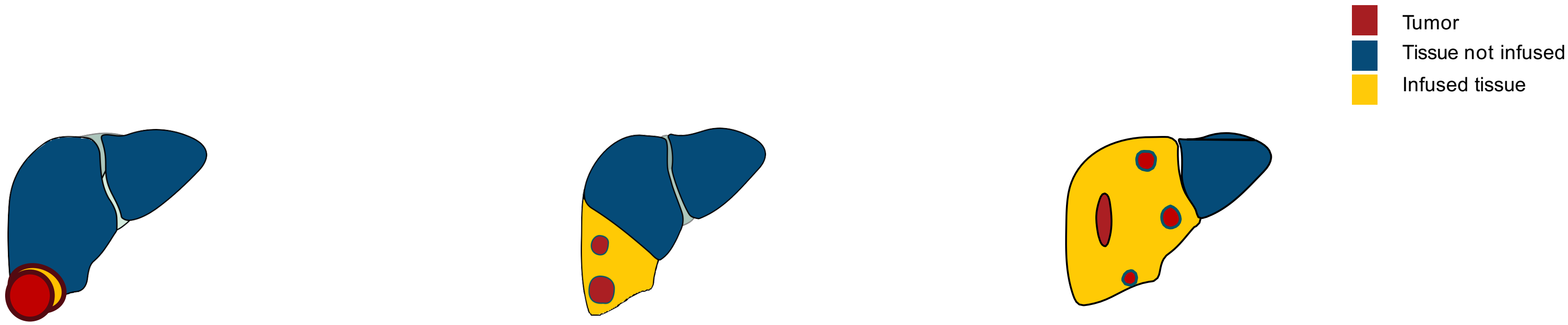
Figure 1: Algorithm of our institutional approach to locoregional therapy once diagnosis of HCC is established. All patients are discussed in a multidisciplinary liver tumor board and decisions are formulated with specific consideration to patient's wishes, BCLC staging, CP score and performance status.

Figure adapted from Forner A et al. The Lancet 2018; 391(10127)1301-14

TARE plays a role in each stage of BCLC (with varied intent)

CIO

Neoadjuvant to Curative Treatment with Y-90



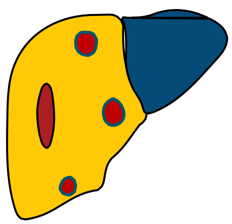
Uninodular Disease
- Bridging to liver transplantation
- Downstage to liver transplantation
- Radiation segmentectomy followed by resection

Segmental Disease
- Downstage to liver transplantation
- Bridging to liver transplantation

Unilobar ± PVT Disease
- Radiation or modified lobectomy to allow resection
- Downstage for resection

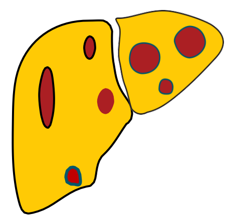
Palliative Treatment with Y-90

Tumor
Tissue not infused
Infused tissue



Unilobar Disease ± Portal Vein Thrombosis (PVT)

- Non surgical candidate (eg, due to disease burden, insufficient future liver remnant)
- Lobar treatment



Bilobar Disease ± PVT

- Treat both lobes, usually on different days

Salem R, Thurston KG. *J Vasc Interv Radiol* 2006;17(8):1251–1278. TheraSphere® Reference Manual (US-USTHSP-2013-0569-1).

Y90
Why Not?

Safety + Efficacy

Versatility

Efficacy of TARE for Early HCC Is Well Established

Original Research
Vascular and Interventional Radiology

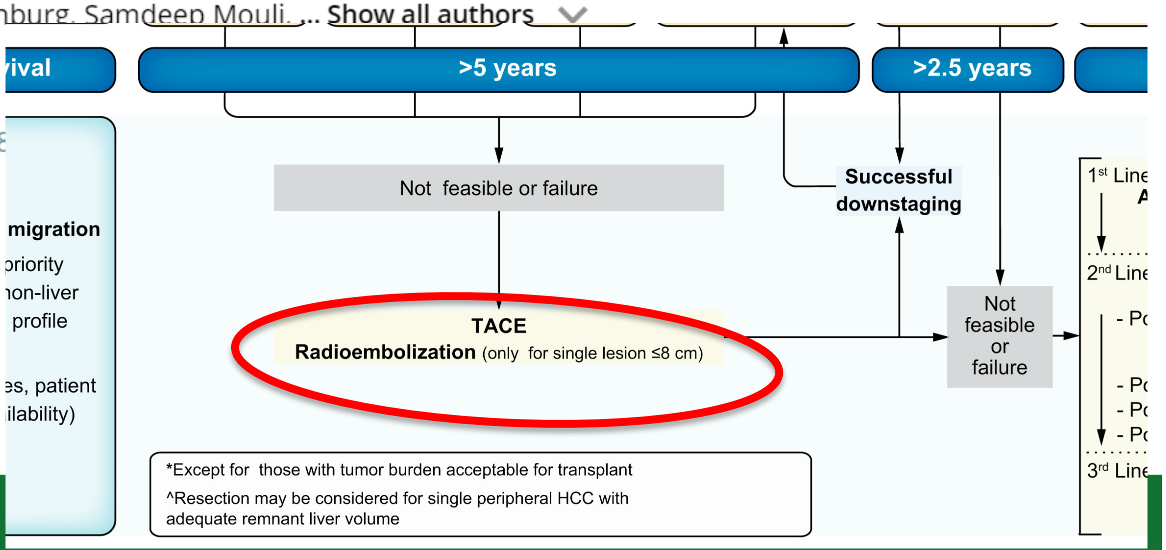
Free Access

Radiation Segmentectomy: Potential Curative Therapy for Early Hepatocellular Carcinoma

Robert J. Lewandowski, Ahmed Gabr, Nadine Abouchaleh, Rehan Ali, Ali Al Asadi, Ronald A. Mora, Laura Kulik, Daniel Ganger, Kush Desai, Bartley Thornburg, Samdeep Mouli, ... Show all authors

Author Affiliations

Published Online: Apr 24 2018 | https://doi.org/10.1148



CIO

Safety

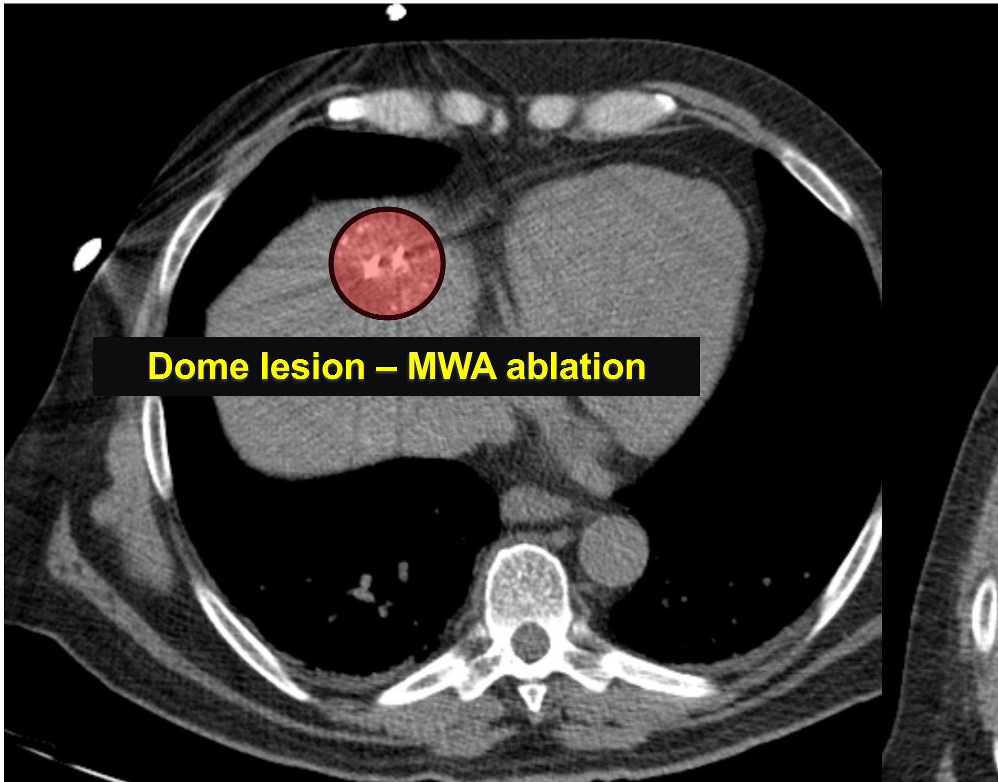
Low toxicity

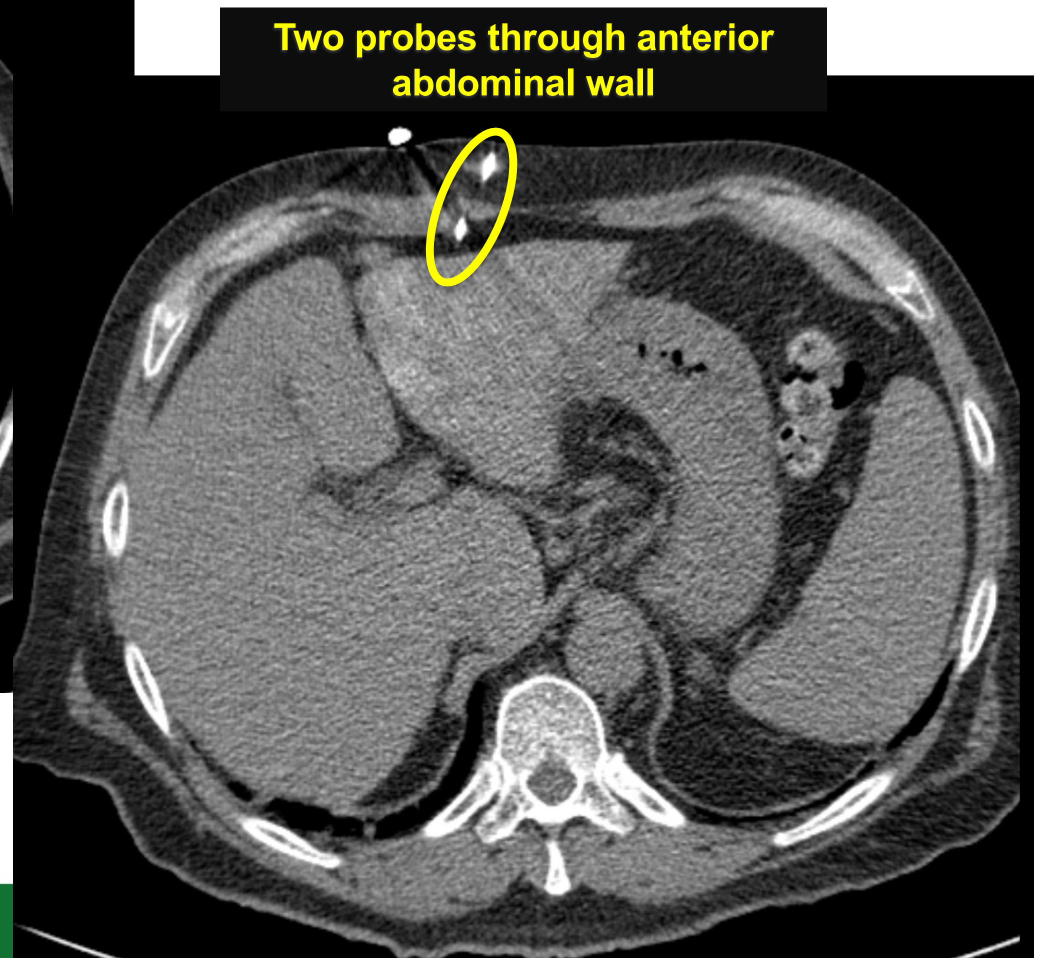
Light/moderate anesthesia

Outpatient

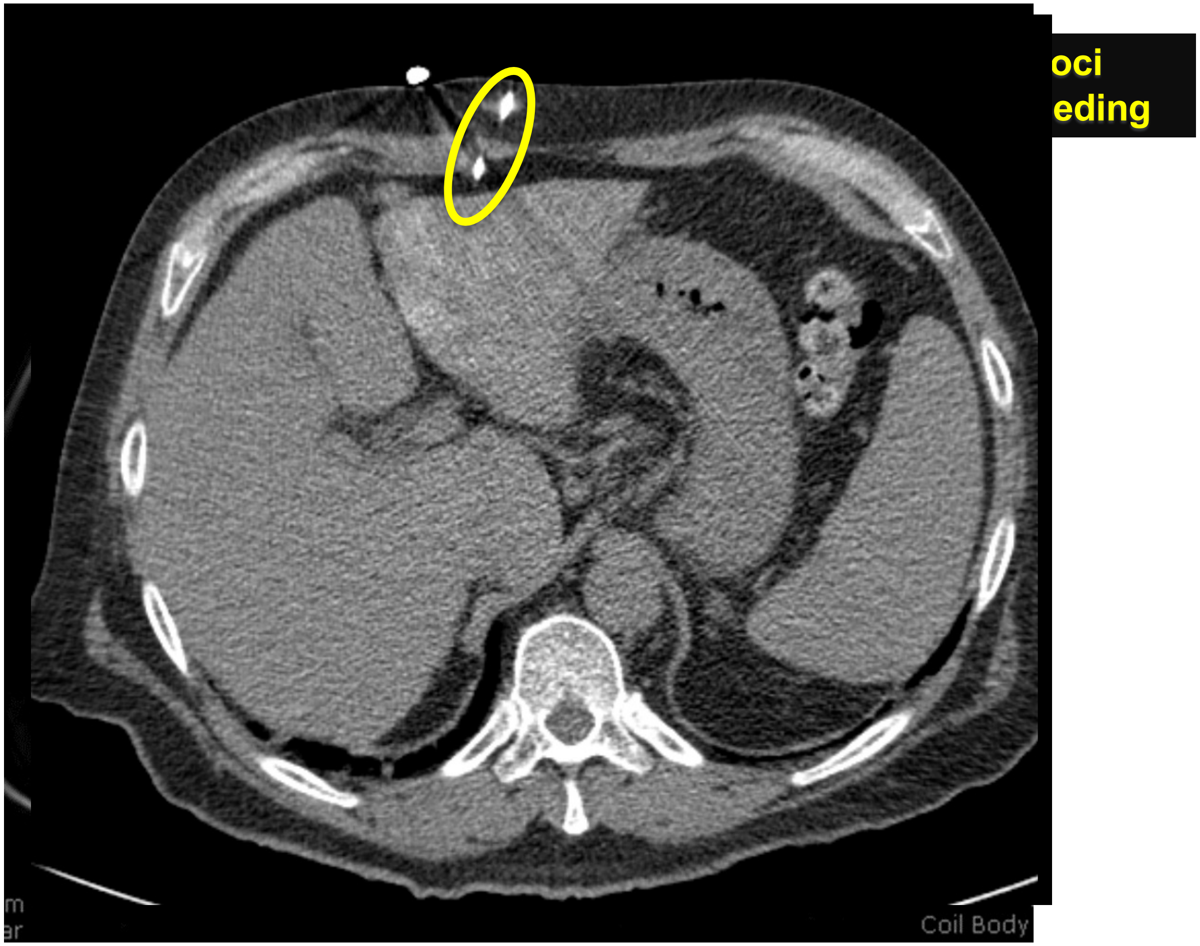
“Never Events”

Potentially catastrophic complications can occur with ablation


Dome lesion – MWA ablation


Two probes through anterior abdominal wall

Follow-Up MRI



Versatility with Y90

Don’t need to worry about lesion location or size

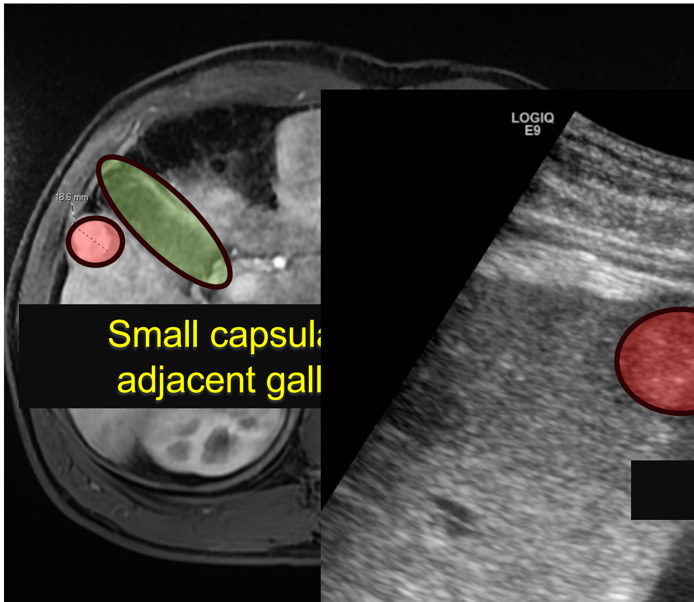
Less concern about adjacent organ injury

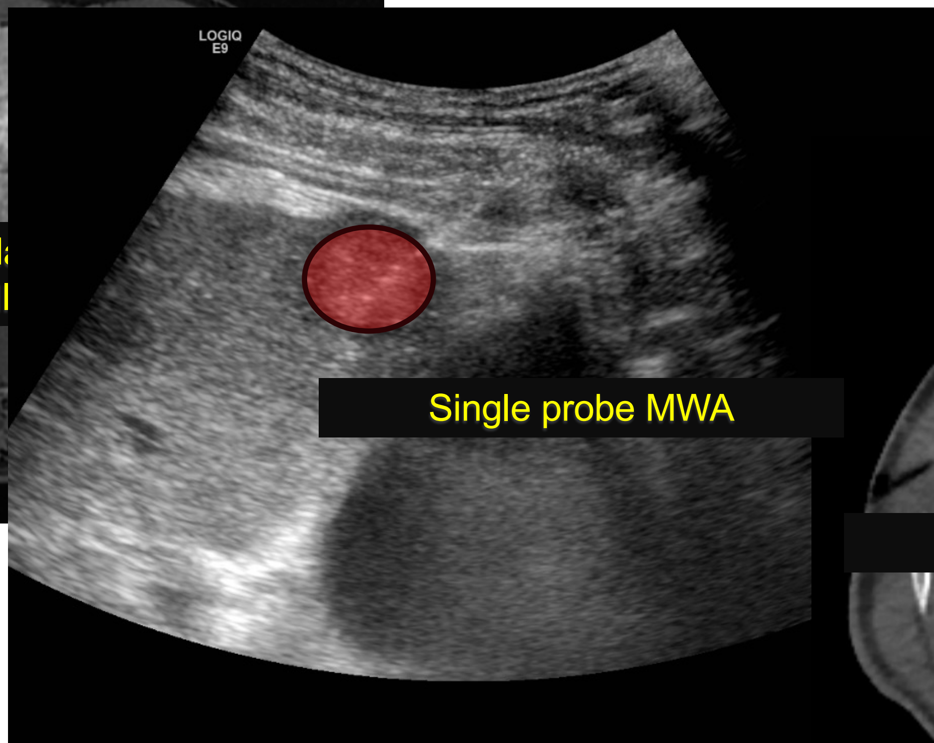
Example

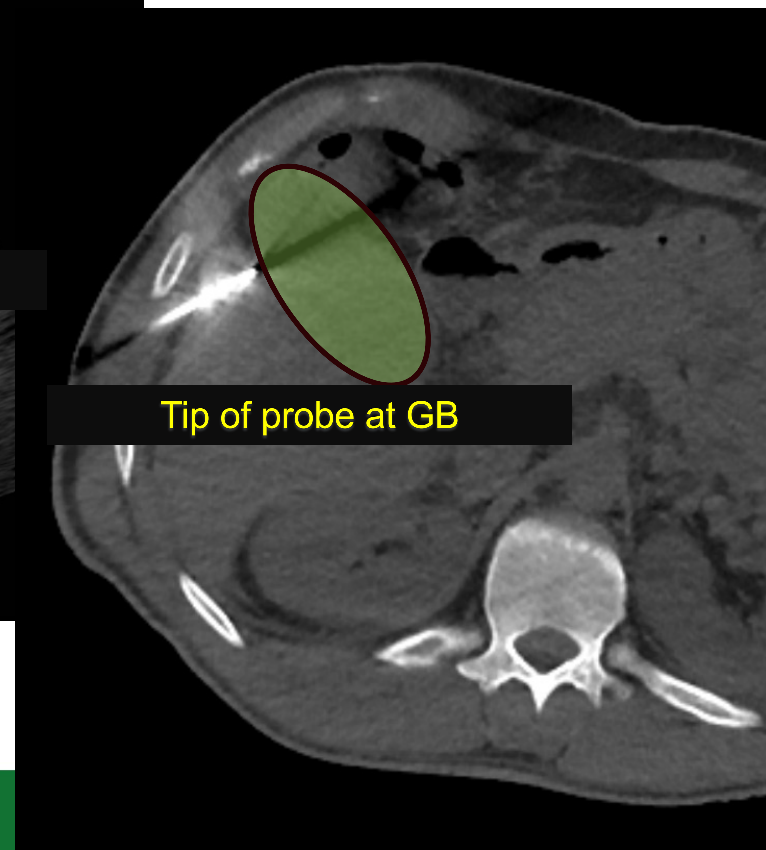
Segment 3 subcapsular lesion abutting stomach

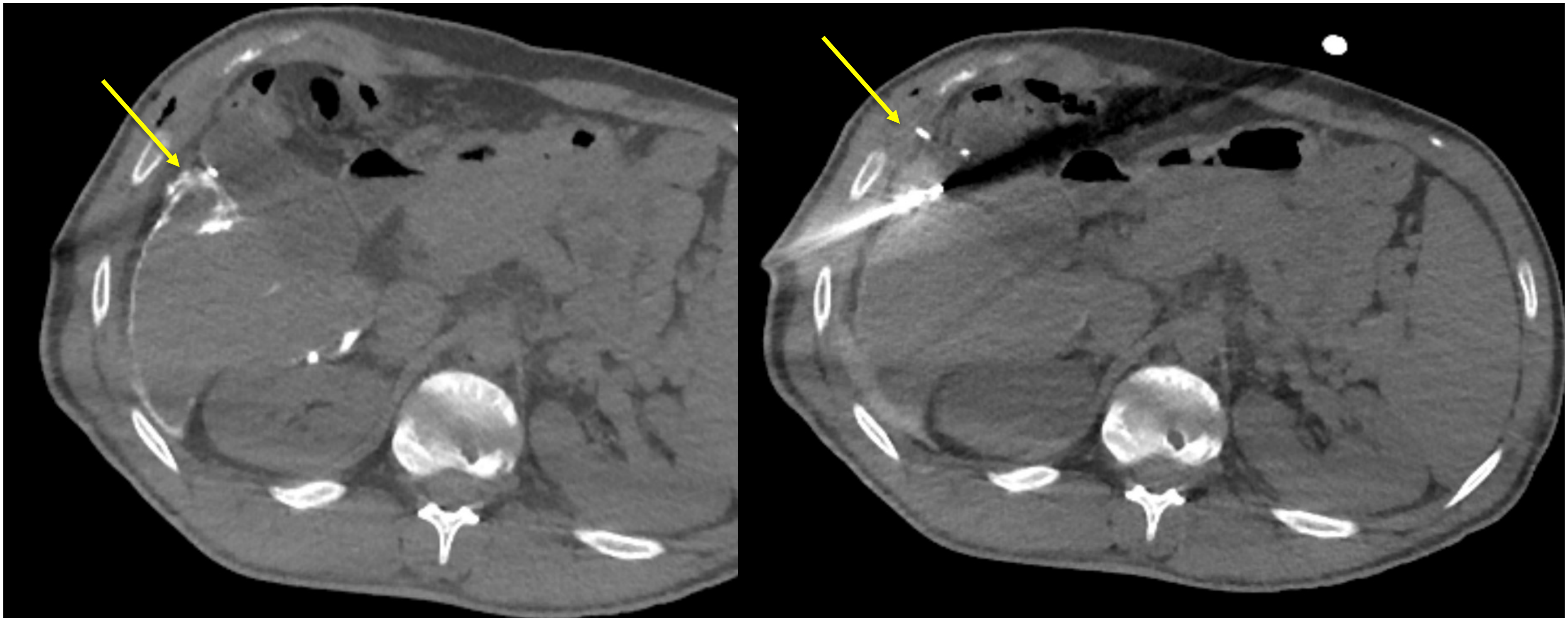
Let's compare this to ablation…

Subcapsular lesion abutting gallbladder


Small capsul
adjacent gall


LOGIQ
E9
Single probe MWA

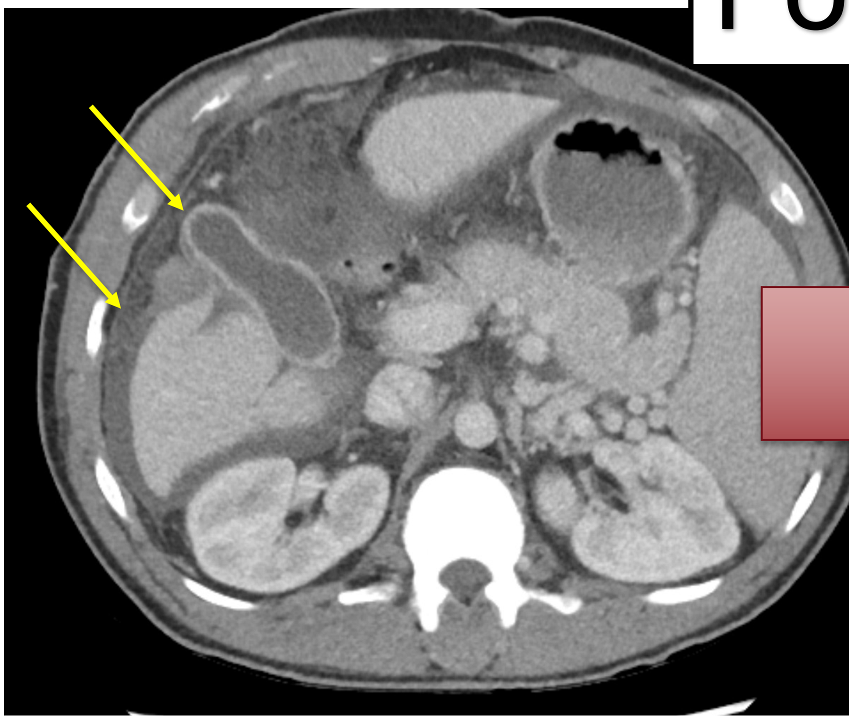

Tip of probe at GB



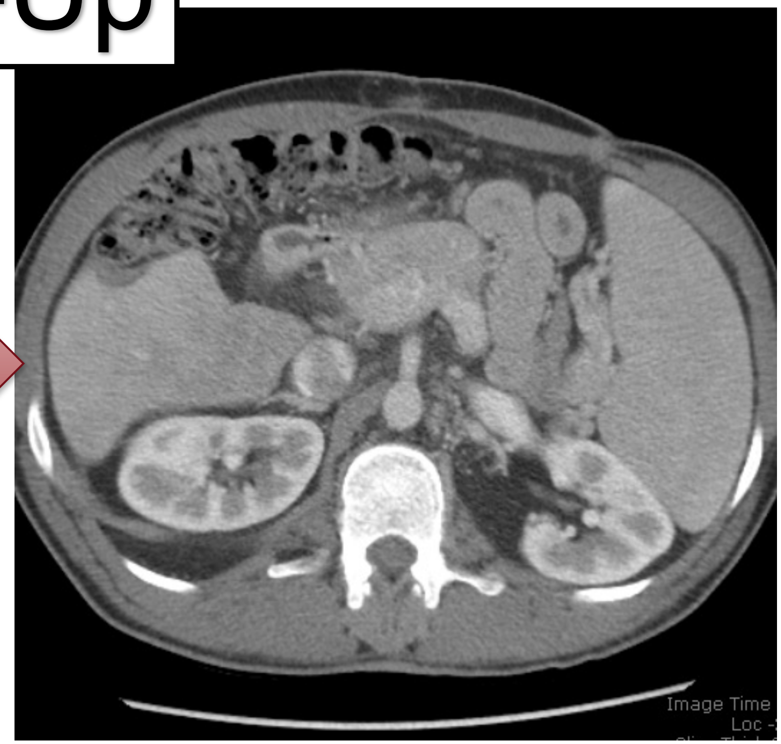
Adjunct techniques: Hydrodissection and GB decompression
(All to burn a 2cm tumor)

CiO

Follow-Up



Gallbladder injury with bile leak and peritonitis



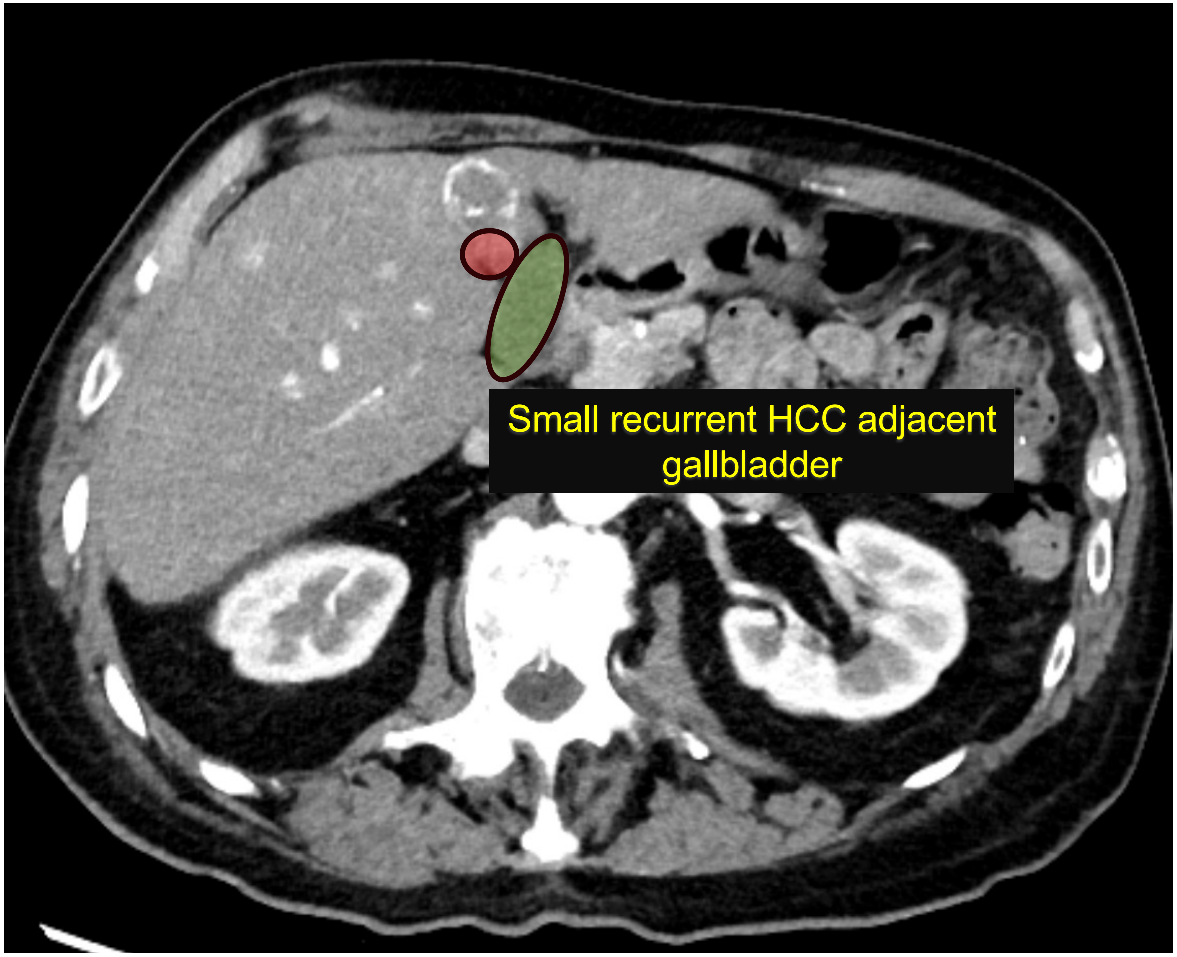
OR for cholecystectomy

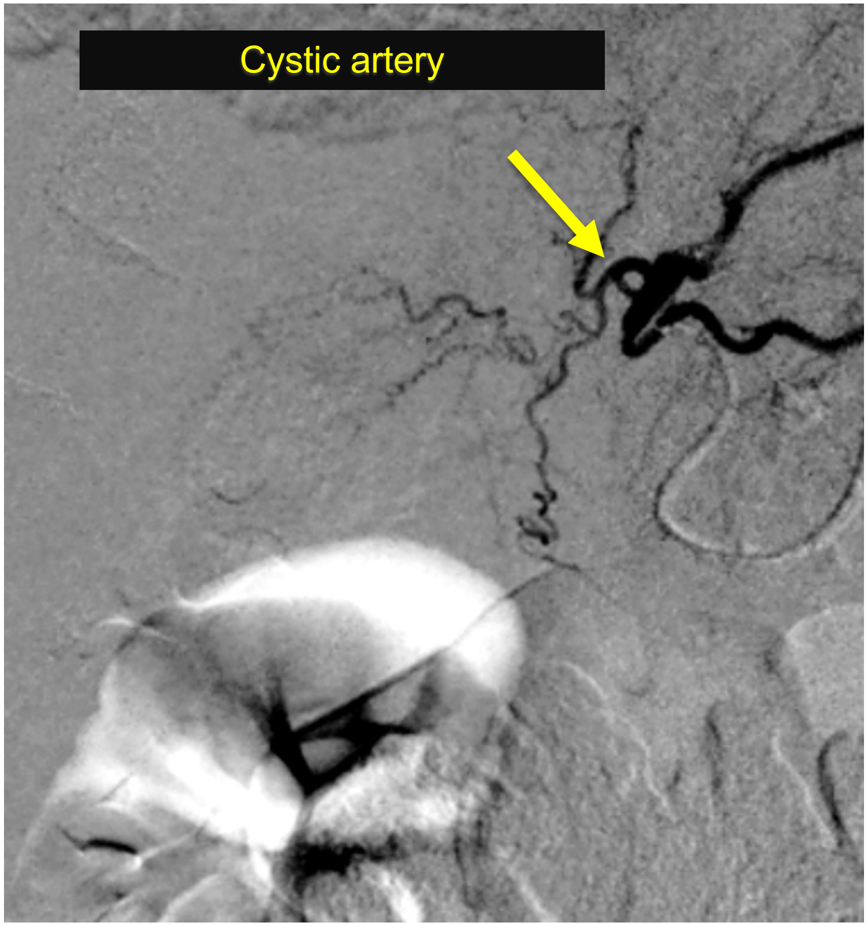
CIO

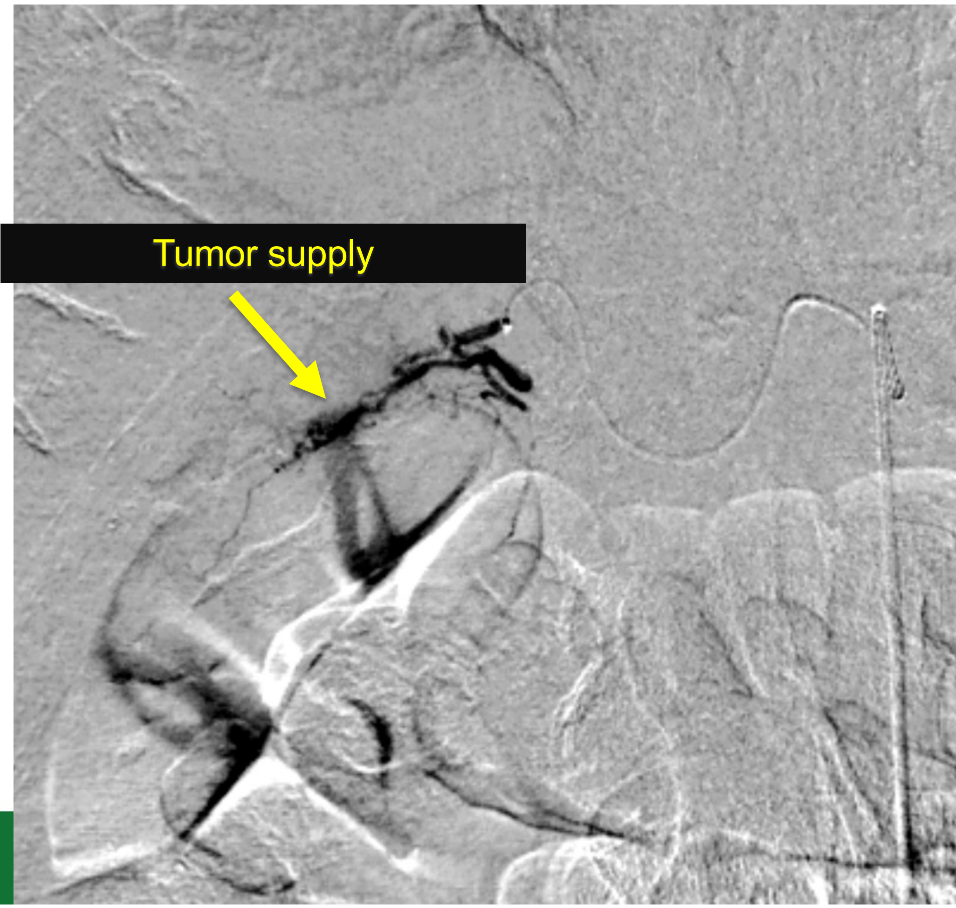
Comparatively…

Another tumor next to GB

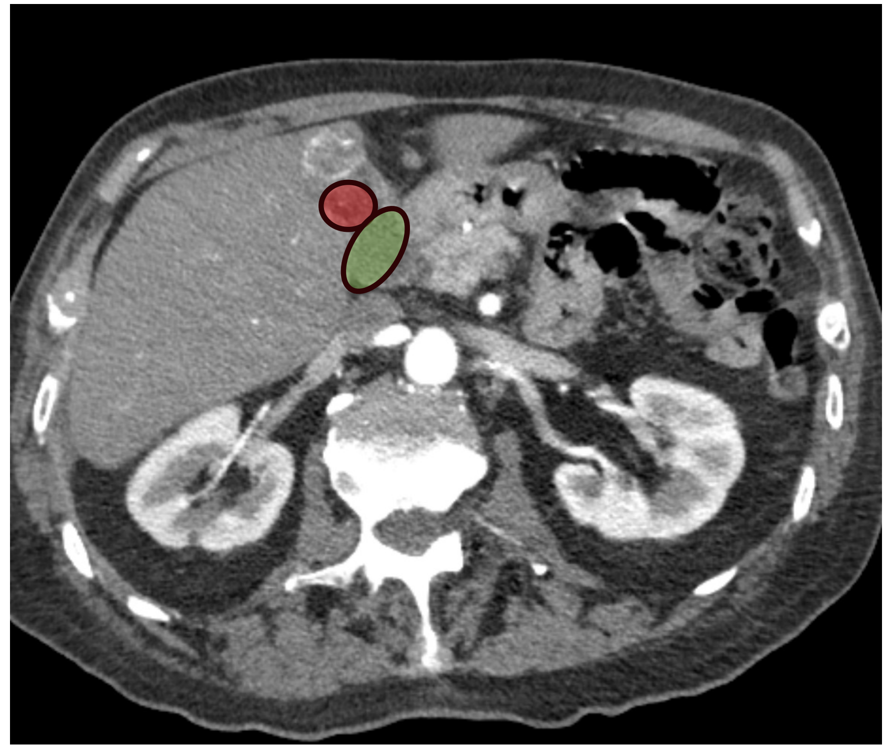
CiO


Small recurrent HCC adjacent gallbladder


Cystic artery


Tumor supply

Angio-CT confirmation → TARE



Follow-up - CR

CiO

Versatility + Safety

Eur J Nucl Med Mol Imaging. 2015 Dec;42(13):2038-44. doi: 10.1007/s00259-015-3122-6.
Epub 2015 Jul 21.

Gastric injury from (90)Y to left hepatic lobe tumors adjacent to the stom

Vanessa L Gates [1], Ryan Hickey [1], Kar
Robert J Lewandowski [1], Riad Salem [2, 3]

Affiliations + expand

PMID: 26194715 DOI: 10.1007/s00259-015-3122-6

Conclusion: Patients with left lobe tumors adjacent to or abutting the stomach do not exhibit acute or chronic radiation effects following radioembolization with glass microspheres.

Transarterial Yttrium-90 Radioembolization of Hepatocellular C Artery: Multi-ins

Siddharth A Padia [1], Guy E John

Affiliations + expand

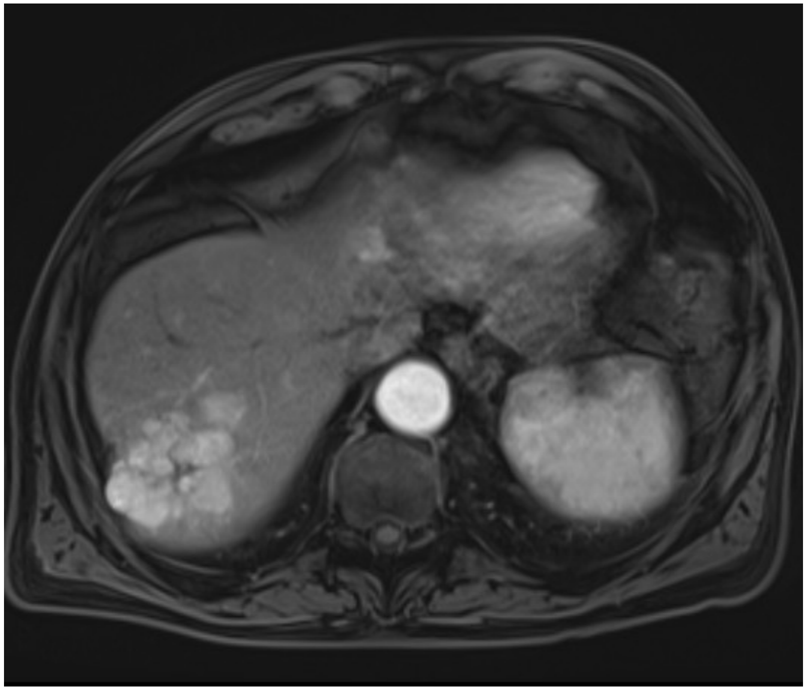
PMID: 33187861 DOI: 10.1016/j.jvir.2020.08.014

Conclusions: Direct infusion of ^{90}Y microspheres via the cystic artery appears to have an acceptable safety profile, without resulting in acute cholecystitis warranting invasive intervention. In selected patients with HCC in whom other treatments may be contraindicated and the tumor is supplied via the cystic artery, treatment with selective ablative radioembolization can be considered.

CIO

Contralateral Hypertrophy

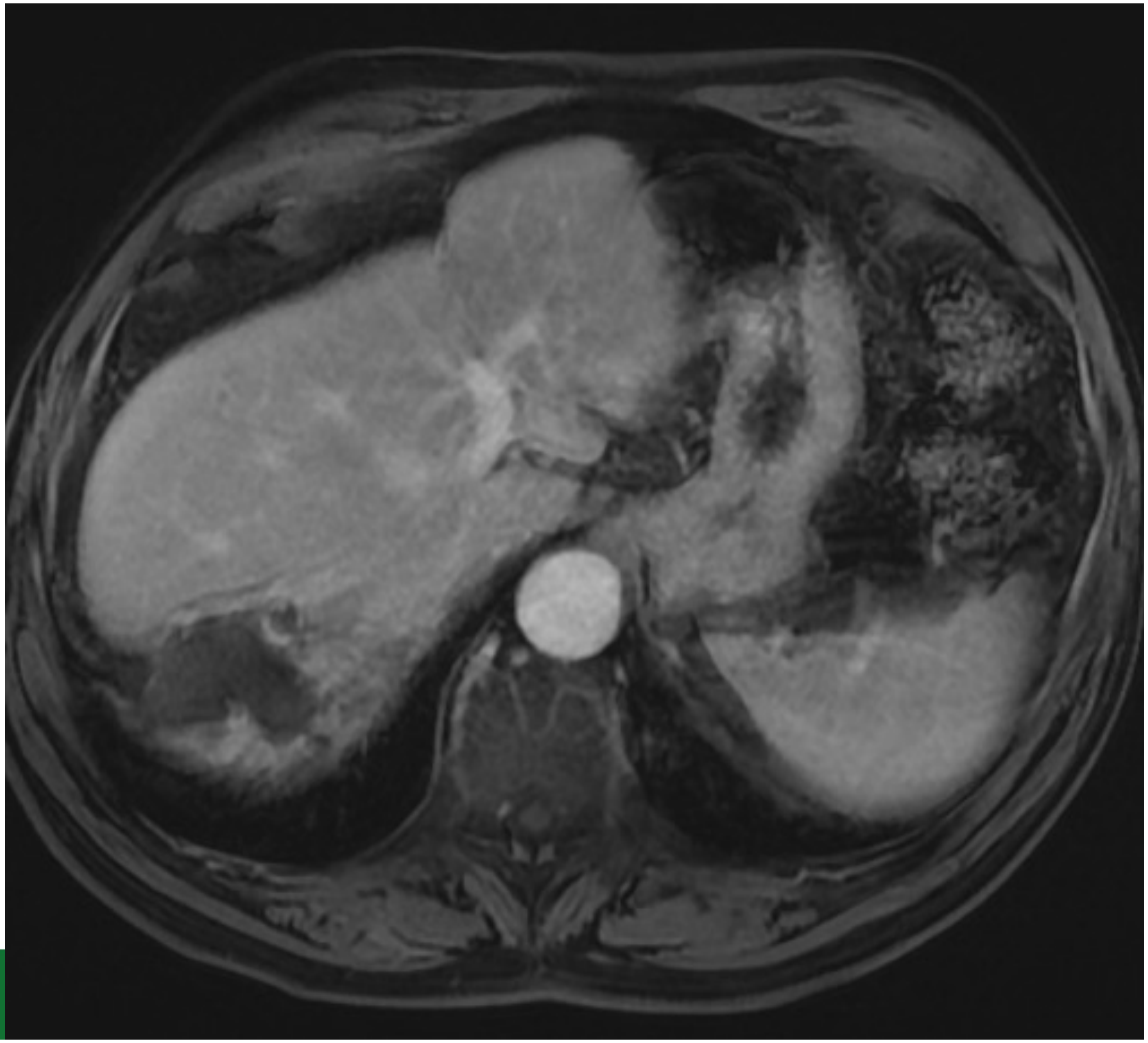
- TARE not only has the ability to treat tumor
- “Ablative” dosing permits target tumor lobe atrophy with contralateral lobe hypertrophy
- Important for consideration of future liver remnant if planning resection



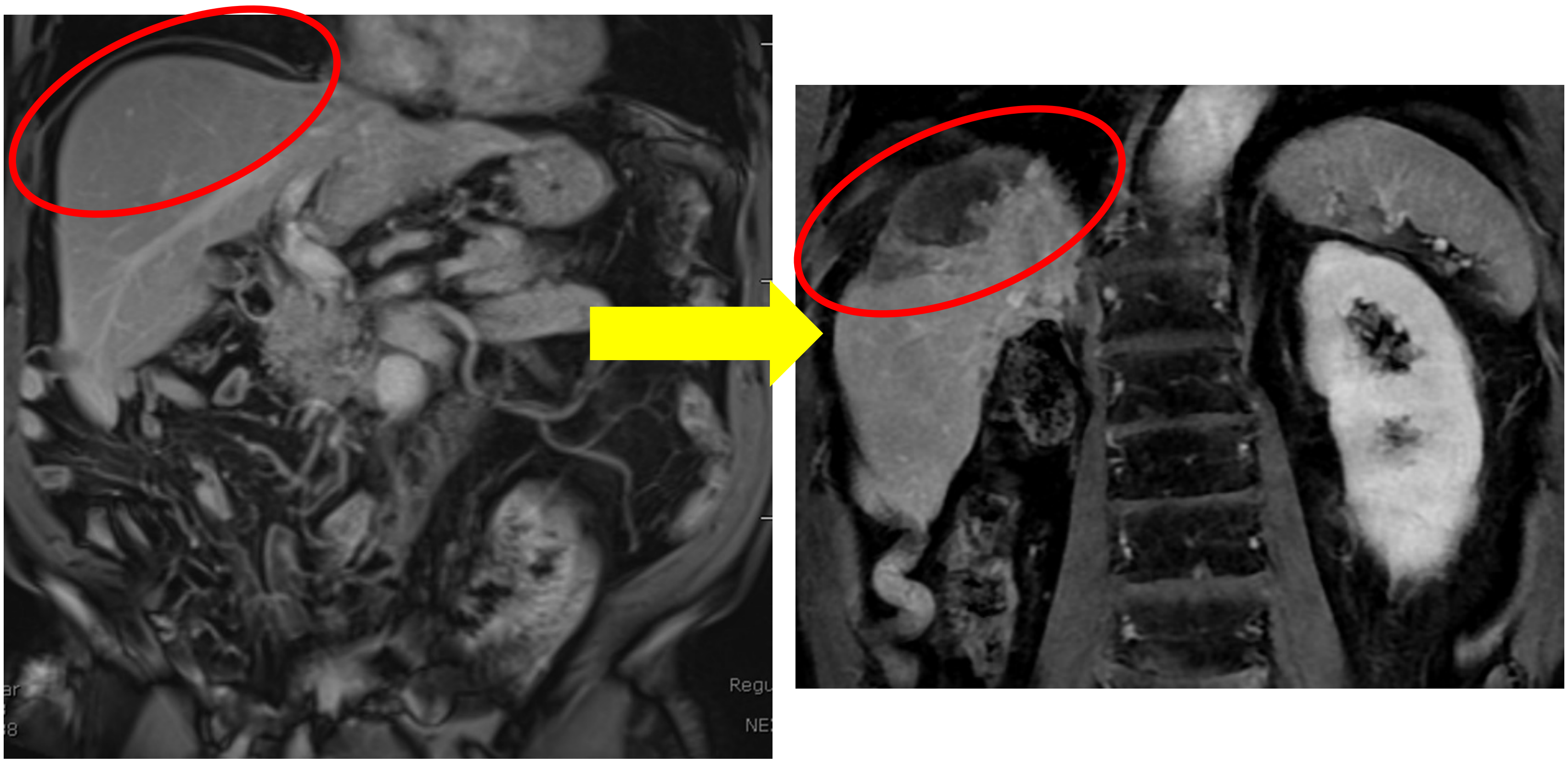
71-yr-old Male with large 6.1 x 6.9cm HCC
Segmental + Lobar TARE

9-Month Follow-Up

2-Year Follow-Up



CIO



Conclusion

Y90 TARE has broad applicability across the BCLC algorithm

- Both palliative and curative intent

Outpatient, moderate sedation, favorable toxicity

- Lifestyle oriented

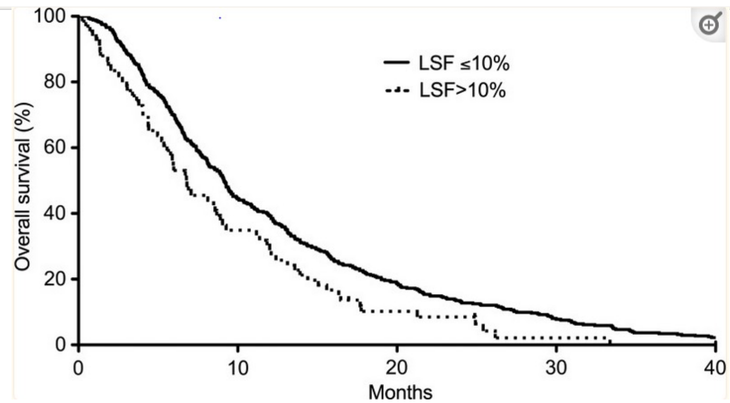
Benefit of contralateral hypertrophy

Managing High Lung Shunts

Ripal T. Gandhi, MD, FSIR, FSVM
Miami Cardiac & Vascular Institute
Miami Cancer Institute
Clinical Professor, FIU Herbert Wertheim College of Medicine


CIO

Lung Shunt



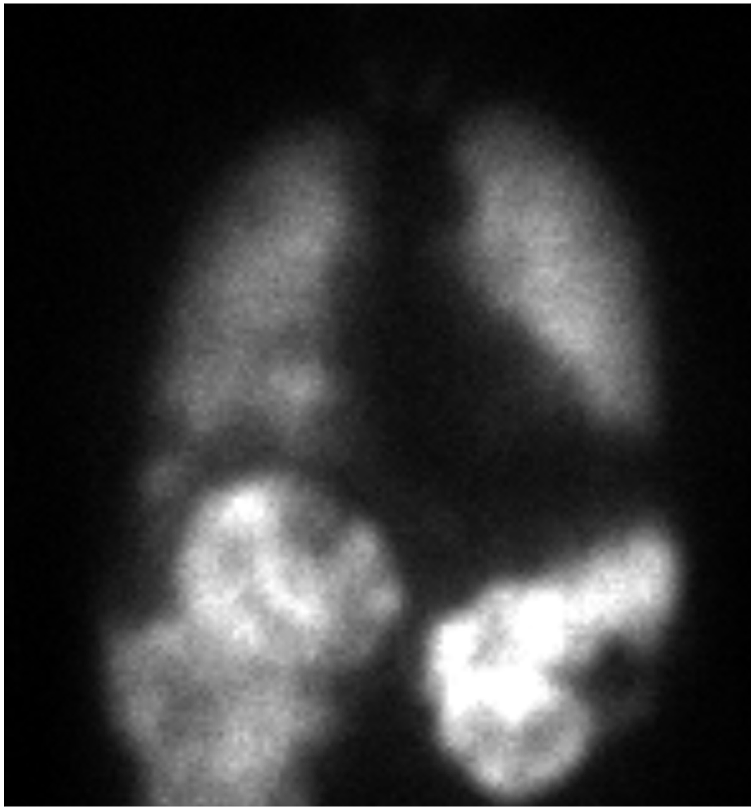
- High hepatopulmonary shunts (HPS)
  - Radiation-induced lung injury (RILI)
  - Increased LSF is an independent prognostic factor for decreased survival
- Lung Shunt Fraction (LSF) Calculation:

$$Geometric\ mean = \sqrt{Anterior\ view\ counts \times Posterior\ view\ counts}$$

$$Lung\ shunt\ fraction\ (LSF) = \frac{Lung\ geometric\ mean}{(Lung\ geometric\ mean + Liver\ geometric\ mean)}$$

Narsinh KH, et al. *Radiology*. 2017;282(1):281-288.

- HPS pathophysiology
  - Vascular growth factors in local tumor environment
  - Irregular vessels allow passage of small particles (<45 µm)
- High HPS
  - Traditionally considered high if >10-20%
  - More accurately
    - >30 Gy single treatment
    - >50 Gy lifetime dose



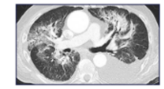
HPS = 40%

Evolving Lung Dose Threshold

Traditional lung dose threshold	• 30 Gray single administration, • 50 Gray lifetime
What is new lung dose threshold?	• Resin: 15-20 Gy • Glass: 25-30 Gy

EVIDENCE-BASED REVIEW

Radiation Pneumonitis after Yttrium-90 Radioembolization: A Systematic Review



Bela Kis, MD, PhD, and Marcell Gyano, MD, PhD

The maximum tolerated lung dose for Y90 is an expert opinion (level 5 evidence) based on a case series of 5 patients

For patients who develop radiation pneumonitis, the dose to lungs was significantly higher in patients with glass vs resin:
Glass: 41.4 Gray
Resin: 21.5 Gray

69% of patients in the resin group and 20% in the glass group received less than 30 Gy lung dose but still developed radiation pneumonitis

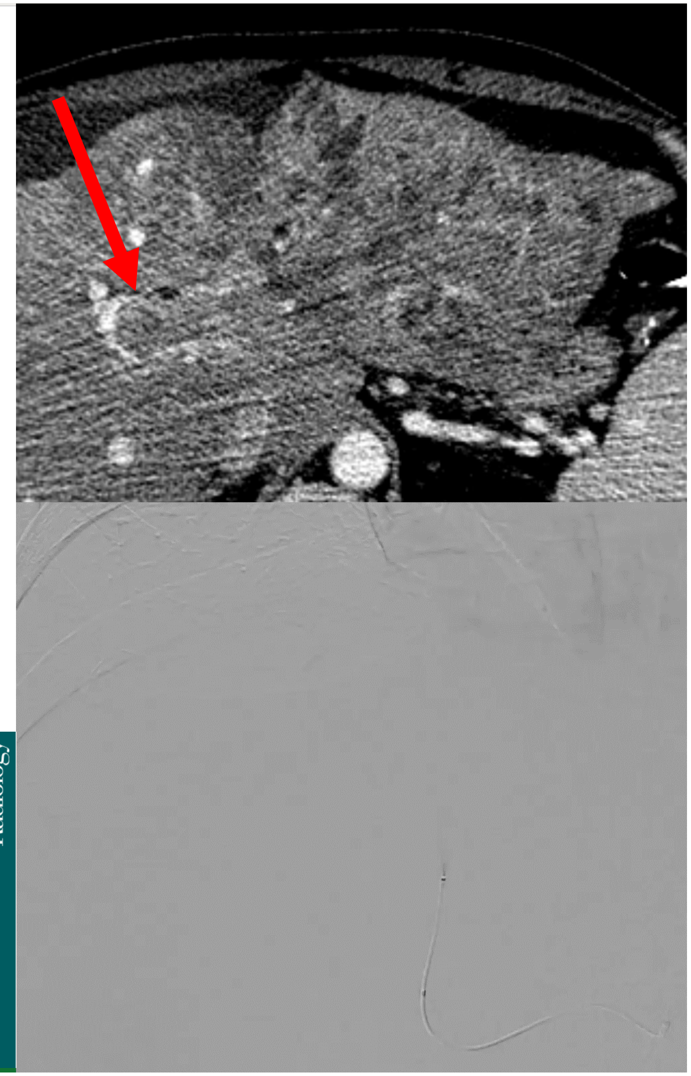
CIO

Kis B, Gyano M. *JVIR*. 2025;36(2):207-218.

Radiation Pneumonitis

High lung shunts -- Risk Factors

1. HCC
2. Vascular invasion (portal vein and hepatic vein tumor thrombus, arterioportal shunts)
3. Large tumor burden >50%
4. Infiltrative disease



Radiology

Characteristics of Primary and Secondary Hepatic Malignancies Associated with Hepatopulmonary Shunting[1]

Ron C. Gaba, MD
Sean P. Zivin, MD
Mark S. Dikopf, MD
Ahmad Parvinian, BS
Leigh C. Casadaban, BS
Yang Lu, MD, PhD
James T. Bui, MD

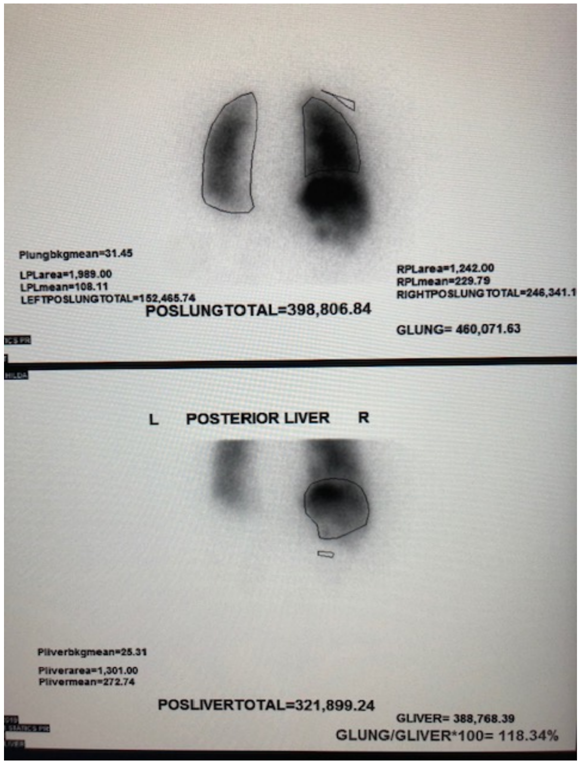
Purpose: To identify liver tumor characteristics associated with low (<10%), intermediate (10%–20%), and high (>20%) lung shunt fraction (LSF) at technetium 99m (^{99m}Tc) macroaggregated albumin (MAA) imaging performed before yttrium 90 (^{90}Y) radioembolization (RE).

Materials and In this single-center retrospective study, 141 patients

CiO

Radiation-Induced Lung Injury

- Incidence: Extremely rare (far less than 1%)
- Be conservative with pulmonary compromise (ie, COPD, lung rsxn)
- Systemic chemotherapy may predispose patients to developing radiation pneumonitis

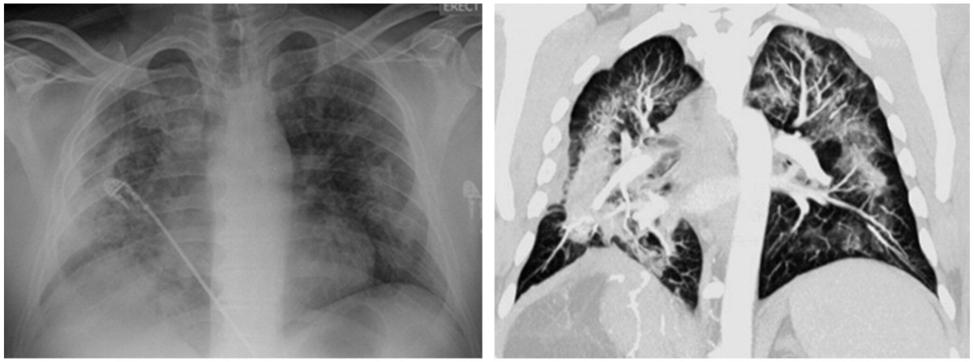


Wright CL, et al. *J Vasc Interv Radiol*. 2012;23(5):669-674.

Radiation-Induced Lung Injury

Restrictive ventilatory dysfunction

- Initial insult
  - 1-3 months after exposure
  - Fever, non-productive cough, dyspnea
  - Imaging: Patchy consolidation with peripheral sparing (bat-wing), atelectasis, effusion
- Fibrosis
  - 6-12 months after exposure
  - Debilitating PA HTN/cor pulmonale
  - Imaging: Fibrosis, traction bronchiectasis, localized honeycombing



a. b.

Wright CL, et al. *J Vasc Interv Radiol*. 2012;23(5):669-674.

Radiation Pneumonitis: Treatment

1. Steroids improve symptoms and lung function
2. Bronchodilators
3. Pentoxifylline – radioprotective; prevents early and late lung toxicity
4. Supplement O2

Methods to Reduce Lung Shunt

- Dose reduction
  - Keep lung dose <30 gray
  - But must have tumoricidal dose

- Bland or chemoembolization
  - Use large particles
  - Under embolize
  - 29-69% reduction

ELSEVIER

Techniques in Vascular and Interventional Radiology

Management of High Hepatopulmonary Shunts in the Setting of Y90 Radioembolization

Brian J. Schiro, MD, Edgar St. Amour, MD, Christopher Harnain, MD, and Ripal T. Gandhi, MD

Treatment paradigms for primary and metastatic malignancies involving the liver have evolved in recent years to include targeted liver therapies. Transarterial radioembolization is at the forefront of therapy in many treatment algorithms. However, due to significant hepatopulmonary shunting, some patients are excluded from this proven treatment due to the possibility of radiation-induced lung injury. In this article, we review techniques to mitigate hepatopulmonary shunts to improve the likelihood of inclusion and successful treatment in these patients.

CIO

Schiro BJ, et al. *Tech Vasc Interv Radiol.* 2019;22(2):58-62.

Methods to Reduce Lung Shunt

- Hepatic vein occlusion
- Occlusion of portosystemic shunts
  - Embolize on arterial side
  - Placement of balloon in the portal vein
- Ablation of shunt
- Systemic therapy (immunotherapy, kinase inhibitor/chemotherapy)
  - 3-6 months

RESEARCH ARTICLE | VOLUME 22, ISSUE 2, P58-62, JUNE 2019 Download Full Issue

Management of High Hepatopulmonary Shunts in the Setting of Y90 Radioembolization

Brian J. Schiro, MD • Edgar St. Amour, MD • Christopher Harnain, MD • Ripal T. Gandhi, MD

Published: March 16, 2019 • DOI: https://doi.org/10.1053/j.tvir.2019.02.004 • Check for updates

Cardiovasc Intervent Radiol (2015) 38:1330–1334
DOI 10.1007/s00270-014-0990-2
CIRSE CrossMark
CASE REPORT

High-Flow Arterio-Hepatic Venous Shunt in Hepatocellular Carcinoma: Use of Multi-Electrode Radiofrequency for Shunt Obliteration

Uei Pua

Selective Internal Radiation Therapy of Hepatocellular Carcinoma: Potential Hepatopulmonary Shunt Reduction after Sorafenib Administration

Jens M. Theysohn, MD, Jörg F. Schlaak, MD, Stefan Müller, MD, Judith Ertle, MD, Thomas W. Schlosser, MD, Andreas Bockisch, MD, and Thomas C. Lauenstein, MD

Schiro BJ, et al. *Tech Vasc Interv Radiol.* 2019;22(2):58-62. Pua U. *CVIR.* 2015;38(5):1330-34.
Theysohn JM, et al. *JVIR*. 2012;23(7):949-952.

Methods to Reduce Lung Shunt

- External beam radiation to portal vein, hepatic vein, and/or IVC tumor thrombus
  - Retrospective study of 8 patients with HCC invasion into hepatic veins and/or IVC were treated with EBRT; all had acceptable lung shunt on mapping
  - 1 patient 35% prior to EBRT → 7% after EBRT
  - Mechanism of action: Due to RT-induced venous occlusive disease or fibrotic change
- Low-dose radioembolization
  - Achieve a dose <30 Gy
  - Segmental rather than lobar treatment

Hepatopulmonary shunt reduction using external beam radiation therapy prior to yttrium-90 radioembolization for HCC

L. Young[1], H. McGee[2], M. Buckstein[2], A. Fischman[2], R. Patel[2], N. Tabori[2], F. Nowakowski[2], R. Lookstein[2], E. Kim[2]; [1]Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA; [2]Icahn School of Medicine at Mount Sinai, New York, NY

Purpose: Yttrium-90 (Y-90) radioembolization is used to treat patients with advanced-stage hepatocellular carcinoma (HCC). High lung shunts (>30 Gy) preclude the safe use of radioembolization with Y-90 due to the risk of radiation pneumonitis. High lung shunt fractions have been shown to occur in patients with imaging findings of hepatic vein invasion and large tumor burden. External beam radiation (EBRT) has been successfully used with palliative intent in patients with portal vein and IVC tumor thrombus. We present our institutional experience with the use of EBRT to reduce suspected high lung shunt fractions in patients with HCC and gross vascular invasion prior to Y-90 radioembolization.
Materials: This is a retrospective analysis of eight patients from our institution treated between October 2010 and December 2015. Patients had a diagnosis of HCC with tumor extension into the hepatic veins and/or the IVC. Patients were male with a median age of 67 years. Based upon imaging findings, patients were presumed to have high lung shunts and were referred for EBRT prior to Y90 treatment with glass microspheres (TheraSphere, Ottawa, ON, Canada). Patients received EBRT using 6MV photons, to a total dose of 3000cGy in 10 fractions to the area surrounding vascular invasion. Within one to five months after EBRT, patients underwent MAA mapping of their hepatic vasculature and nuclear scan to determine lung shunt fraction.
Results: All eight patients had acceptable lung shunt fractions (<20%) on MAA mapping, post-EBRT. One patient had a lung shunt on MAA mapping of 35% prior to EBRT, which was reduced to 7.1% after EBRT. Patients underwent successful radioembolization with Y90 glass microspheres without serious adverse events. No complications of radiation pneumonitis occurred in any of the eight patients with a minimum duration of follow-up of three months.
Conclusions: High lung shunts exclude many HCC patients from receiving Y90 radioembolization. EBRT to areas of vascular invasion represents a potential treatment to reduce lung shunt fraction as a means to safely deliver Y-90. Further prospective investigation measuring lung shunts prior to and after EBRT needs to be undertaken to confirm these initial findings.

Young L, et al. *JVIR*. 2017;28(2):576.

Lung Shunt Reduction: TACE vs Y90

- HCC patients with high lung shunts were treated with TACE vs Y90 for lung shunt reduction
  - 10 patients underwent Y90
  - 7 patients underwent cTACE
  - Tc-MAA mapping study was done 1 month later
- Results
  - Y90 Group: LSF 13% → 20% (it was lower in 3 patients but higher in 7 patients)
  - TACE Group: LSF 26% → 8.7% (reduced in all patients)
- Conclusion: cTACE appears to be more effective in reducing LSF within 1 month compared to TARE

in vivo *35*: 2305-2312 (2021)
doi:10.21873/invivo.12504

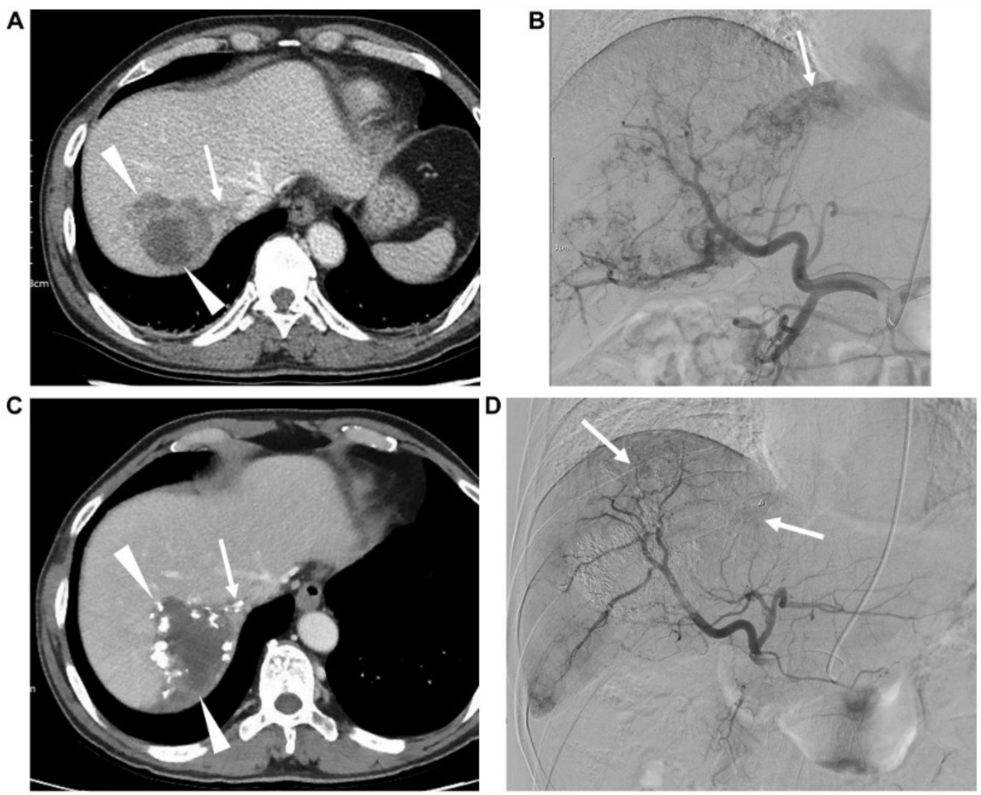
Lung Shunt Reduction for Yttrium-90 Radioembolization: Chemoembolization *Versus* Radioembolization

HYO-CHEOL KIM[1], JIN WOO CHOI[1], MYUNGSU LEE[1], YOON JUN KIM[2], JIN CHUL PAENG[3] and JIN WOOK CHUNG[1]

[1]Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea;
[2]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea;
[3]Department of Nuclear Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

Kim HC, et al. *In Vivo*. 2021;35(4):2305-2312.

Lung Shunt Reduction: TACE vs Y90



- 60 y/o Male with HCC with tumor thrombus in right hepatic vein
- Lung shunt was 63.3%
- Patient had cTACE and mapping study 5 wks later showed LSF of 7.7%

in vivo *35*: 2305-2312 (2021)
doi:10.21873/invivo.12504

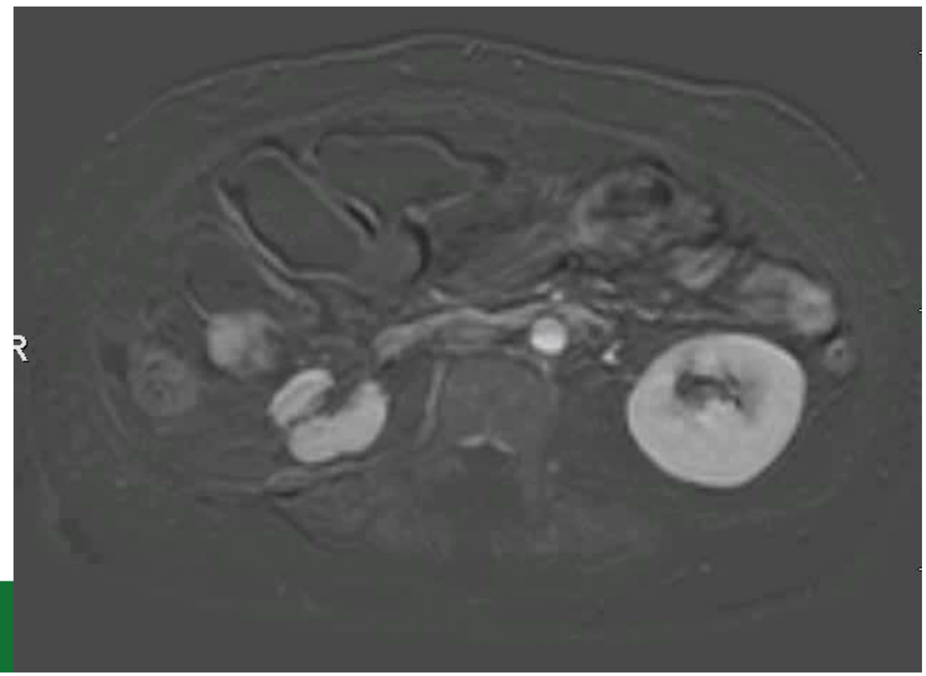
Lung Shunt Reduction for Yttrium-90 Radioembolization: Chemoembolization *Versus* Radioembolization

HYO-CHEOL KIM[1], JIN WOO CHOI[1], MYUNGSU LEE[1], YOON JUN KIM[2], JIN CHUL PAENG[3] and JIN WOOK CHUNG[1]

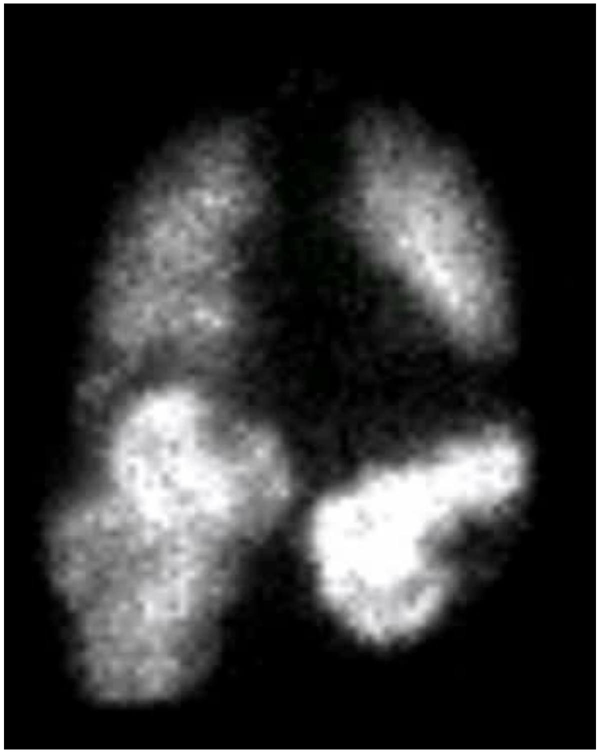
[1]Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Department of Nuclear Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

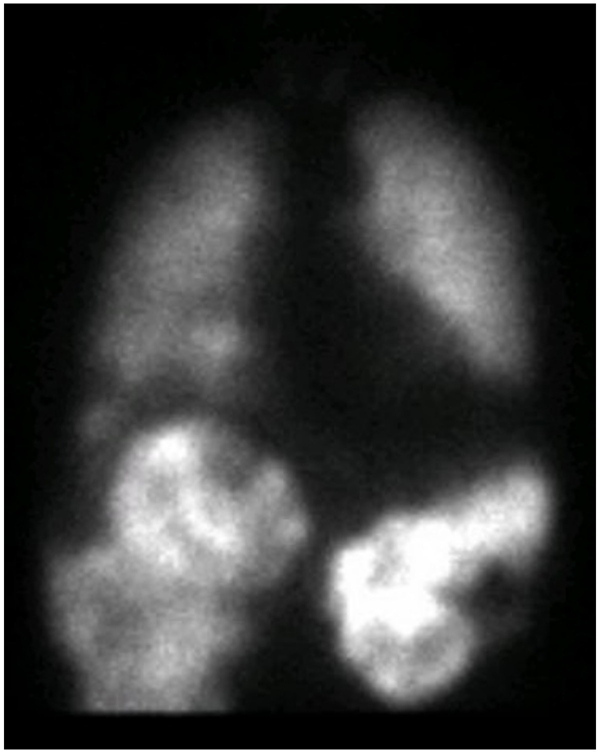
Initial Presentation

- 61 y/o Female with history of hepatitis C with hepatocellular carcinoma
- Patient initially presented with a subcapsular hemorrhage from a bleeding HCC
- She had 1 prior TACE at OSH 3 months prior
- ECOG performance status 0
- Liver function tests are normal
- AFP 24,657 (AFP prior to TACE 26,333)



Pre-Y90 Mapping Angiogram

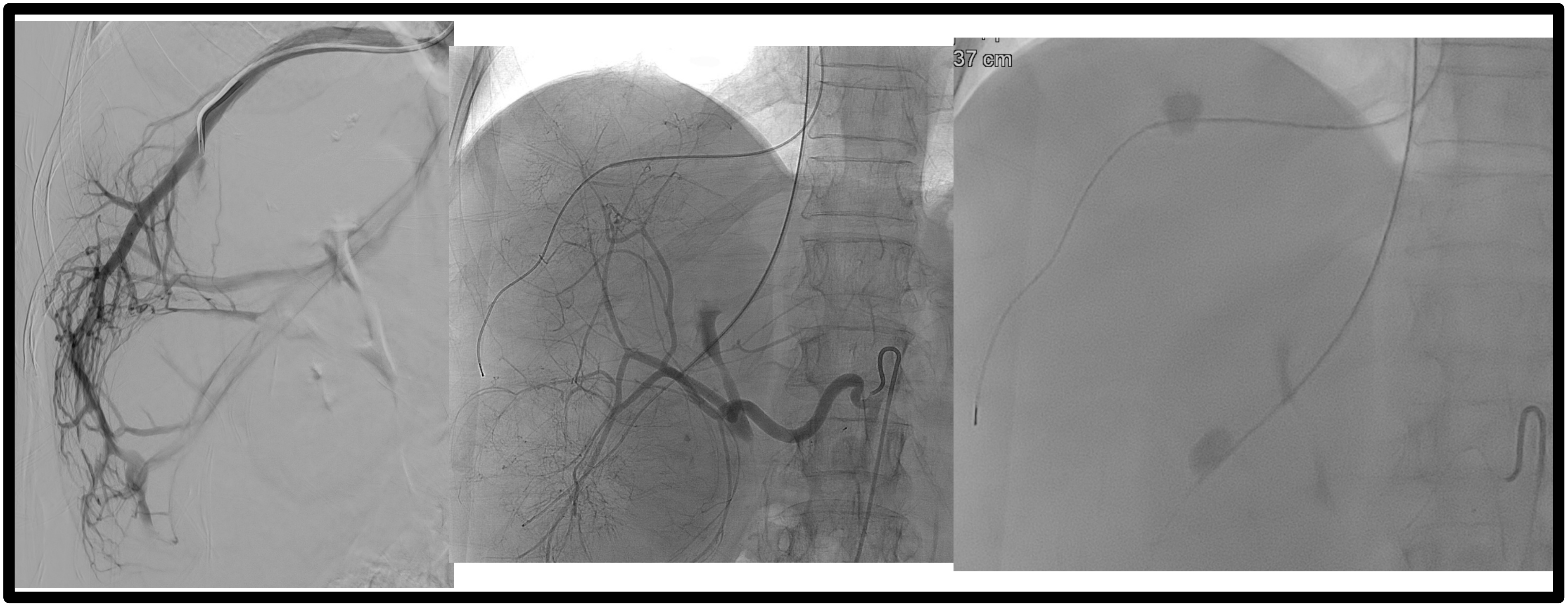




Lung Shunt 26% (>30 Gray to lungs per calculation)

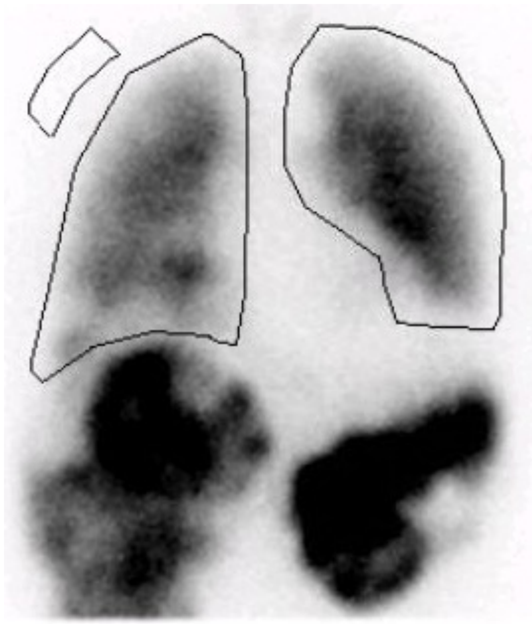
Methods to Reduce Lung Shunt

Hepatic vein balloon occlusion



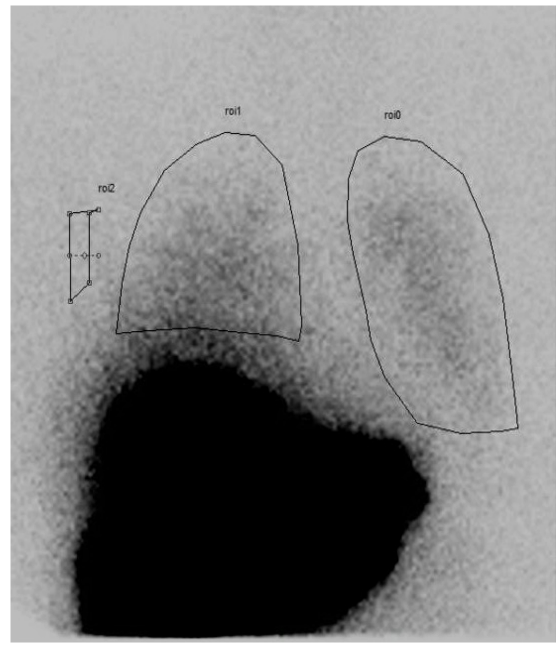
Lung Shunt

Before hepatic vein occlusion balloon



26%

After hepatic vein occlusion balloon



8%

Reduction of Arteriohepatovenous Shunting by Temporary Balloon Occlusion in Patients Undergoing Radioembolization

Lourens Bester, MD, and Riad Salem, MD, MBA

Radioembolization with yttrium-90 resin microspheres is a treatment option that selectively targets hepatic tumors. One of the primary limiting factors for this therapy is the degree of arteriohepatovenous shunting, as excessive radiation to the lungs may cause radiation pneumonitis. To safeguard patients against this, a technetium Tc 99m macroaggregated albumin scan is performed before treatment to assess the degree of arteriohepatovenous shunting. As lung shunt fraction increases, activity reductions are mandated, with a 20% shunt sufficient to prohibit treatment. Temporary occlusion of shunts may be achieved by placement of balloon catheters in the hepatic veins. This endovascular technique used to reduce arteriohepatovenous shunting allows otherwise untreatable patients to undergo radioembolization.

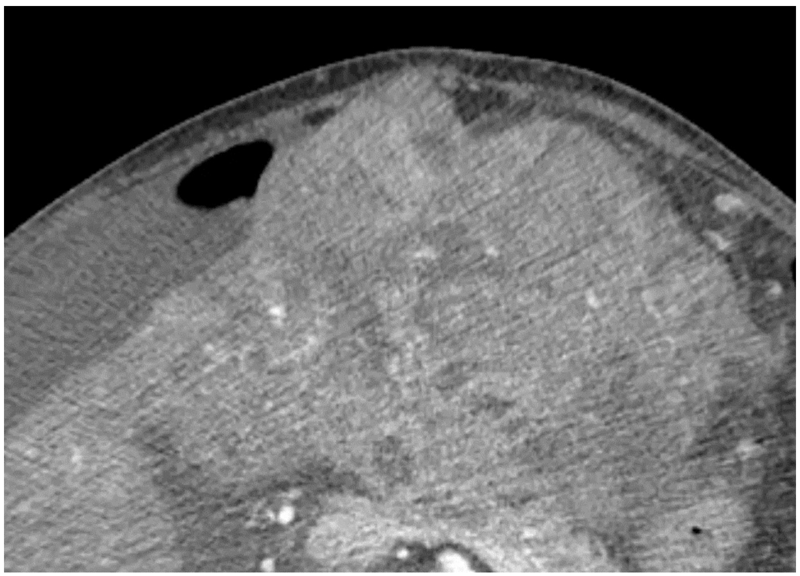
J Vasc Interv Radiol 2007; 18:1310–1314

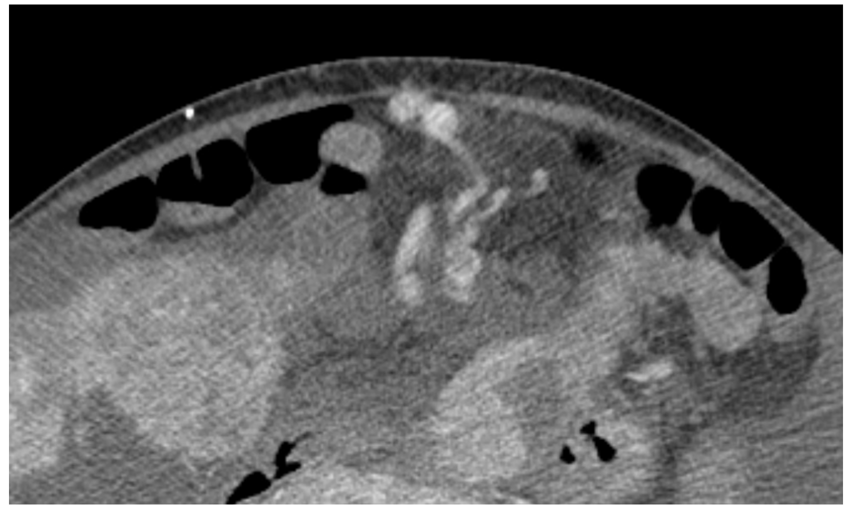
Abbreviations: MAA = macroaggregated albumin, SPECT = single-photon emission computed tomography

	Lung Shunt Tc-MAA	Bremsstrahlung after balloon occlusion
Patient 1	28.7%	5.8%
Patient 2	27%	<2%
Patient 3	25%	<2%

Methods to Reduce Lung Shunt

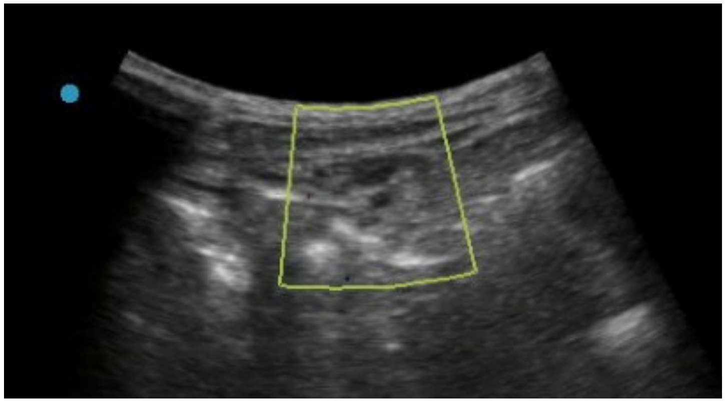
- Collateral vein embolization
  - Paraumbilical veins

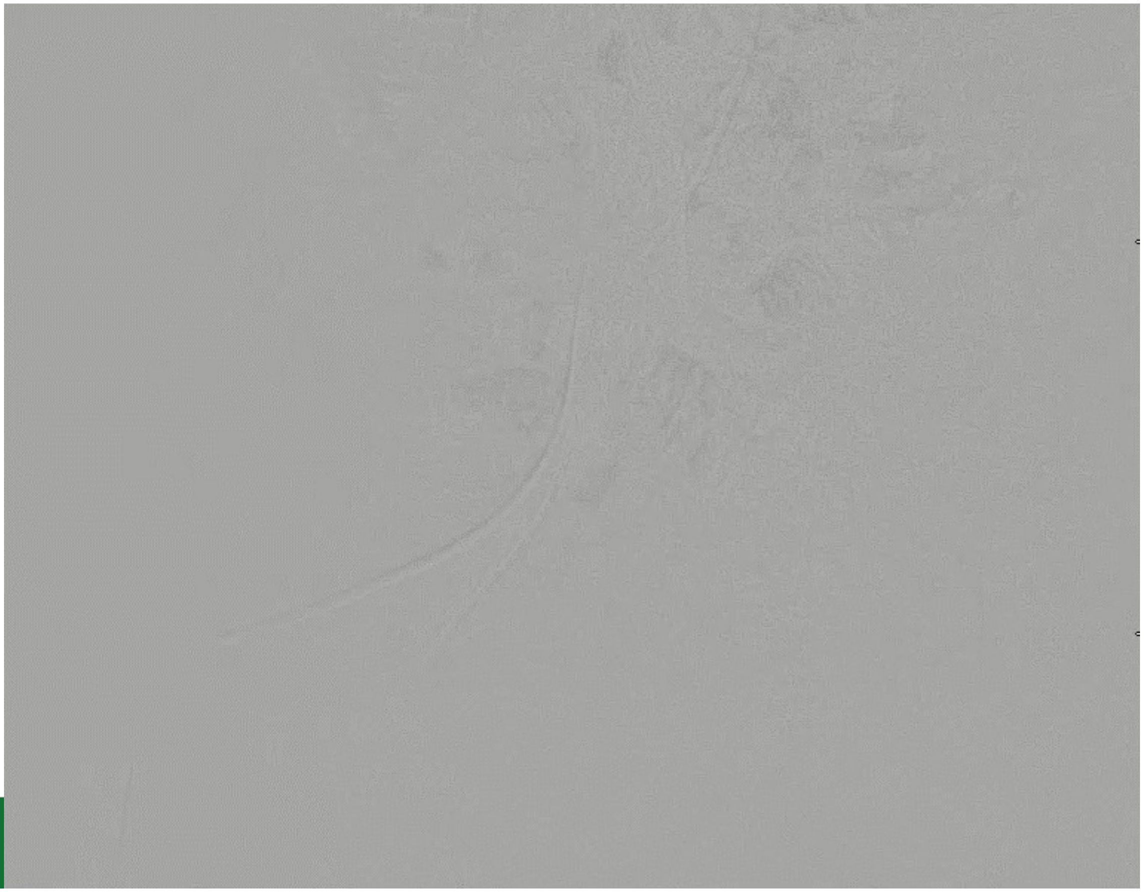




Methods to Reduce Lung Shunt

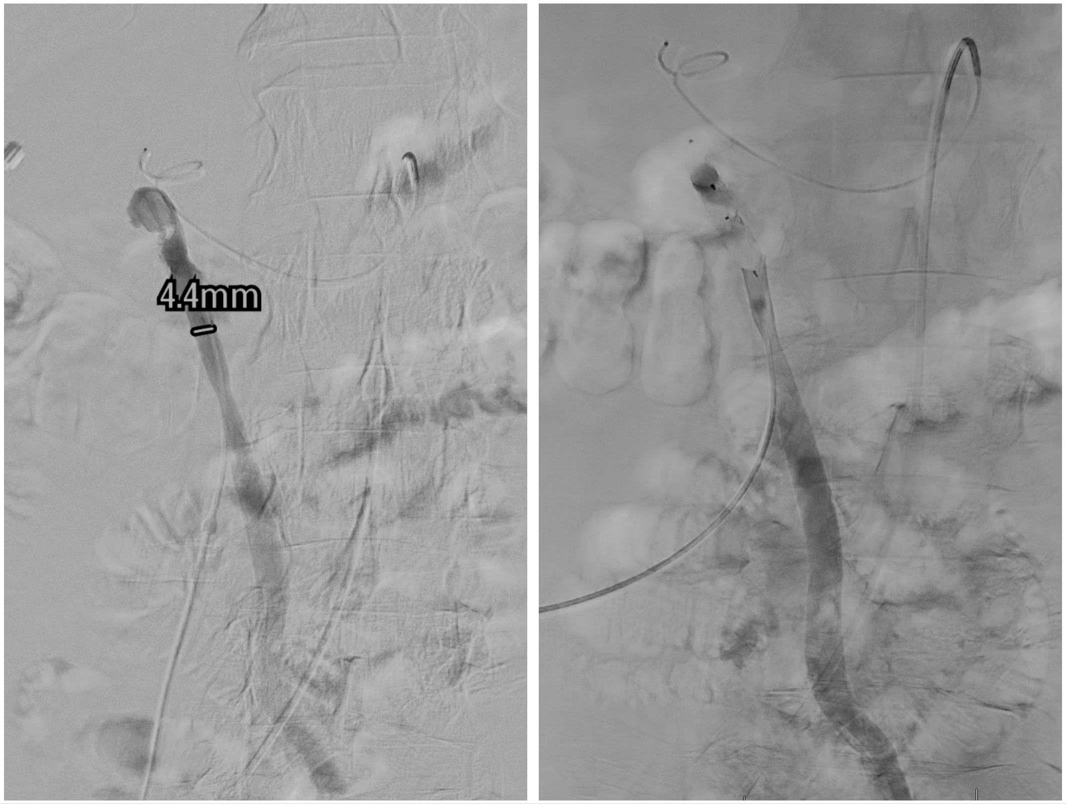
- Collateral vein embolization
  - Paraumbilical veins
  - Direct percutaneous access





Methods to Reduce Lung Shunt

- Umbilical vein embolization successfully decreased lung shunt to allow for successful Y90



Conclusions

- Patients with high lung shunts tend to have a worse prognosis
- High hepatopulmonary shunt is a relative contraindication for Y90
- Focus should be on the total Y90 dose administered to the lungs
    - >30 Gy single treatment
    - >50 Gy lifetime dose
- Multiple techniques are available to reduce lung shunt
    - – Dose reduction should be the initial attempt as long as can maintain a therapeutic dose to the tumor

Various Chemo Agents that You Will Encounter

Zach Berman, MD

Associate Professor at Clinical Radiology
UC San Diego

CiO

The goal of this talk is to look at the different chemotherapeutics you might see combined with TARE. To do this, we will discuss:

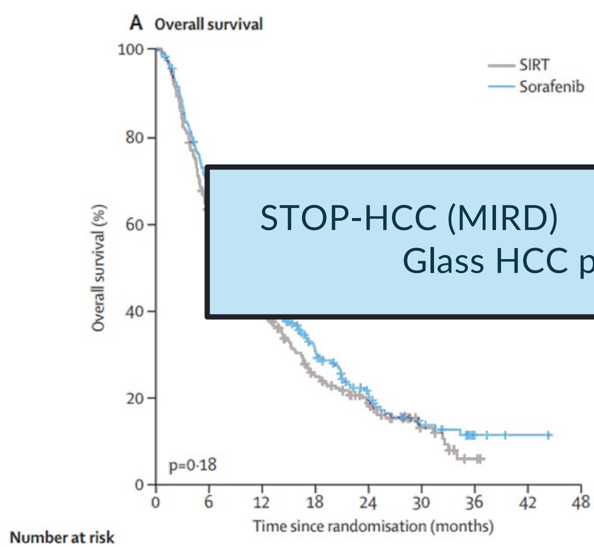
- Safety of combination of TARE and systemic therapies
- Efficacy of systemic therapeutics that positively affect TARE
- The future of systemic modulation of TARE

Part 1: Is it safe to combine?

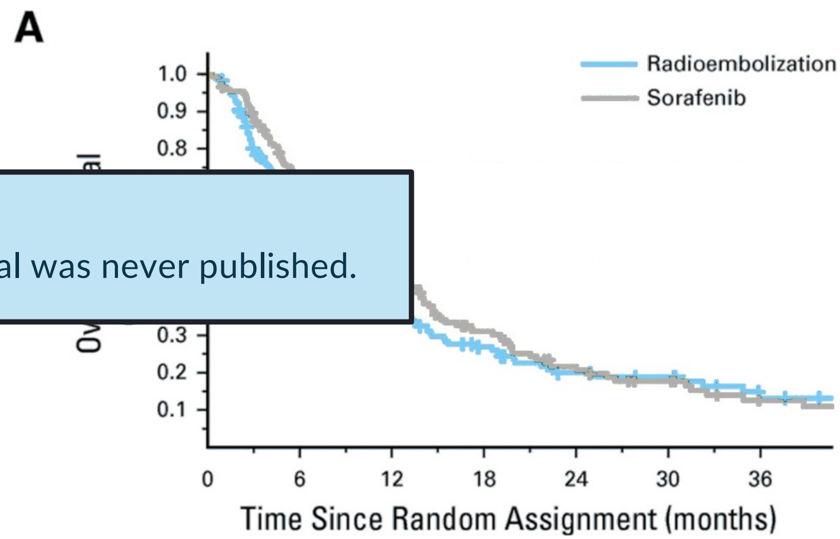
At least three phase 3 trials have shown safety of both glass and resin Y90 with TKIs

SARAH Trial (BSA)
Resin Y90 vs Sorafenib (median OS **~9 mo**)

SIRveNIB Trial (BSA)
Resin Y90 vs Sorafenib (median OS **~9 mo**)



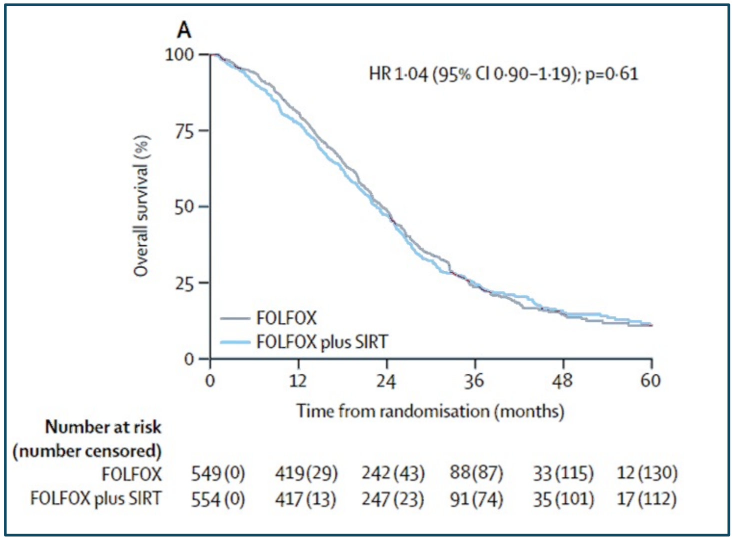
STOP-HCC (MIRD)
Glass HCC phase 3 trial was never published.



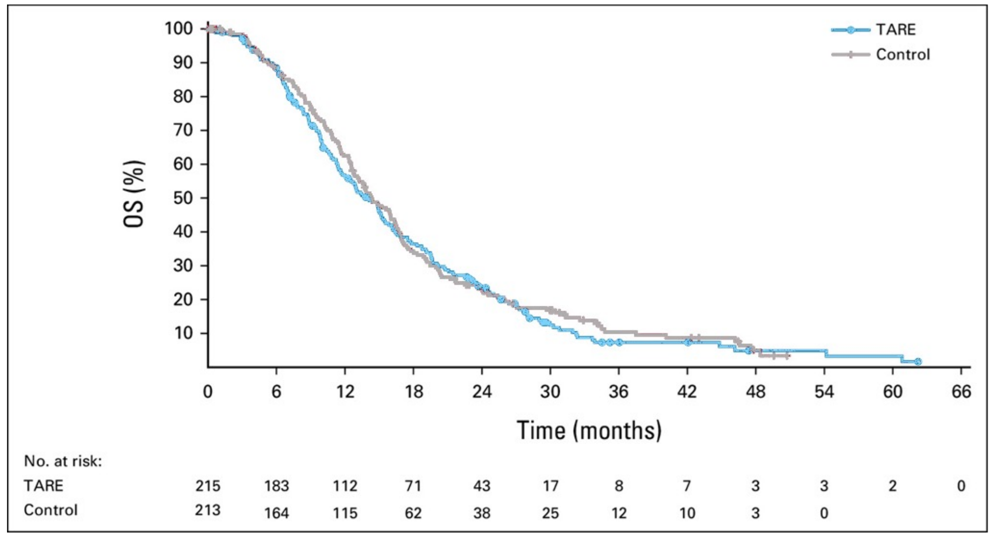
Vilgrain V, et al. *The Lancet Oncol*. 2017;18:12. Chow, Pierce KH, et al. *JCO*. 2018;36(19) :1913-1921.

Similar phase 3 trials have shown safety of both glass and resin Y90 with Ox/Iri/5FU based therapy

SIRFLOX, FOXFIRE, FOXFIRE Global (Resin)



EPOCH (Glass)



*Technically positive with PFS/hPFS as primary endpoints; but hasn't moved the needle without OS

Wasan Harpreet S, et al. *The Lancet Oncol*. 2017;18:9. Mulcahy M, et al. *JCO*. 2021;39(35):3897-3907.

The actual indication of resin microspheres is with infusion 5FU!

Randomised trial of SIR-Spheres® plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer

B. Gray, G. Van Hazel, M. Hope, M. Burton, P. Moroz, J. Anderson, V. Gebski

Royal Perth Hospital, Sir Charles Gairdner Hospital, University of Western Australia, Australia

74 pts. Hepatic artery infusion pump +/- SIRT

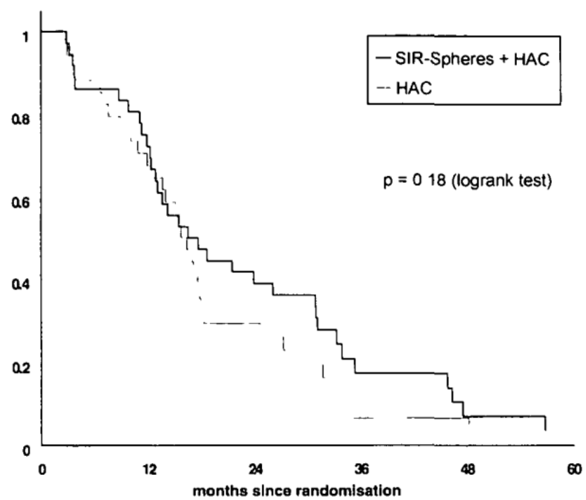


Table 3. Survival rates per year.

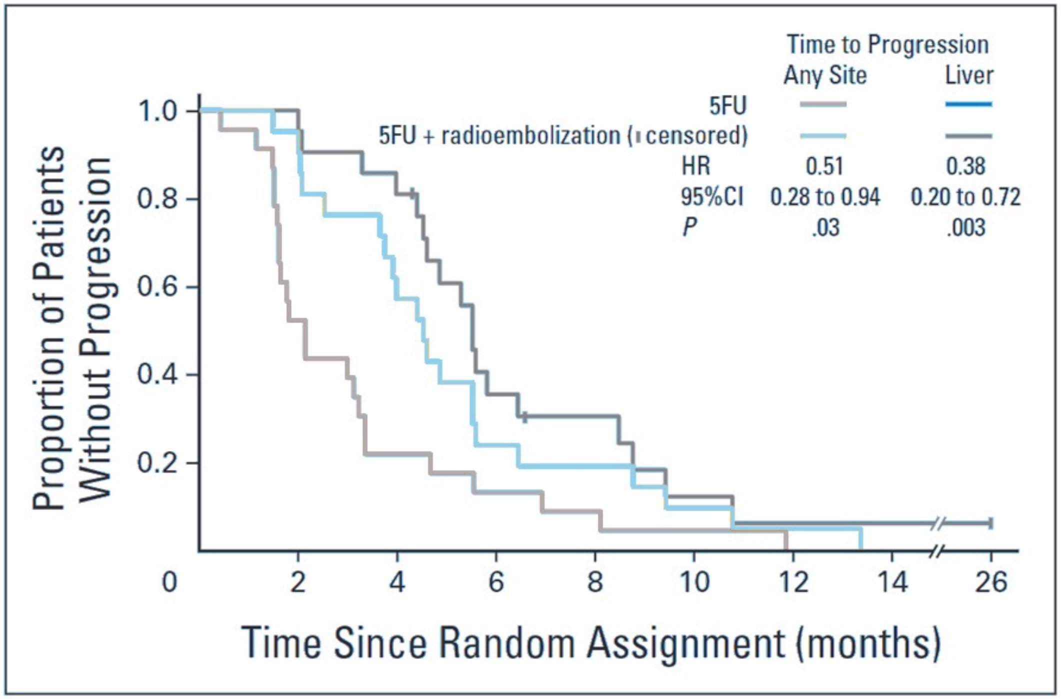
	HAC	SIRT + HAC
1 year	68%	72%
2 years	29%	39%
3 years	6%	17%
5 years	0%	3.5%

Gray B, et al. *Ann Oncol*. 2001;12(12):1711-1720.

Part 2: Does it work?

And there is a long history of the safety of Y90 RE with 5FU

Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy

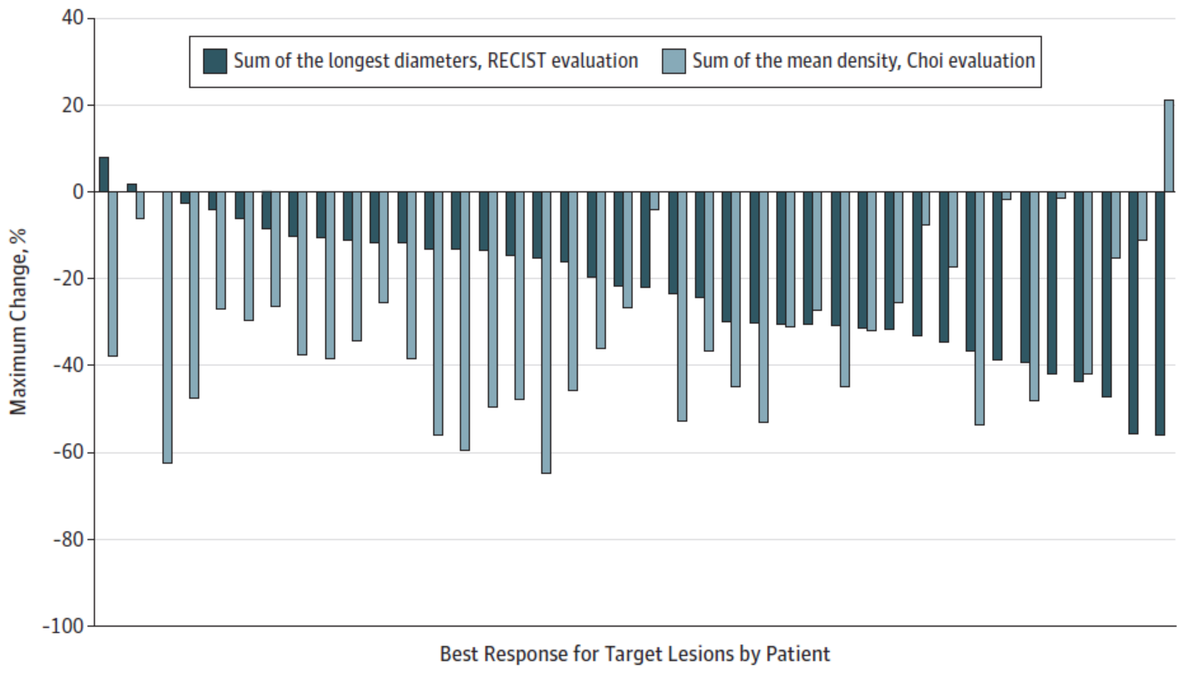


Hendlisz A, et al. *J Clin Oncol* . 2010;28(23):3687-3694.

Beyond CRC and HCC, safety has been shown with Cholangiocarcinoma

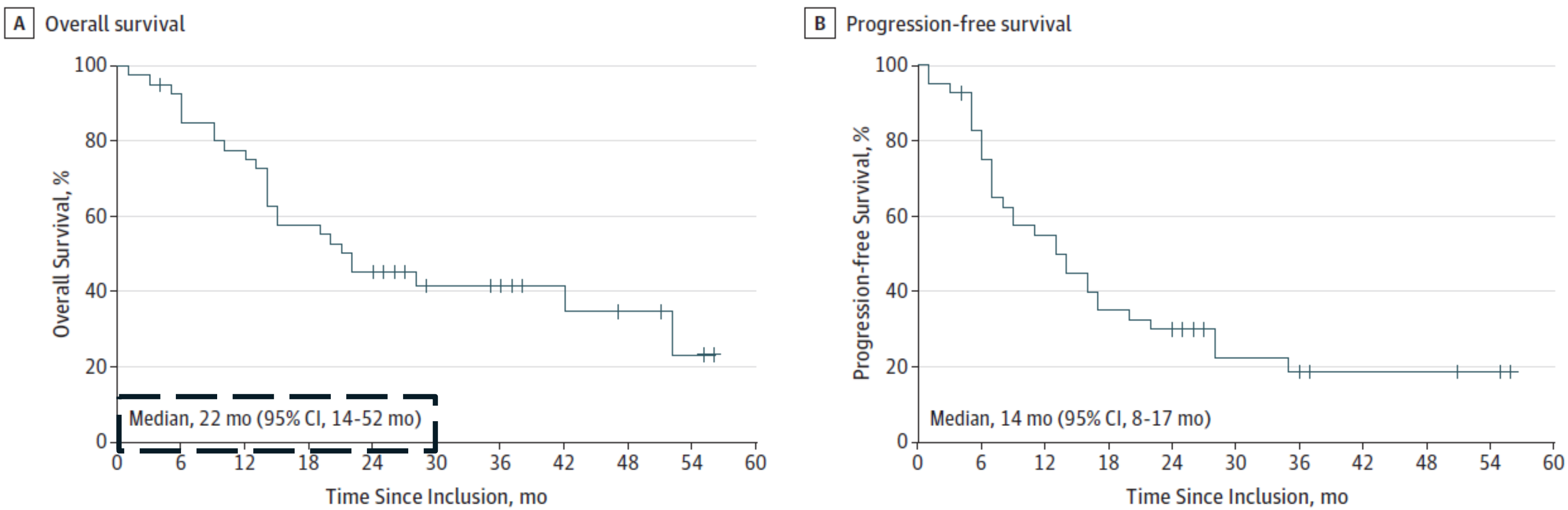
Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma

"MISPHEC" Trial
7 center trial in France | 41 patients
Glass Y90 followed by GemCis



Edeline J, et al. *JAMA Onc*. 2020;6(1):51-59.

GEMCIS + Y90 has a higher numerical OS than other trials (eg, ABC-03)



9 of 46 (20%) were able to get resection (previously not felt to be resectable)

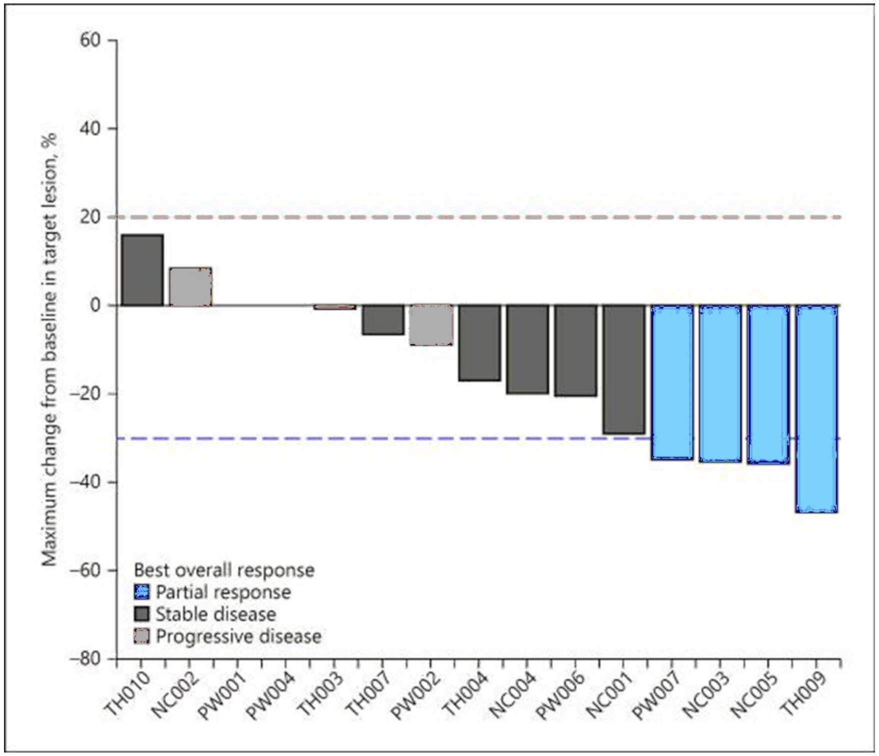
Edeline J, et al. *JAMA Onc*. 2020;6(1):51-59.

Which is reproducible: resin showed very similar efficacy

3 Asian centers
- 24 patients (Phase 2)
- Resin SIRT (personalized dose of 120 Gy to tumor)
- GemCis as background systemic chemotherapy

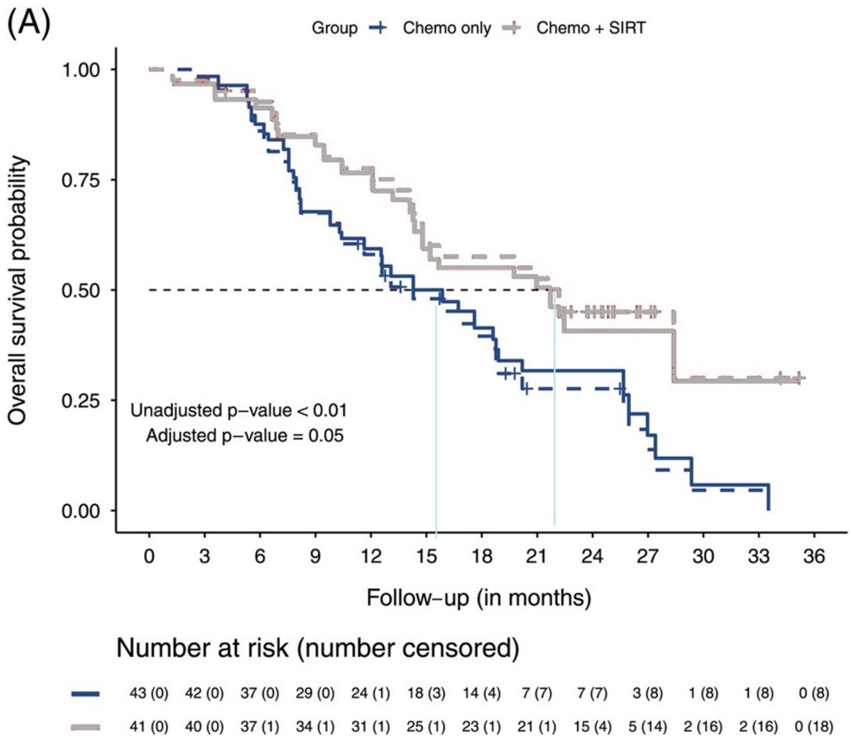
PFS 9 mo (vs 6.6 mo w/o SIRT)

mOS 22 mo (vs 13.6 mo w/o SIRT)



Chan, et al. *Liver Cancer*. 2022.

Efficacy of combination therapy is consistent over multiple prospective trials



Study population	HR
CISGEM + SIRT vs. CISGEM or GEMOX (population 2)	
OS	0.59 [0.34; 0.99]
PFS	0.52 [0.31; 0.89]

Chemotherapy with or without selective internal radiation therapy for intrahepatic cholangiocarcinoma: Data from clinical trials. Edeline, et al. 2024.

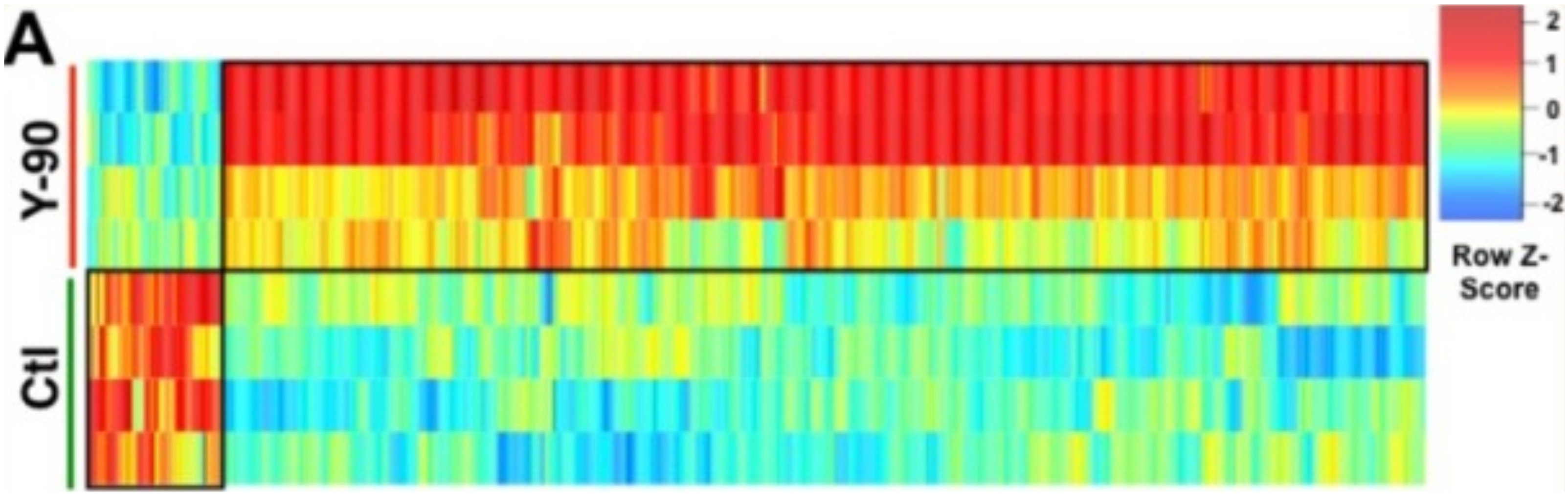
Early Evidence is also seen in NETs for combination therapy

- Everolimus + Y90 (Kim HS, et al. Cancer Published Online: February 16, 2018. (doi:10.1002/cncr.31192).
  - 46% response rate
  - PFS 18.6 mo
  - mOS 46.3 mo
  - N=13
- Capecitabine and temozolomide followed by Y90 (Soulen MC et al. Pancreas 2018; 47: 980–984.)
  - ORR 74%
  - hPFS 42.5 mo
  - mOS 41 mo from tx, 106 mo from dx
  - N = 19

Ongoing phase 2 trial looking directly into this (N=50)

Radioembolization in combination with immunotherapy for HCC shows promise

Y90 changes the immune microenvironment compared to controls



Chew V, et al. *Gut*. 2019;68(2):335-346.

Radioembolization in combination with immunotherapy for HCC shows promise

SOLID (N=24)

- TARE + durvalumab
- Locally ad
  (BCLC B o
- ORR 83% (CR 29%), DCR was 91.0%
- mPFS was 6.9 months
- **mOS was not reached at 24 mo**

Y90 + pembro (N=27)

- TARE + pembrolizumab
- ment,
  and/or
  diffuse disease
- ORR 31%, DCR was 84.6%
- mPFS was 10 months
- **mOS was 27.3 mo**

Numerous ongoing phase 2 trials
(eg, ROWAN and EMERALD-Y90) (N=100)

Lee, et al. *Clin Cancer*. 2023. Yu, et al Oncologist. 2024

The goal of this talk was to look at the different chemotherapeutics you might see combined with TARE:

- Safety of combination of TARE and systemic therapies
- Efficacy of systemic therapeutics that positively affect TARE
- The future of systemic modulation of TARE

Tumor Board / MDT– How do I position Y90 as a treatment option?

Ghassan El-Haddad, MD
Vice Chair, Radiopharmaceutical and Nuclear Oncology
Senior Member, Interventional Radiology

Moffitt Cancer Center and Research Institute
Tampa, FL

Positioning Y-90 in the Treatment Algorithm

- **Curative intent**
  - Radiation segmentectomy/lobectomy Unresectable/unablatable HCC
  - Downstaging/bridge to transplant
- **Palliative**
  - Intermediate stage HCC
  - Cholangiocarcinoma
  - Liver dominant metastases (colorectal cancer, NET, …)

POSITIONING Y-90 RADIOEMBOLIZATION IN LIVER CANCER MANAGEMENT

- **Multidisciplinary Approach**
- Collaboration:
  - Oncologists
  - Surgeons
  - Hepatologists
  - interventional radiologists, pathologists
  - radiologists/nuclear medicine physicians

- **Patient Selection and Outcomes**
- Preserved liver function
- ECOG 0-2
- Favorable vascular anatomy
- No significant hepatopulmonary shunt
- Tumor burden <70% of liver volume

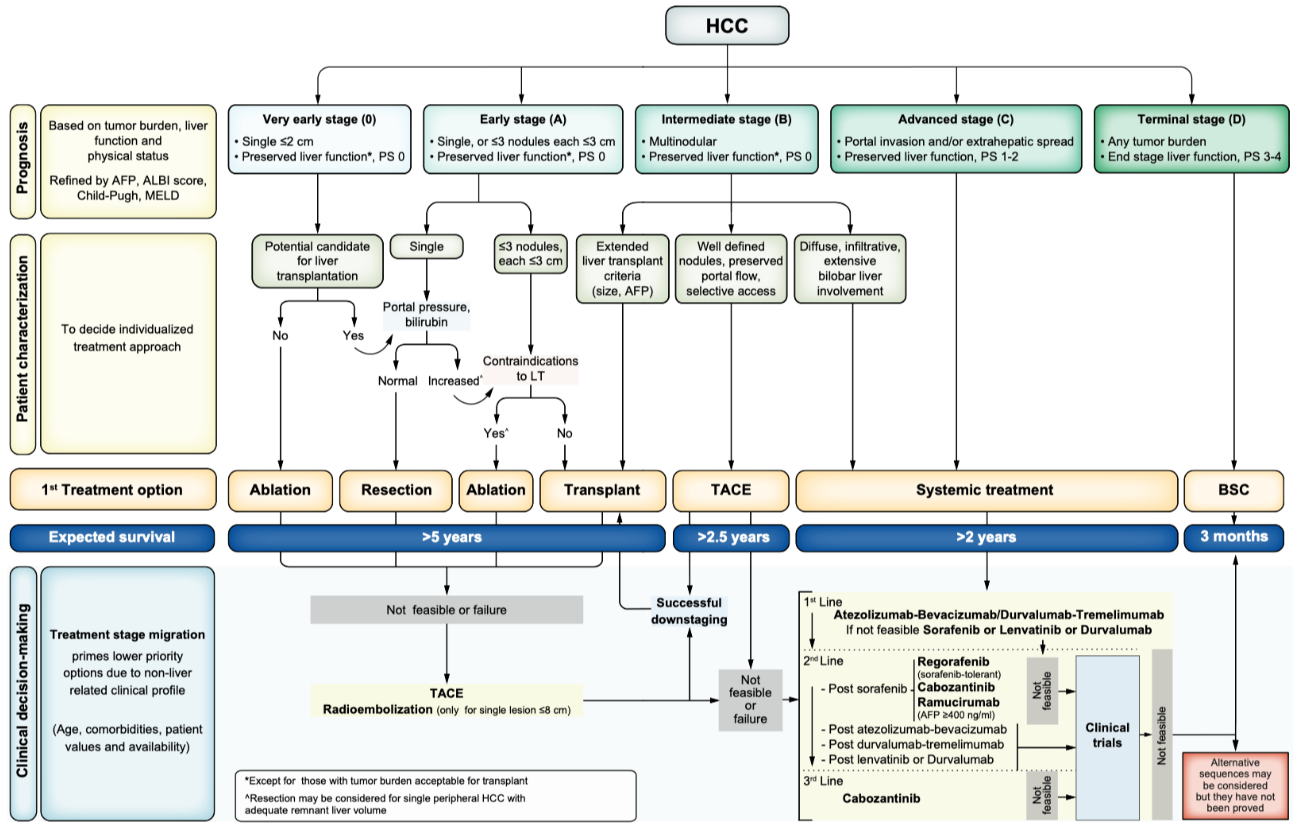


Fig. 1. BCLC staging and treatment strategy in 2022. The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. Individualised clinical decision-making, according to the available data on November 15, 2021, is defined by teams responsible for integrating all available data with the individual patient's medical profile. Note that liver function should be evaluated beyond the conventional Child-Pugh staging. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG-PS, Eastern Cooperative Oncology Group-performance status; LT, liver transplantation; MELD, model of end-stage liver disease; TACE, transarterial chemoembolisation.

Reig M, et al. Journal of Hepatology 2022 vol. 76, 681–693

The LEGACY Study

- Multi-center, single-arm, retrospective study conducted at 3 U.S. sites
- Median follow-up was 29.9 months
  Median dose to perfused liver volume of 410 Gy
- Primary endpoints met:
  - ORR 72.2% (117/162) by mRECIST
  - DURATION OR RESPONSE (>6MONTHS) : 76.1% (89/117)
- 100% of patients achieved CR or PR (localized mRECIST)
- 93% overall survival rate in patients with transplant (21% 34/162) or resection (6.8% 11/162) following TheraSphere at 3 years

KEY BASELINE CHARACTERISTICS (N=162)	% of patients		
Median Age: 66 years	≥ 75 years: **17.9**	BCLC A: **60.5**	BCLC C: **39.5**
Median Tumor Size: **2.6 cm (0.9-8.1 cm)**			

CIO

Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, Fowers K, Lewandowski R, Padia SA. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable Hepatocellular Carcinoma: The LEGACY Study. Hepatology. 2021 Mar 19. doi: 10.1002/hep.31819.

Long-Term Overall Survival After Selective Internal Radiation Therapy for Locally Advanced Hepatocellular Carcinomas: Updated Analysis of DOSISPHERE-01 Trial

Etienne Garin[1,2], Lambros Tselikas[3], Boris Guiu[4], Julia Chalaye[5], Yan Rolland[1,6], Thierry de Baere[3], Eric Assenat[4], Vania Tacher[5], Xavier Palard[1], Desirée Déandreis[3], Denis Mariano-Goulart[4], Giuliana Amaddeo[5], Karim Boudjema[7], Antoine Hollebecque[3], Mohamad Azhar Meerun[4], Helen Regnault[5], Eric Vibert[8], Boris Campillo-Gimenez[1,6], and Julien Edeline[1,9]

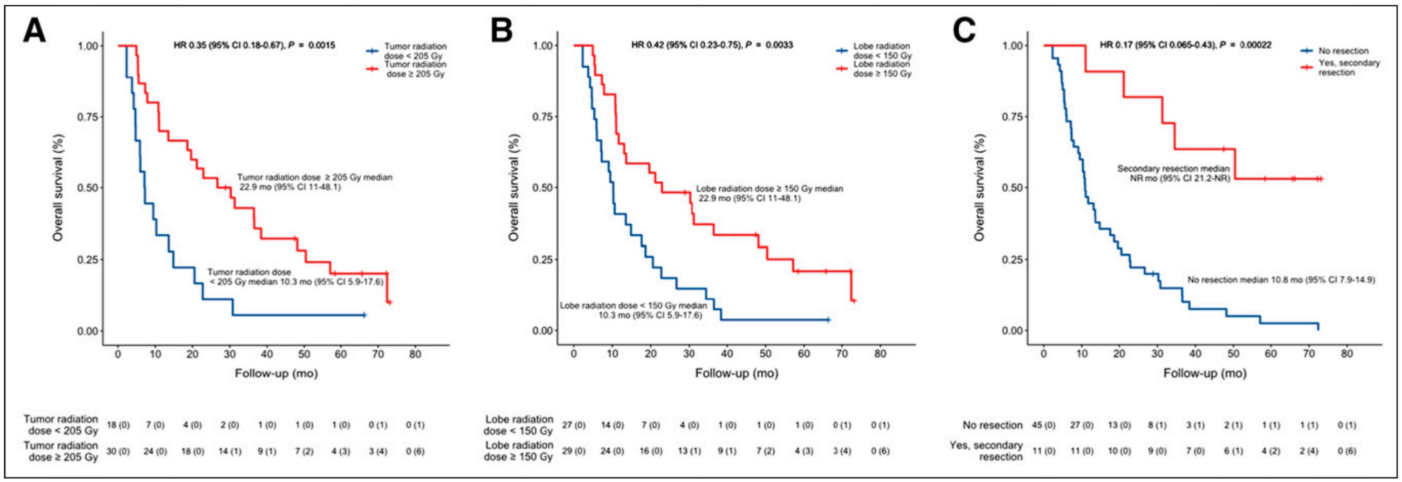


FIGURE 3. Median OS based on group of interest: TD (A), PLD (B), and secondary resection status (C). NR = not reached.

TABLE 1
Summary of Main Demographic and Baseline Characteristics of Patients in Modified Intent-to-Treat Population

Characteristic	PDA (*n* = 28)	SDA (*n* = 28)
Age (y)	64.8 ± 10.1	62.5 ± 63.7
Child classification		
A5	22 (78.6%)	22 (78.6%)
A6/B7	6 (21.4%)	6 (21.4%)
ECOG performance status		
0	16 (57.1%)	13 (46.4%)
1	12 (42.9%)	15 (53.6%)
BCLC classification		
B	3 (10.7%)	2 (7.1%)
C	25 (89.3%)	26 (92.9%)
Portal vein invasion		
Present	18 (64.3%)	21 (75%)
Absent	10 (35.7%)	7 (25%)
Cirrhosis etiology		
Alcohol	9 (32.1%)	9 (32.1%)
Viral hepatitis	7 (25%)	9 (32.1%)
Hemochromatosis	1 (3.6%)	0
NASH	3 (10.7%)	3 (10.7%)
Mixture (alcohol + other)	4 (14.3%)	3 (10.7%)
No cirrhosis	4 (14.3%)	4 (14.3%)
Tumor size (cm)	10.54 ± 2.43	10.92 ± 2.57

ECOG = Eastern Cooperative Oncology Group; BCLC = Barcelona Clinic of Liver Cancer; NASH = nonalcoholic steatohepatitis.

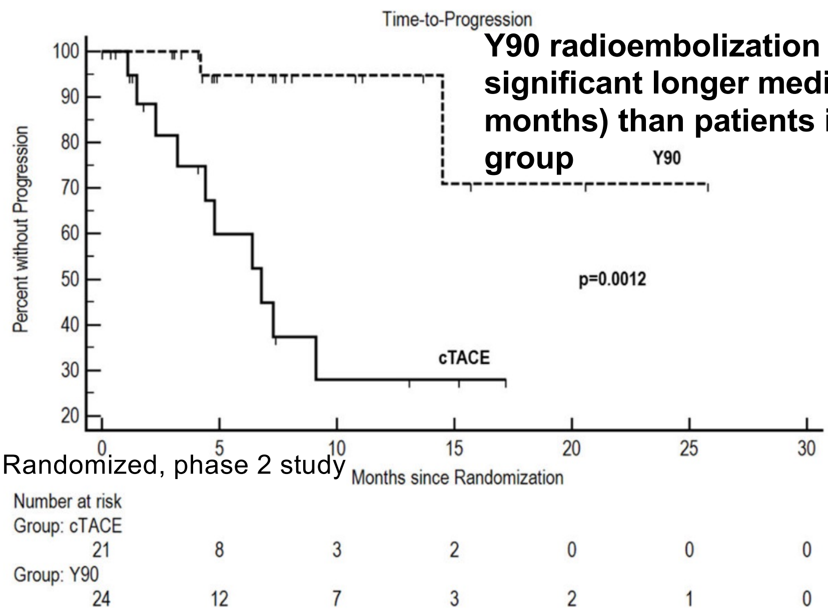
Qualitative data are number and percentage; continuous data are mean ± SD.

Garin E et al. J Nucl Med. 2024 Feb 1;65(2):264-269.

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 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]

Y90 radioembolization group had significant longer median TTP (>26 months) than patients in the cTACE group



Randomized, phase 2 study

Figure 2.
Time-to-progression.

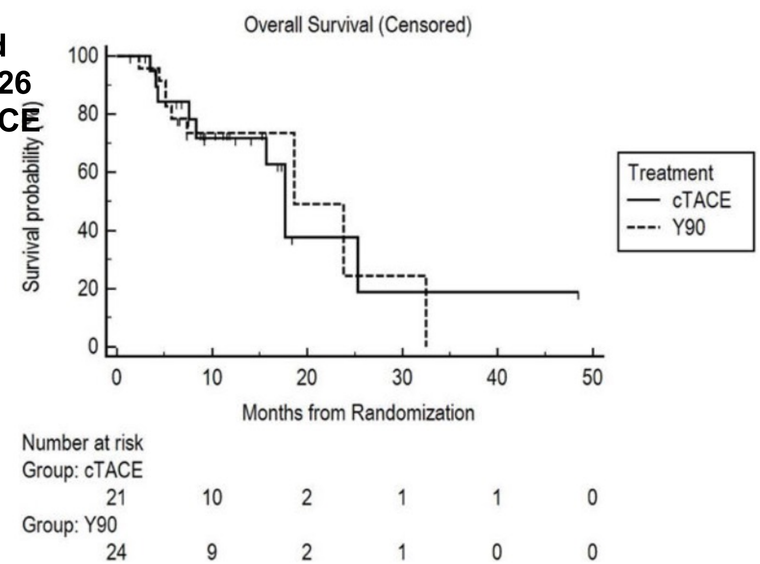


Figure 4.
Overall survival from randomization censored to liver transplantation.

Salem R et al. Gastroenterology. 2016 Dec;151(6):1155-1163.

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

- TARE: 120 Gy
- DEB-TACE: doxorubicin DEBs sized 100–300 micron 300–500 micron, max doxorubicin dose of 150 mg per session.

Early to Intermediate stage HCC

Table 2: Treatment Data in the Safety Group

Treatment Parameter of Interest		
Time from randomization to first t		
Treatment sessions per participant		
1		
2		
3		
4		
5		
Median		
No. of participants with a lesion tr		
Target lesion 1		
Target lesion 2		
Nontarget lesions		
Time interval between treatment s		
Total treatment period (d)[‡]		
Approach		
Unilobar		
Bilobar		
Treatment approach		
Selective		
Lobar		
Near whole liver	7	4
Whole liver	9	0

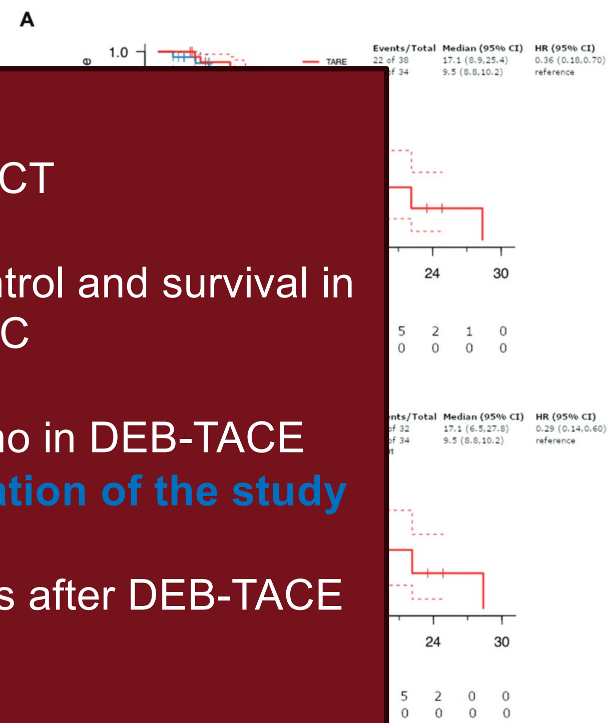
TRACE: Prospective phase II RCT

Y90 TARE superior to DEB-TACE for tumor control and survival in nonsurgical BCLC A and B HCC

TARE median TTP 17.1 mo (n = 38) vs 9.5 mo in DEB-TACE ([HR], 0.36; P = .002), **justifying early termination of the study**

Median OS 30.2 mo after TARE vs 15.6 months after DEB-TACE (HR, 0.48; P = .006)

A



...lization versus Chemoembolization for the ... transarterial radioembolization (TARE) or drug-eluting bead (DEB) transarterial chemoembolization (TACE). Kaplan-Meier plots show time to overall tumor progression in **(A)** the intention-to-treat group and **(B)** the per-protocol group. P values were calculated by using the log-rank test. Dashed lines indicate 95% CIs. HR = hazard ratio.

Dhondt E, et al. Radiology 2022; 303:699–710

Unresectable intrahepatic cholangiocarcinoma

MISPHEC Trial (JAMA Oncology, 2019)

- **Design**: Phase 2 trial combining Y-90 radioembolization with chemotherapy (cisplatin + gemcitabine).
- **Population**: 41 patients with unresectable ICC.
- **Outcomes**:
  - **Response rate**: 39%.
  - **Downstaging to surgery**: 22%.
  - **Median progression-free survival (PFS)**: 14 months.
  - **Median overall survival (OS)**: 22 months.
- **Conclusion**: Y-90 + chemotherapy is effective for downstaging and improving survival.

Edeline J, et al. *JAMA Oncol.* 2020;6(1):51–59.

CIO

Radioembolization with Yttrium-90 Glass Microspheres as a First-Line Treatment for Unresectable Intrahepatic Cholangiocarcinoma-A Prospective Feasibility Study

Prospective

Participants: 24 patients (mean age 72.3 years; 50% female).

Tumor characteristics:

- Solitary: 16 patients.
- Multifocal: 8 patients.
- Unilobar: 14 patients.
- Bilobar: 10 patients.

Median radiation dose: 135.5 Gy

- **HPFS**: Median 5.5 months.
- **OS**: Median 19.4 months.
  - **Solitary tumors**: OS 25.9 months.
  - **Multifocal tumors**: OS 10.7 months (**P = .02**).
- **Imaging-based prognosis**:
  - Patients with stable disease at 3 months had significantly longer OS (37.3 months) vs. those with progression (10.7 months) (**P = .003**).
- **Toxicity**: Two Grade 3 events (8%); overall well-tolerated.

Kis B, et al. J Vasc Interv Radiol. 2023 Sep;34(9):1547-1555.

Yttrium90-TARE with or without chemotherapy may improve survival in patients with locally advanced unresectable intrahepatic cholangiocarcinoma

- **Design**: Retrospective study:
- Chemotherapy alone.
- Chemotherapy + Y-90.
- Y-90 alone.
- **Findings**: **Downstaging to resection**: ~36–37% in Y-90 groups vs. 4% in chemo-only.
- **Median OS**: 13.9 (chemo), 19.6 (chemo+Y-90), 24.2 months (Y-90 only).
- **Conclusion**: Not statistically significant in the adjusted model, in univariate analysis patients with unresectable iCCA who received Y90-TARE in their treatment plan experienced better survival outcomes compared to those treated with chemo-only

Garita E, etal. Discov Oncol. 2025 Jul 22;16(1):1386.

Colorectal Cancer

EPOCH Trial (Phase III, Multicenter)

- **Design**: Randomized trial comparing second-line chemotherapy alone vs. chemotherapy + Y-90 TARE.
- **Population**: Patients with CRLM who progressed on first-line chemotherapy.
- **Outcomes**:
  - **Progression-Free Survival (PFS)**: 8.0 months (TARE) vs. 7.2 months (control).
  - **Hepatic PFS (hPFS)**: 9.1 vs. 7.2 months.
  - **Overall Survival (OS)**: No significant difference (14.0 vs. 14.4 months).
  - **Objective Response Rate (ORR)**: 34% (TARE) vs. 21.1% (control).
- **Conclusion**: TARE improves local control but not OS in unselected patients.

Mulcahy MF, et al. J Clin Oncol. 2021 Dec 10;39(35):3897-3907.

RESIN Registry (Multicenter Prospective Study)

- **Participants**: 498 patients across 42 institutions.
- **Treatment Lines**:
  - First-line: 13.9 months OS.
  - Second-line: 17.4 months OS.
  - Third-line: 12.5 months OS.
- **PFS**: 7.4 months overall.
- **Toxicity**: Grade ≥3 in 23% at 6 months, mostly liver-related.
- **Conclusion**: TARE is effective as second-line therapy, with manageable toxicity.

Emmons EC, et al. Radiology. 2022 Oct;305(1):228-236.

Neuroendocrine Tumors

Ki67 score as a potential predictor in the selection of liver-directed therapies for metastatic neuroendocrine tumors: a single institutional experience

Smit Singla[1], Charles M. LeVea[2], Venkata K. Pokuri[3], Kristopher M. Attwood[4], Michael M. Wach[1], Garin M. Tomaszewski[5], Boris Kuvshinoff[4], Renuka Iyer[3]

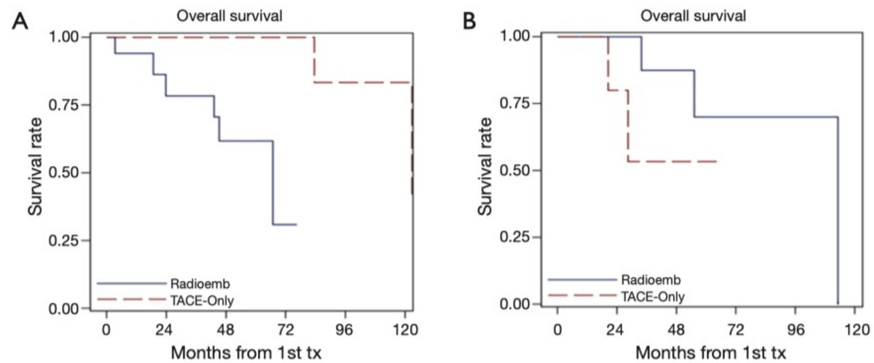


Figure 2 Kaplan-Meier survival curves. (A) Survival analysis based on interaction of treatment type and Ki67 score <3%; (B) survival analysis based on interaction of treatment type and Ki67 score ≥3%.

Table 3 Summary of overall survival based on interaction of treatment type and Ki67 proliferative index

Variable	3-year survival (95% CI)	5-year survival (95% CI)	Median survival (95% CI)	Median follow-up (range)
All patients	0.82 (0.6–0.9)	0.70 (0.5–0.8)	113 (55.2–NR)	53.7 (1–143.8)
Y-90: Ki67 ≥3%	0.88 (0.4–0.9)	0.7 (0.2–0.9)	113 (33.9–113)	56.5 (0–109)
TACE: Ki67 ≥3%	0.53 (0.1–0.9)		NR (20.4–NR)	33.3 (3–65.5)
Y-90: Ki67 <3%	0.78 (0.5–0.9)	0.62 (0.3–0.8)	66.8 (23.8–NR)	50 (3.9–76.5)
TACE: Ki67 <3%	1 (1.0–1.0)	1 (1.0–1.0)	122.6 (83.4–NR)	90.4 (10.6–144)

Y-90, yttrium-90; TACE, transarterial chemoembolization.

Table 4 Multivariate analysis for survival based on interaction of treatment type and Ki67 proliferative index

Variable	Hazard ratio (95% CI)	P value
Ki67 score <3: Y-90 versus TACE	13.5 (1.2–148.9)	0.035
Ki67 score ≥3: Y-90 versus TACE	0.1 (0.01–0.9)	0.036

Y-90, yttrium-90; TACE, transarterial chemoembolization.

Singla S, et al. J Gastrointest Oncol. 2016 Jun;7(3):441-8.

Table 1. Suggested guideline for selection of liver-directed therapy for well-differentiated NET liver metastases

Clinical scenario	cTACE/TAE	TARE
DOTA-avid liver only/dominant, progressive disease on SSA	+ + +	−
DOTA-avid liver only/dominant, radiographically stable, but severe hormonal symptoms or high 5-HIAA	+ + +	−
DOTA-avid diffuse or liver-dominant, one or few enlarging liver lesions, rest stable on current therapy	+ + + (also ablation)	+ (rad seg)
DOTA-avid diffuse or liver-dominant, but one or few liver lesions with low uptake	+ + + (also ablation)	+ (rad seg)
DOTA-avid, bulky liver lesion(s)	+ + +	+
Progression after PRRT	+ + +	−
Not DOTA-avid	+ + +	+
One lobe predominant bulky disease	+ + +	+ + +
Rapid bilobar progression*	+	+ + +
History of biliary instrumentation (Whipple, biliary stent, drain)	−	+ + +

+ + +, preferred treatment strategy

+, reasonable treatment strategy

−, not recommended

Rad seg, radiation segmentectomy. Radiation segmentectomy may be considered for patients with one or more lesions within a 1–2 Cuinaud liver segments. Delivery of ablative radiation dose is expected to cause irreversible injury to the treated liver segment. Therefore, this technique should be used judiciously with the goal of preservation of liver reserve

*Patients with rapid bilobar liver disease progression may benefit from combination of TARE and radiosensitizers capecitabine and temozolomide (21)

Summary

- **Multidisciplinary discussion is essential** for optimal timing and patient selection
- Personalized dosimetry improves outcomes
- Y-90 can serve as definitive therapy, bridge to surgery/transplant, or salvage option post-systemic therapy
- Expanding role as evidence for combination strategies grows

Patient Follow-Up

Osman Ahmed, MD
Professor of Radiology
University of Utah

CIO

Patient Follow-Up
Post Radioembolization

- Treatment response
- Toxicity assessment
- Need for re-treatment
- Part of multidisciplinary care unit

Laboratory Assessment

- Initial toxicity assessment post procedure and 1 month
  - Post embolization syndrome typically lasts up to 30 days
  - Assess liver function and monitor for RILD
- Trend tumor markers (ie, AFP)
- Serial monitoring 3-6 months with imaging and labs

Toxicity Surveillance

- **Post-radioembolization syndrome:** fatigue, low-grade fever, nausea, pain
- **GI ulceration:** from LGA or RGA embolization (epigastric pain, melena)
- **Radioembolization-Induced Liver Disease (RILD):**
  - 2-8 wks post TARE
  - Ascites, jaundice, hepatomegaly, rising bilirubin
- **Management:** Supportive care, hepatology co-management, early steroids for severe toxicity

Imaging Assessment

Cross-sectional imaging with dedicated MRI or CT

Typically avoid imaging until 3 months

- Post Y90 imaging in acute (ie, 1 month) setting may be harder to distinguish treatment changes vs viable tumor
- Can consider early imaging for assessment of contralateral disease

Serial monitoring 3-6 months with imaging and labs

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Hepatocellular Carcinoma

Clinical Presentation

Liver-confined, unresectable, and deemed ineligible for transplant[a,r,s,hh]
- Inadequate hepatic reserve[u]
- Tumor location[z]
- Extent of disease[z]

Treatment[r,kk]

Locoregional therapy[ee]
- Ablation
- Arterially directed therapies[ll]
- RT[gg]

→ Response Assessment

- Clinical trial
- Systemic therapy[mm]

→ Response Assessment

- Best supportive care[nn]

Response Assessment

Assess for response and
- Reconsider resection,[s] transplant, locoregional therapy or
- Subsequent-line systemic therapy if progression on or after systemic therapy[mm]

→ Surveillance

Surveillance

- Imaging[a,ii,jj] every 3-6mo for 2y, then every 6mo
- AFP[a,jj] every 3-6mo for 2yr, then every 6mo
- See relevant pathway (HCC-2 through HCC-6) if disease progresses
- Consider early imaging per local protocol (for locoregional therapy)

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Surveillance

- Imaging[a,ii,jj] every 3-6mo for 2y, then every 6mo
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- Consider early imaging per local protocol (for locoregional therapy)

Conclusion

Patient follow-up important to ensure response and tolerability to therapy	Structured follow-up ensures proper assessment	Collaboration and communication are key