Embolotherapy for Neuroendocrine Tumors: State of the Science

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Intra-arterial treatments
Setting the stage. . . . .

- TAE-bland embolization
  - Arterial injection of embolic particles
  - Causes PES: post-embolization syndrome (pain etc. . .)
  - Requires hospitalization and several days recovery (pain medications)
  - 3-4 treatments, vessel occlusion

- TACE-chemoembolization
  - Arterial injection of embolic particles + DRUG
  - Causes PES: post-embolization syndrome (pain etc. . .)
  - Requires hospitalization and several days recovery (pain medications)
  - 3-4 treatments routine, vessel occlusion

- Radioembolization
  - Arterial injection of 30 micron non embolic particles
  - Does NOT cause PES: embolization is not intent/mechanism of action
  - Same day discharge
  - 1.6 treatments per patient, no vessel occlusion

Bland/chemoembolization/DEBs

Hepatic Neuroendocrine Metastases: Chemo- or Bland Embolization?

Pitt et al J Gastro Surg 2008

Hepatic Arterial Embolization and Chemoembolization in the Management of Patients with Large-Volume Liver Metastases

Paresh P. Kamat · Sanjay Gupta · Joe E. Ensor · Ravi Murthy · Kamran Ahrar · David C. Madoff · Michael J. Wallace · Marshall E. Hicks

Kamat et al CVIR 2008

Chemoembolization and Bland Embolization of Neuroendocrine Tumor Metastases to the Liver

Alexander T. Ruutiainen, BS, Michael C. Soulen, MD, Catherine M. Tuite, MD, Timothy W.I. Clark, MD,[1] Jeffrey I. Mondschein, MD, S. William Stavropoulos, MD, and Scott O. Trerotola, MD

Ruutiainen et al JVIR 2007

Liver Embolizations of Patients with Malignant Neuroendocrine Gastrointestinal Tumors

Eriksson et al Cancer 1998

Table 4
Outcomes of TACE.

First author	30-Day mortality (%)	Grade 3 and 4 CTCAE (%)	Median TTP (months)	Radiological response (%)			Clinical response (%)	Biochemical response (%)	Survival from time of treatment					Median survival from 1st treatment (months)
				CR + PR	SD	PD	PR + SD		1YS	2YS	3YS	4YS	5YS	
Diamandidou [19]	5	4.3	NR	78	NR	NR	67	73	NR	NR	NR	NR	NR	NR
Drougas [21]	0	0	NR	73.3	6.7	6.7	100	100	60	NR	33	27	27	16
Eriksson [22]	0	3.6	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brown [15]	6.3	11	17.5[a]	NR	NR	NR	NR	NR	70	NR	54	NR	54	NR
Kim [27]	1.3	6.5	24	37	23	17	NR	80.7	NR	NR	NR	NR	30	15
Dominguez [20]	0	4.65	10.5	53	13	27	93	46	NR	NR	NR	NR	NR	NR
Desai [18]	2.3	16	NR	32	21	21	NR	79	NR	NR	NR	NR	NR	NR
Schell [33]	0	0	NR	79.2	16.7	4.2	100	NR	NR	NR	NR	NR	71.5	NR
Kress [28]	0	6.5	NR	7.6	54	19	0	67	NR	NR	NR	NR	48	57
Loewe [29]	8.7	2.7	NR	73	22.7	4.5	67	62	95.7	95.7	85.6	79.9	65.4	69
Roche [31]	4.6	5.9	18	74	15	15	93	52	NR	NR	NR	NR	31	NR
Gupta [25] (carcinoid)	0.34	8.5	22.7	75	16	8.7	NR	NR	95.3	68.6	NR	NR	28.6	33.8
Gupta [25] (PNET)			16.1	37	59	4	NR	NR	68.8	48.7	NR	NR	13.7	23.2
Touzios [35]	5.6	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	50	50
Osborne [13]	0	2	22[a]	NR	NR	NR	91	NR	NR	NR	NR	NR	NR	NR
Strosberg [34]	0	2.5	NR	48	52	NR	80	91	NR	NR	NR	NR	38	36
Granberg [24]	0	0	NR	34	57	8.7	92	13.3	NR	NR	NR	NR	NR	NR
Ho [26]	4.3	8.6	19.7	45	36	18	80	NR	80	66	41	38	29	32
Bloomston [14]	5	23	19	82	12	6	92	80	72	58	48	36	29b	33.3
Ruutiainen [32] (TAE)	1.4	22	6	50	38	NR	93	NR	86	69	NR	NR	49[b]	39
Ruutiainen [32] (TACE)		25	12	66	22	NR	92	NR	64	59	NR	NR	39[b]	44
Christante [16]	7	0	19	58.4	22	NR	61	NR	78	NR	NR	NR	27	39
Pitt [30] (TACE)	0.8	2.4	NR	NR	NR	NR	86	NR	NR	NR	NR	NR	19	25.5
Pitt [30] (TAE)	1.8	6.6	NR	NR	NR	NR	83	NR	NR	NR	NR	NR	13	25.7
Vogl [36] Group 1	0	0	10.2[a]	11.1	50	38.9	NR	NR	NR	NR	NR	NR	11.1[c]	32.9
Vogl [36] Group 2			16.4[a]	23.3	53.3	23.3	NR	NR	NR	NR	NR	NR	46.7[c]	42.8
Gaur [23]	0	5.6	13.7	65	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
De Baere [17]	0	0	15	80	15	5	81	NR	NR	NR	NR	NR	NR	NR
Whitney	0	17.4	18	89	11	0	NR	NR	NR	NR	NR	NR	NR	69

[a] Reported as mean.
[b] 10 YS available.
[c] From time of diagnosis.

Yang et al Surg Onc 2012

Hepatic Arterial Embolization versus Chemoembolization in the Treatment of Liver Metastases from Well-Differentiated Midgut Endocrine Tumors: A Prospective Randomized Study

Frédérique Maire[a] Catherine Lombard-Bohas[d] Dermot O'Toole[a]
Marie-Pierre Vullierme[b] Vinciane Rebours[a] Anne Couvelard[c]
Anne Laure Pelletier[a] Magaly Zappa[b] Frank Pilleul[e] Olivia Hentic[a]
Pascal Hammel[a] Philippe Ruszniewski[a]

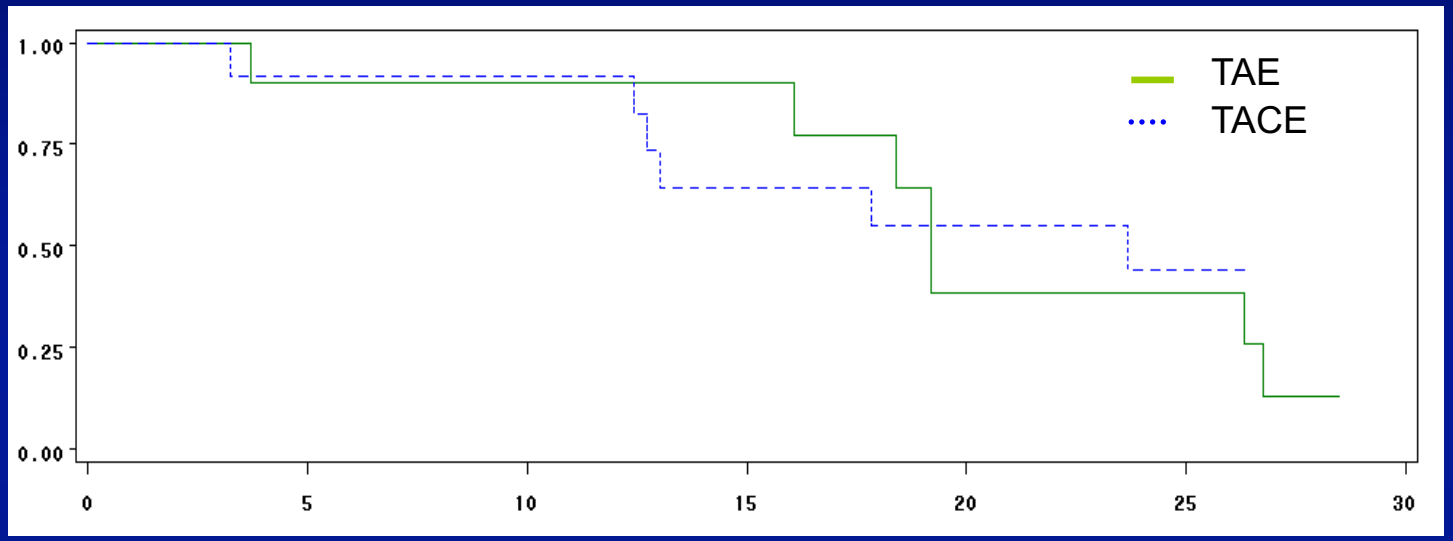
Table 1. Patient profile according to treatment with hepatic intra-arterial chemoembolization or embolization

	Chemoembolization (n = 12)	Embolization (n = 14)	p
Gender			0.07
Male	7	9	
Female	5	5	
Median age	65 (38–71)	56 (41–79)	0.53
Resection of the primary tumor	10	12	1
Previous resection of liver metastases	2	2	1
Carcinoid syndrome	8	11	0.6
Concomitant treatment with somatostatin analogues	8	11	0.66
Median urinary 5-HIAA, μmol/day	192	94	0.46
Median serum chromogranin A, mmol/l	135	192	0.20
Body mass index	24	23	0.97
Liver involvement			1
<25%	7	6	
25–50%	3	5	
>50%	2	3	
Evolutivity			1
Liver involvement of >50% and no evaluable progression	1	2	
Progression of >25% in less than 3 months	4	4	
Progression of >25% in more than 3 months	7	8	
Median follow-up, months	17.2	15.4	0.83
Disease progression	7	6	0.43

Figures in parentheses are ranges.

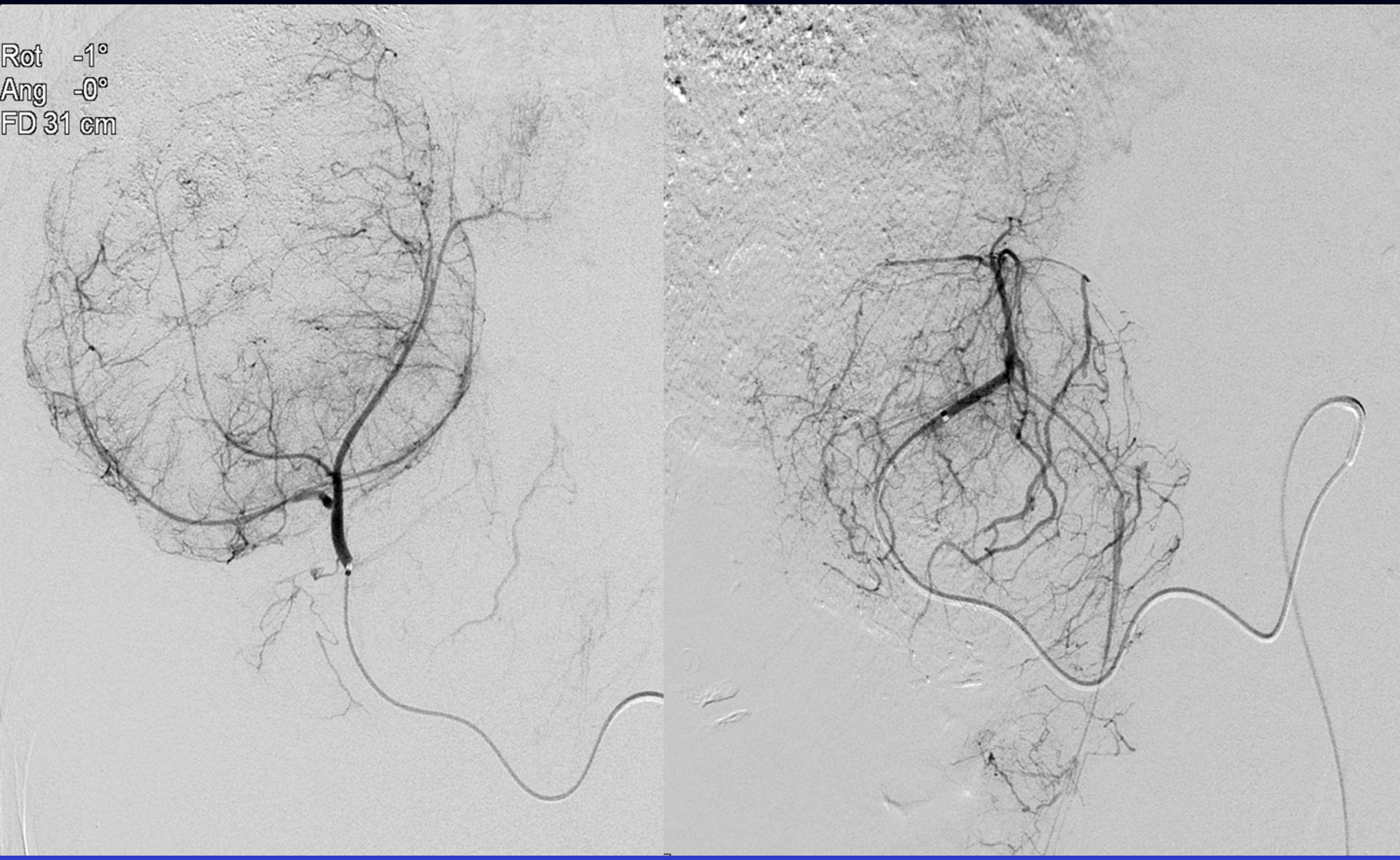
Maire et al Neuroendocrinology 2012

Progression free survival rates

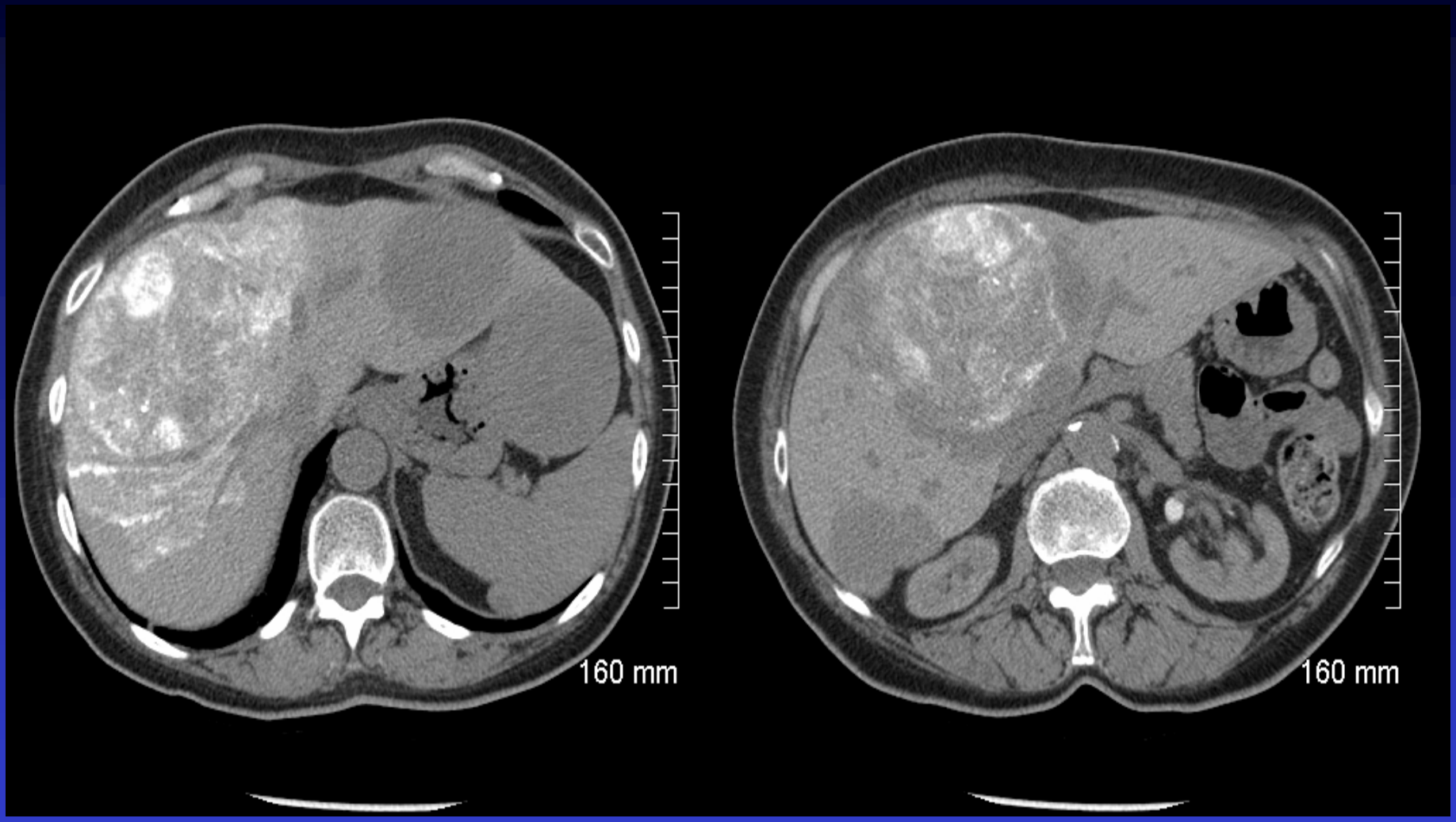


	TACE	TAE	P
median PFS	19.2 [16.1-26.8]	23.6 [12.7-NA]	
2-year PFS rates	38%	44%	0.90

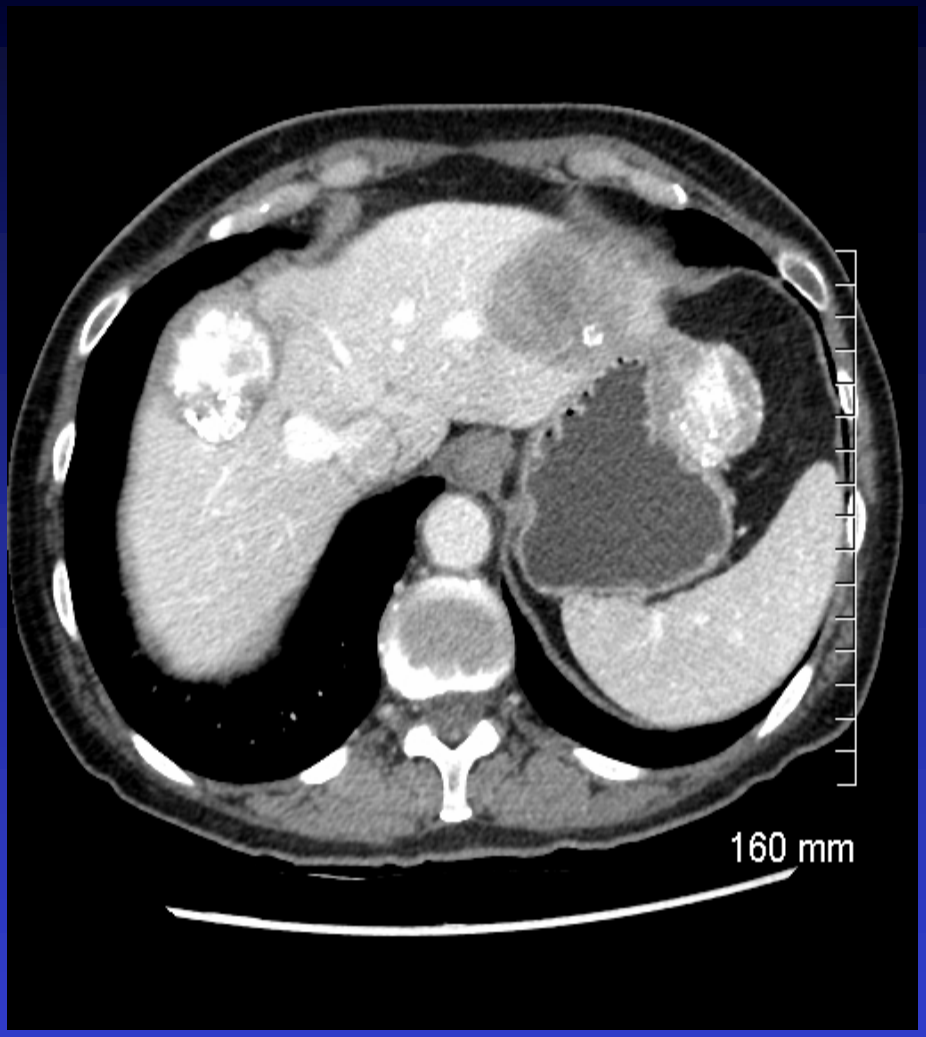
Maire et al Neuroendocrinology 2012

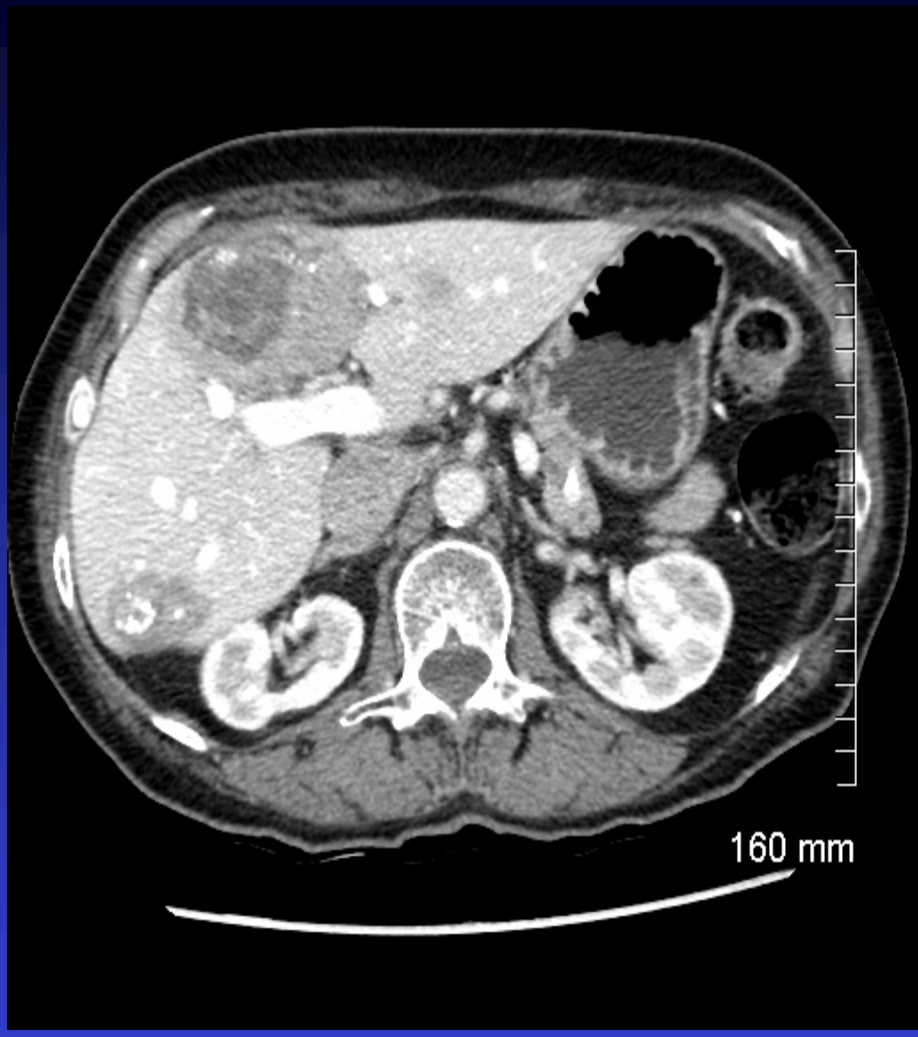


Courtesy: Bill Rilling

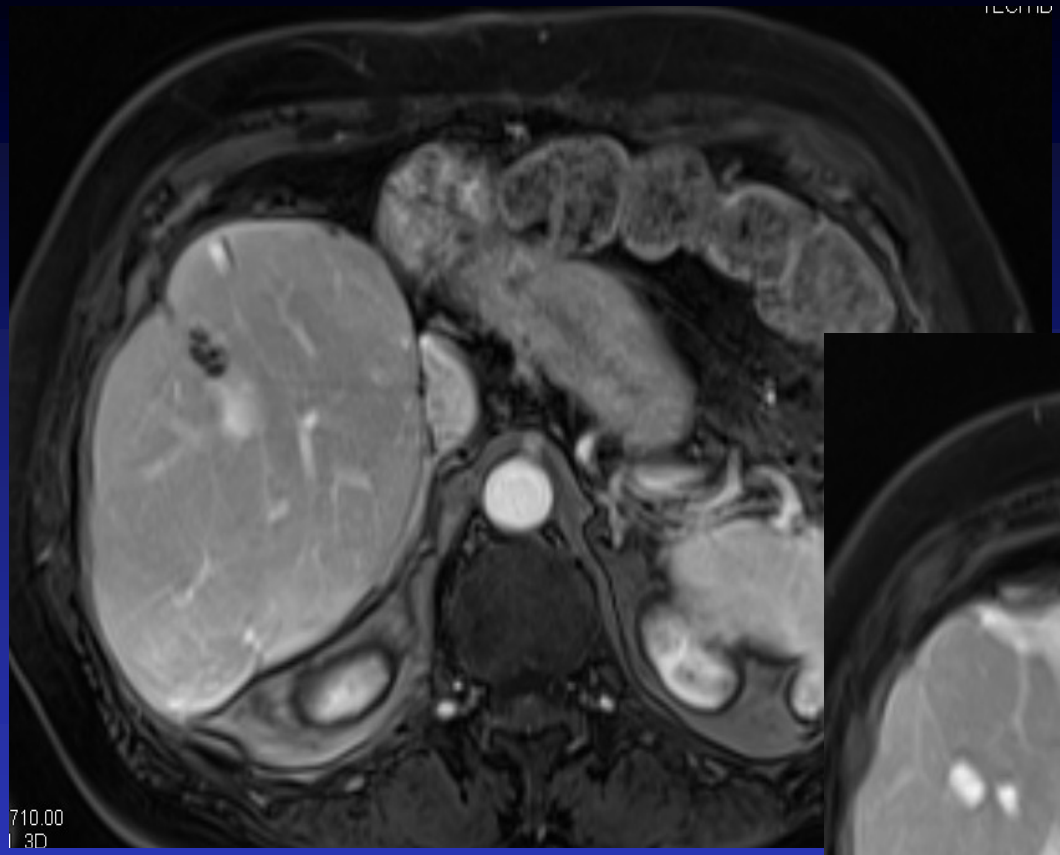


Courtesy: Bill Rilling





Courtesy: Bill Rilling



5 years post resection
NAD

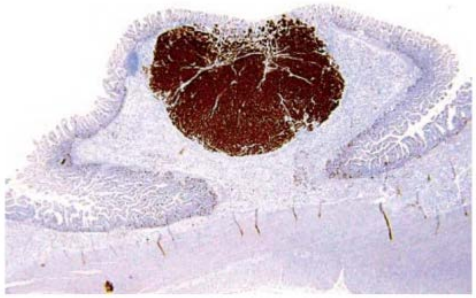
Courtesy: Bill Rilling

NETs: key questions for the IR

- **Which tumor grade?**

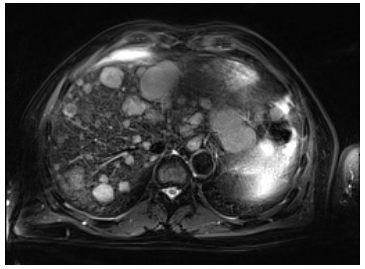
Differentiation	Grade	Mitotic count (per 2 mm^2)	Ki-67 Index (%)	WHO
Well-differentiated	Low grade (G1)	<2	≤2	NET, Grade 1
Well-differentiated	Intermediate grade (G2)	2-20	3-20	NET, Grade 2
Poorly differentiated	High grade (G3)	>20	>20	NET, Grade 3

- **Tumor symptoms (diarrhea, flush…)?**



- **Is there any tumor progression?**

- **Liver-only or liver-dominant disease?**



BLAND/CHEMO-EMBOLIZATION: contraindications

Only relative… (≠ HCC patient)

- **Performance status >2**
- **(Complete portal vein occlusion)**
- **Hepatic insufficiency**
- **High bilirubin level (>2-3 mg/dL)**
- **High (>50%? >75%?) tumor burden**

  Gupta et al., Cancer 2005
  Kamat et al., CVIR 2008

  - Higher mortality (liver failure / progression)
  - Especially if additional sepsis, rapidly worsening PS, anasarca, carcinoid heart disease
- **Biliary-enteric anastomosis**

  Kim et al., JVIR 2001
  Khan et al., AJR 2011

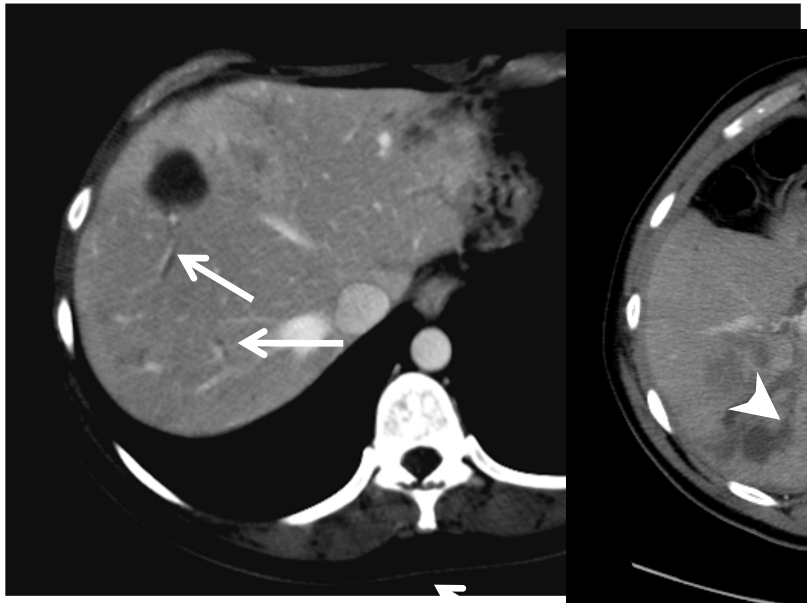
  - Risk of liver abcess +++
  - Agressive antibiotic prophylaxis ± Bowel preparation ?

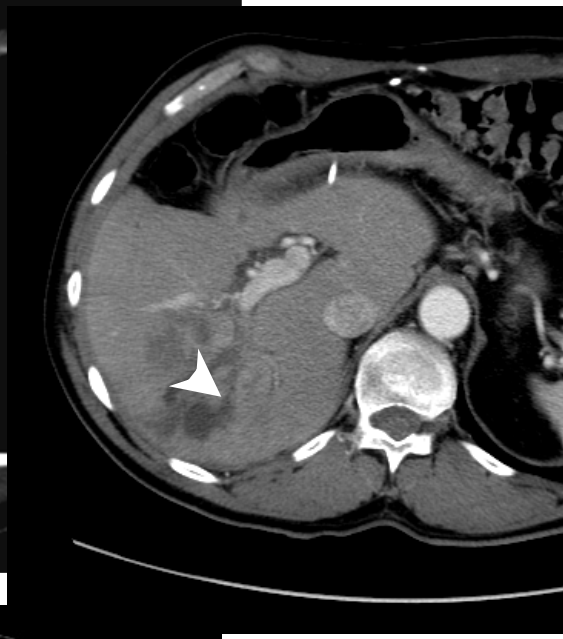
→ **Switch to Y90?**

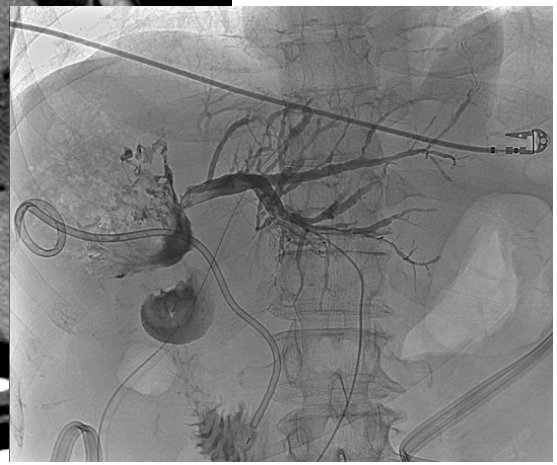
Gupta S., Seminars in Interv Radiol 2013

Liver / Biliary injuries

- Dilatation of bile ducts
- Portal vein narrowing
- Portal vein thrombosis
- Biloma / liver necrosis



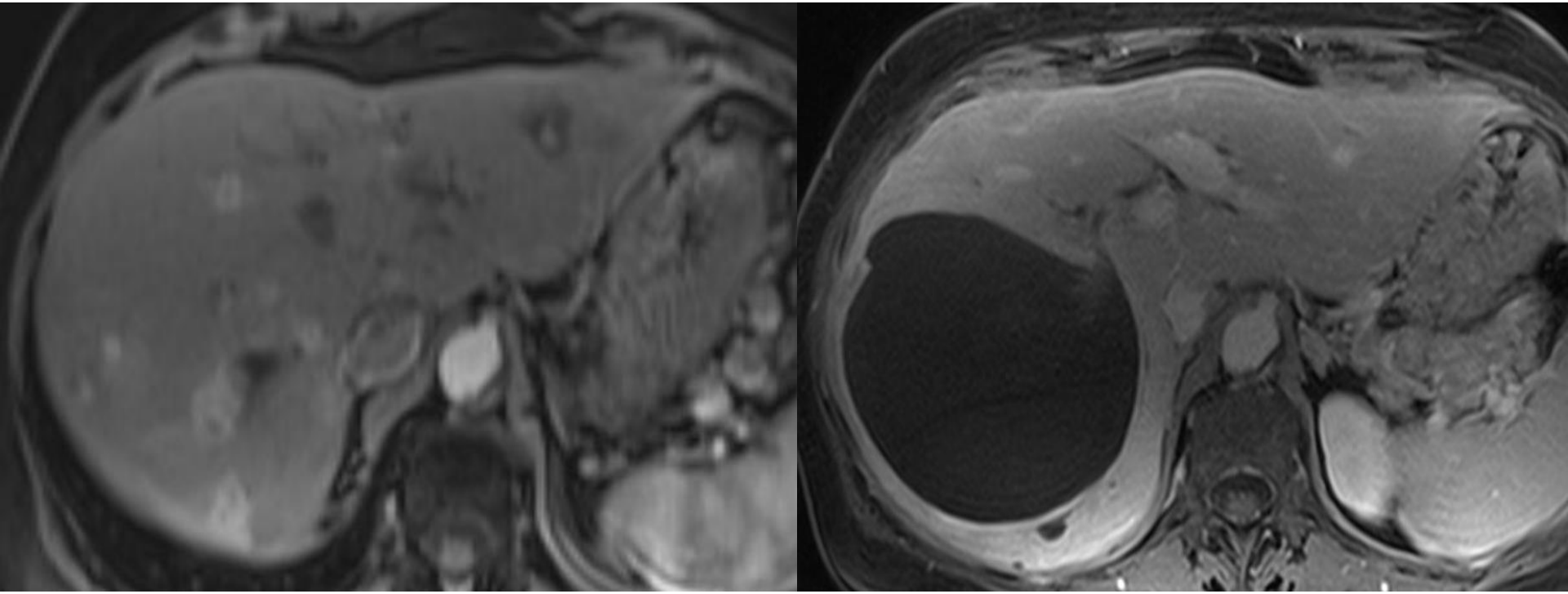




Risk of liver / biliary injury = 6.6 with DEBs *versus* lipiodol

Guiu et al., J Hepatol, 2012
Baghat et al., CVIR 2013
Joskin et al., CVIR 2015

69 y/o female with NET, 2 treatments with DEB-TACE
4 months post therapy



Underwent external drainage and internal stent placement with total resolution of biloma

Embolotherapy for NETs: other complications

- **Post-embolization Syndrome** (pain, fever, nausea…)
  - Can be considered as «normal» effect of embo
  - Usually improves within 3 to 5 days
- **Acute liver failure**
- **Cholecystitis, gastric ulcer**
- **Tumor lysis syndrome**
- **Liver abscess**

Rare

Except in cases of biliary–enteric anastomosis

- A specific complication: **CARCINOID CRISIS**

  = massive release of serotonin / vasoactive peptides
  - Potentially life-threatening
  - Facial flushing, hypotension/hypertension, arrhythmia, …
  - Treatment = 200µg IV octreotide… resuscitation
  - Prevention = octreotide premedication, presence of anesthesiologist

Gupta, Seminars in Interv Radiol 2013

Transarterial therapies for NETs: RESULTS

	Bland/Chemo	Y90
Symptomatic response	50 – 100%	62 – 100%
Imaging response	20 – 95%	12 – 88%
Overall survival	13.7 – 83% at 5y	28% at 5y

Devcic et al., J Nucl Med 2014
Gupta, Seminars in Interv Radiol 2013

- **Wide range because of marked heterogeneity**
  - **Tumor**: tumor histology / differentiation, tumor burden, extrahepatic mets…
  - **Treatment**: octreotide or not, early or late treatment, type of treatment…
  - **Imaging follow-up**: frequency/timing of imaging, response criteria…
- **Embolotherapy and SIRT/Radioembolization ≈ equally effective**
- **Less data with Radioembolization**

Radioembolization

Arterial Particle Comparison

GOAL: implant radiation to tumor

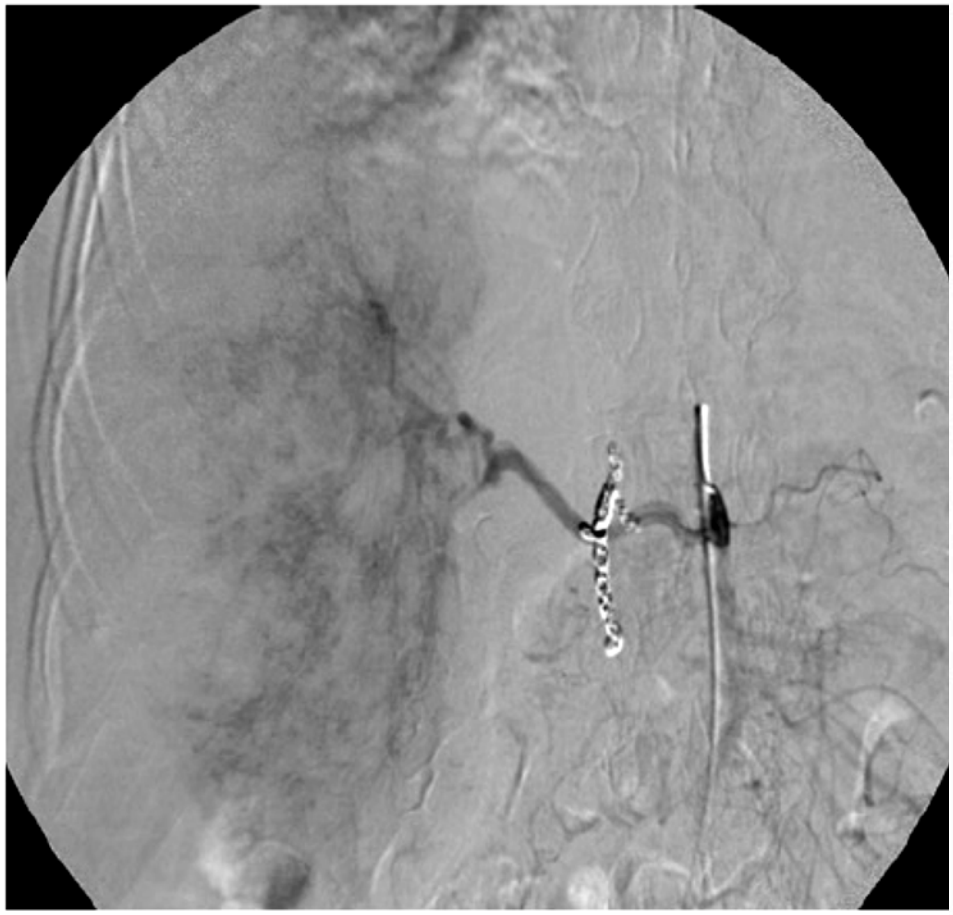
^{90}Y-microspheres
25-35 microns

GOAL: block all blood to tumor

TAE, TACE and Drug Eluting Beads
100-700 microns

Microembolization

Pre Tx



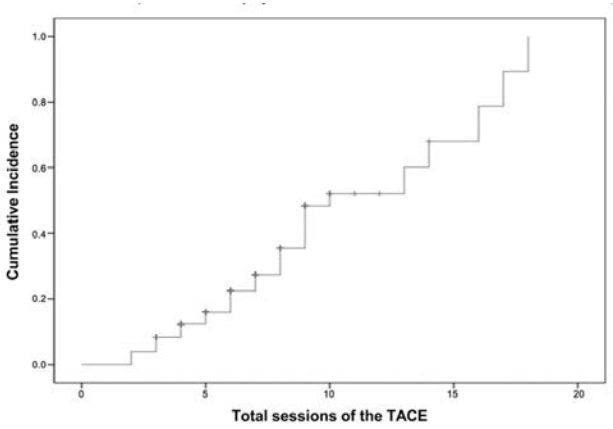
Immediate Post Tx

Sato et al CVIR 2006

IA therapies for NETs: do we have to choose?

- **Should TACE and Y90 really compete each other?**
  - Probably NO: survival is linked to the number of treatment lines

- **Which technique as 1st line therapy?**
  - More data for TACE but…
  - More chance to lose arterial patency after TACE (>2-3 sessions, embolizing agent…)
  - Y90 = probably better preserves arteries, less toxicity, outpatient procedure

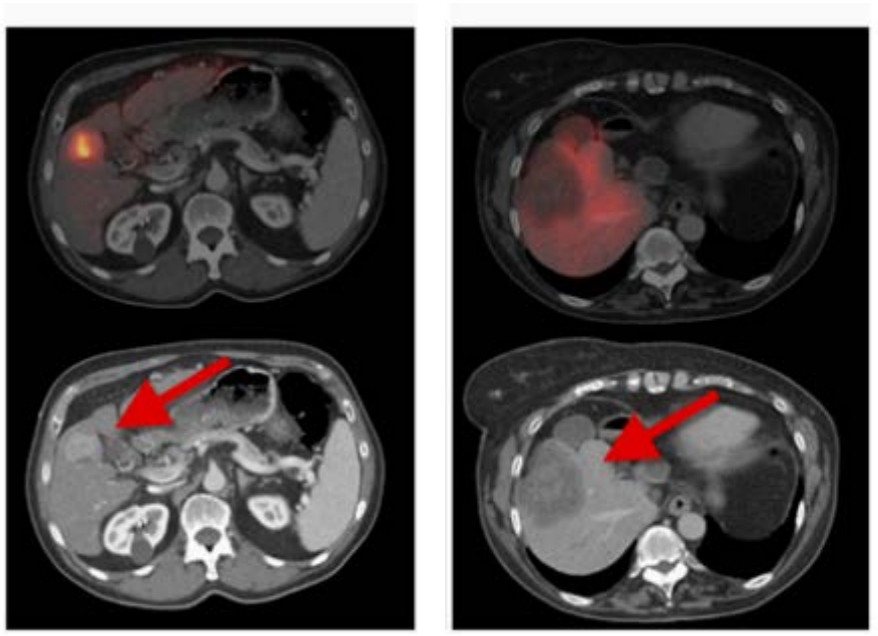


TACE/TAE can cause arterial injury
Preventing any further IA treatment!

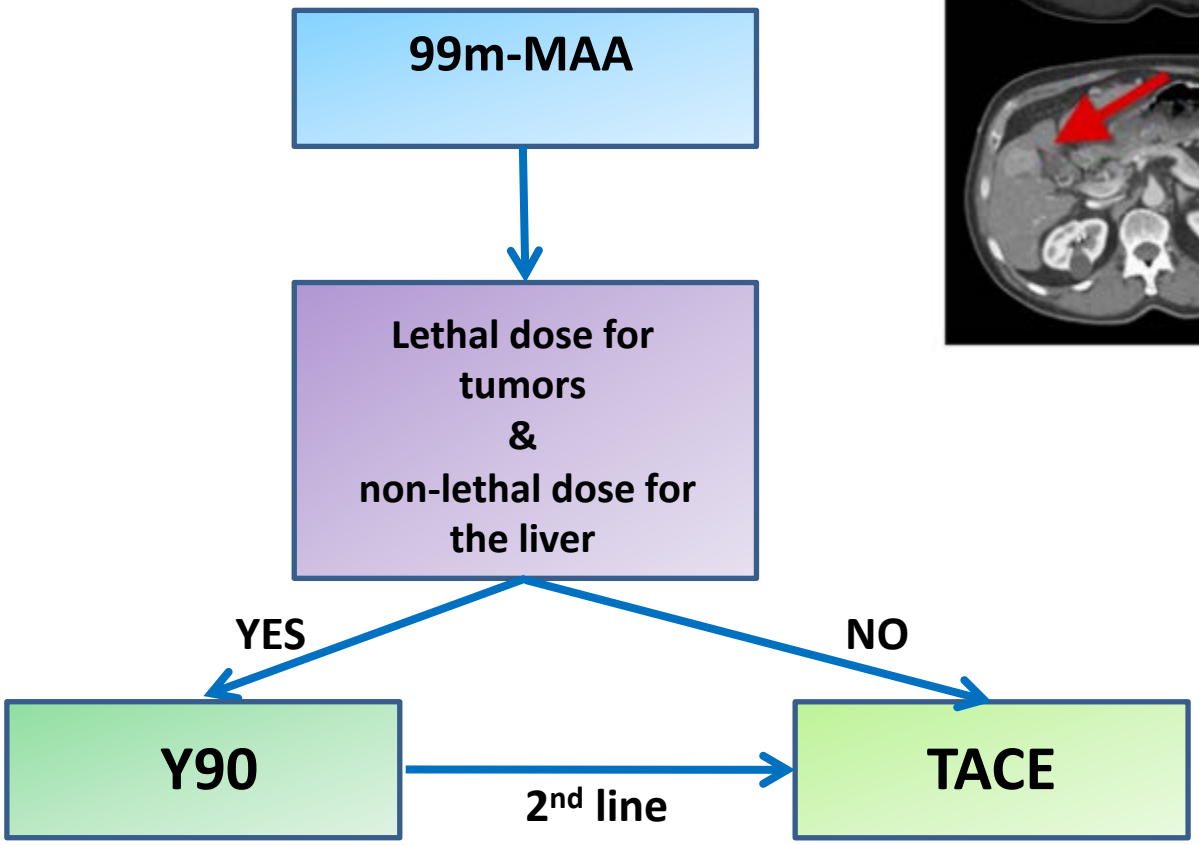
Suh et al., Brit J Radiol 2014

- **Y90 is the best 1st line treatment for all patients??**

1st line Y90 or TACE: leave the choice to MAA…



Ihan et al., J Nucl Med 2015



Radioembolization for Unresectable Neuroendocrine Hepatic Metastases Using Resin ^{90}Y-Microspheres: Early Results in 148 Patients

TABLE 4. Toxicity and Hepatic Response After ^{90}Y-Microsphere Treatment

Toxicity (CTCae 3.0 grade 3–4 only) in 161/185 treatments (87%)	
None	124/185 = 67%
Fatigue	12/185 = 6.5%
Nausea	6/185 = 3.2%
Pain	5/185 = 2.7%
Ascites	1/185 = 0.5%
Imaging response (CT/MRI/OctreoScan) in 168/185 treatments (91%)	
Stable disease	42/185 = 22.7%
Partial response	112/185 = 60.5%
Complete response	5/185 = 2.7%
Progressive disease	9/185 = 4.9%

Kennedy et al AJCO 2008

Radioembolization for Neuroendocrine Liver Metastases: Safety, Imaging, and Long-term Outcomes

Khairuddin Memon, M.D.,* Robert J. Lewandowski, M.D.,* Mary F. Mulcahy, M.D.,† Ahsun Riaz, M.D.,* Robert K. Ryu, M.D.,* Kent T. Sato, M.D.,* Ramona Gupta, M.D.,* Paul Nikolaidis, M.D.,* Frank H. Miller, M.D.,* Vahid Yaghmai, M.D.,* Vanessa L. Gates, M.S.,* Bassel Atassi, M.D.,* Steven Newman, M.D.,† Reed A. Omary, M.D.,* Al B. Benson, 3rd, M.D.,† and Riad Salem, M.D., M.B.A.*,†

- 40 patients with liver dominant metastases
  - Unresectable (determined by surgery)
  - Refractory to systemic therapy
  - Imaging confirmed progressive disease

Radioembolization for Neuroendocrine Liver Metastases: Safety, Imaging, and Long-term Outcomes

WHO	
Response State	**N (%)**
CR	1 (1.2)
PR	52 (62.7)
SD	27(32.5)
PD	3 (3.6)
EASL	
50-99% necrosis	36 (43.4)
100% necrosis	17 (20.5)

Red Journal 2011

Radioembolization for Neuroendocrine Liver Metastases: Safety, Imaging, and Long-term Outcomes

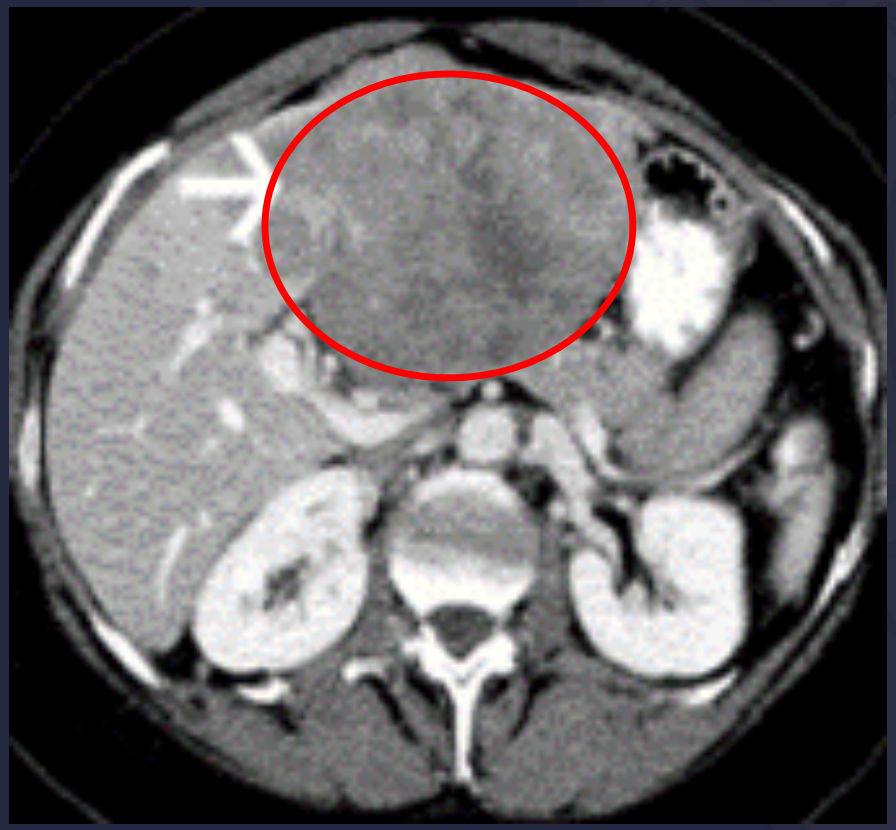
Survival	
Median Survival in months (Range)	34.4 (1.1 - 75.5)
1-year [N (%)]	29 (72.5%)
2-year [N (%)]	25 (62.5%)
3-year [N (%)]	18 (45%)
Symptomatic Response	
Yes	21/25 (84%)
No	4/25 (16 %)

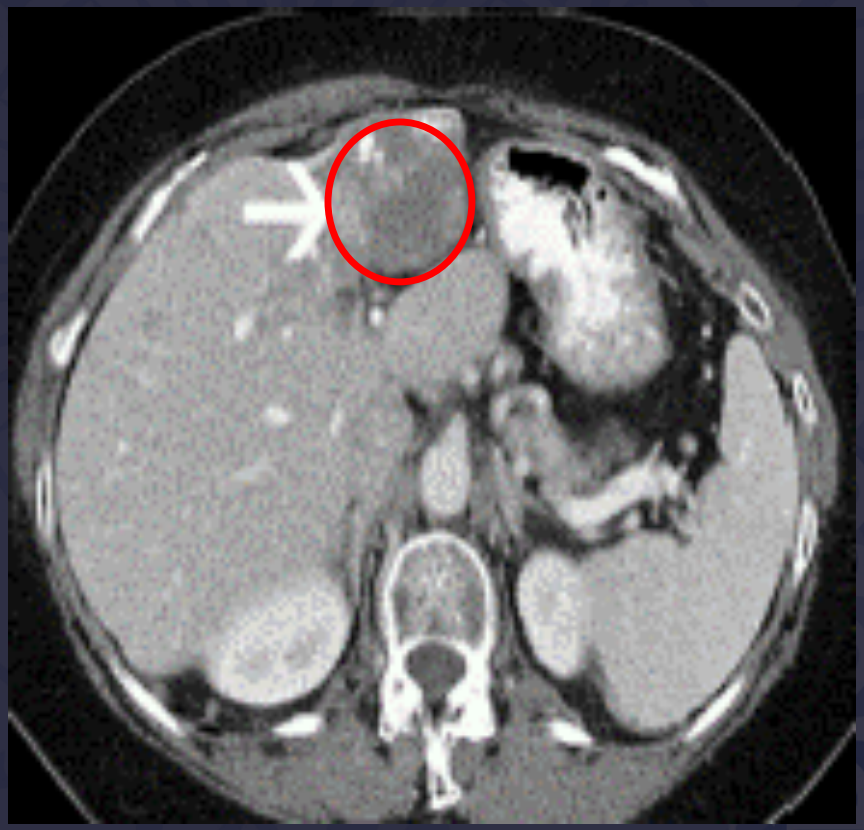
Red Journal 2011

PATIENT SELECTION: NORTHWESTERN

- DISEASE BURDEN
  - Large, bulky tumors
  - Bilobar multi-focal disease
  - Infiltrative disease
  - Hypovascular Tumors
- CLINICAL INDICATORS
  - Significant carcinoid symptoms
  - Compromised performance status
- SPECIAL CONSIDERATRIONS
  - Failed other embolic therapy
  - Biliary tree compromised

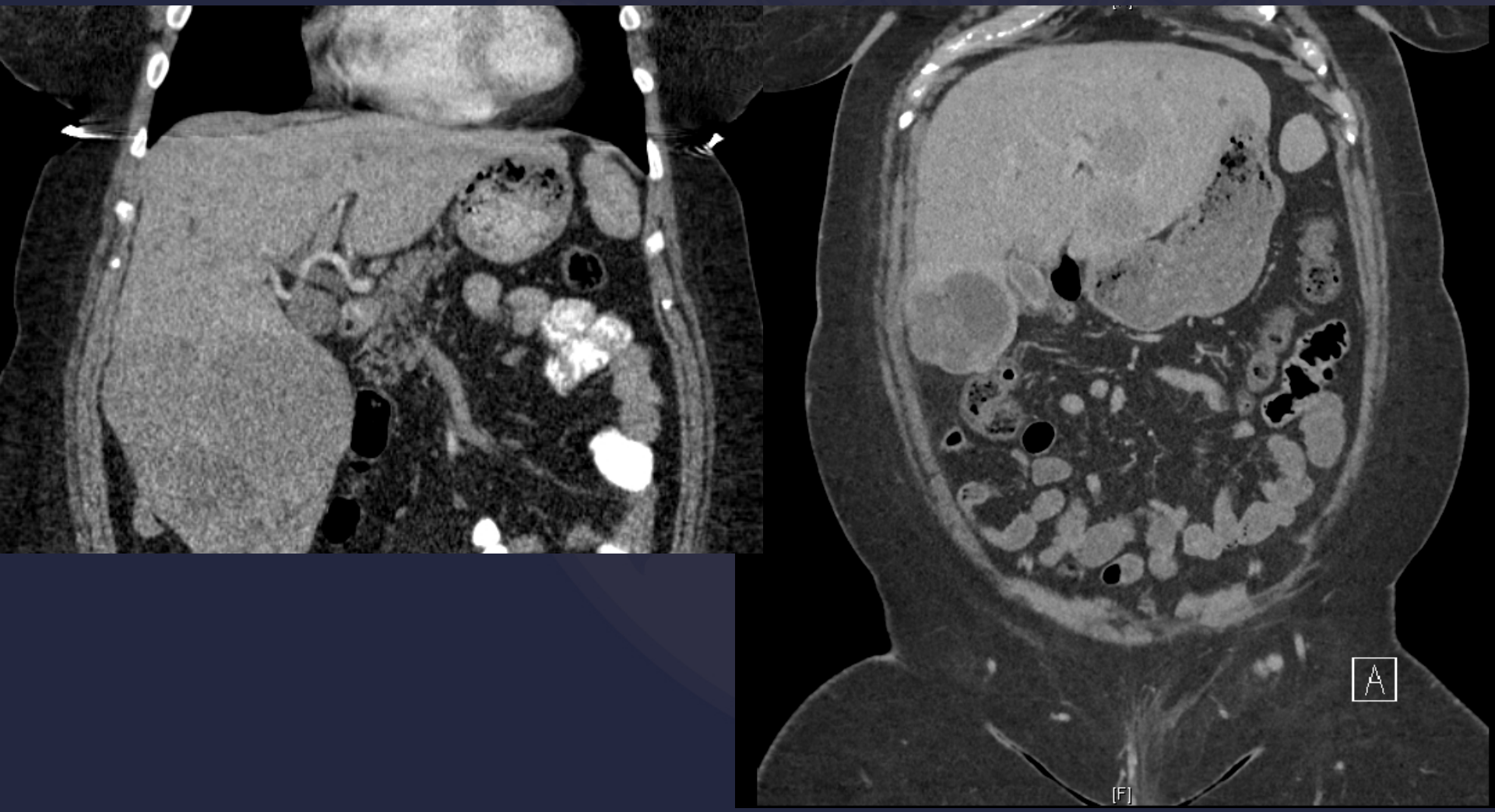
Large, Bulky Tumors



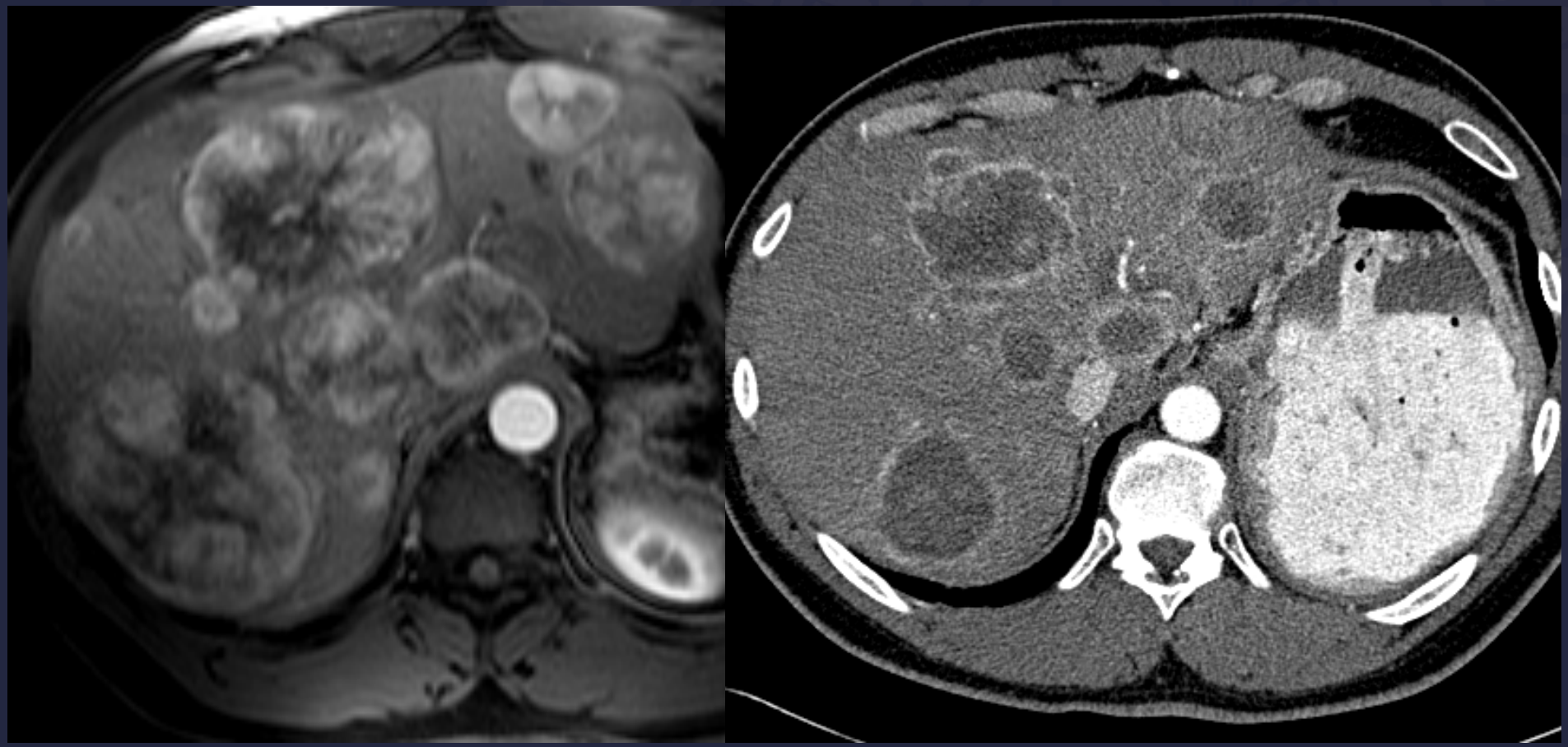


Rhee et al Ann Surg 2008

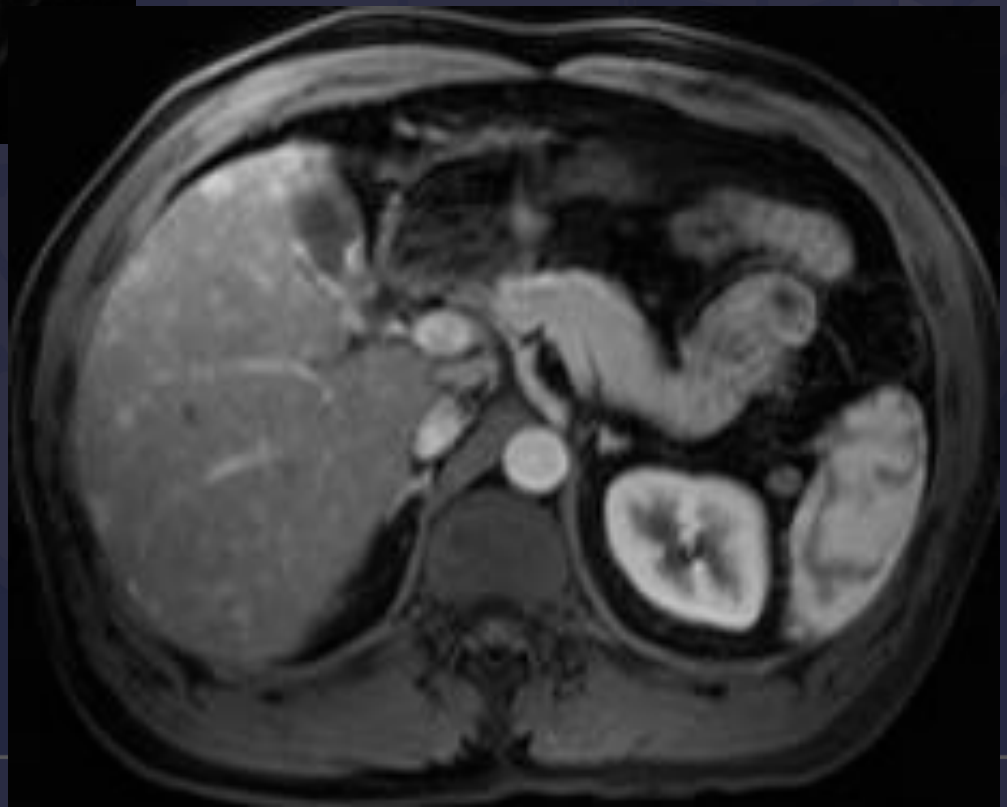
Pre and Post Y90 → NET



MULTIFOCAL/BILOBAR TUMORS

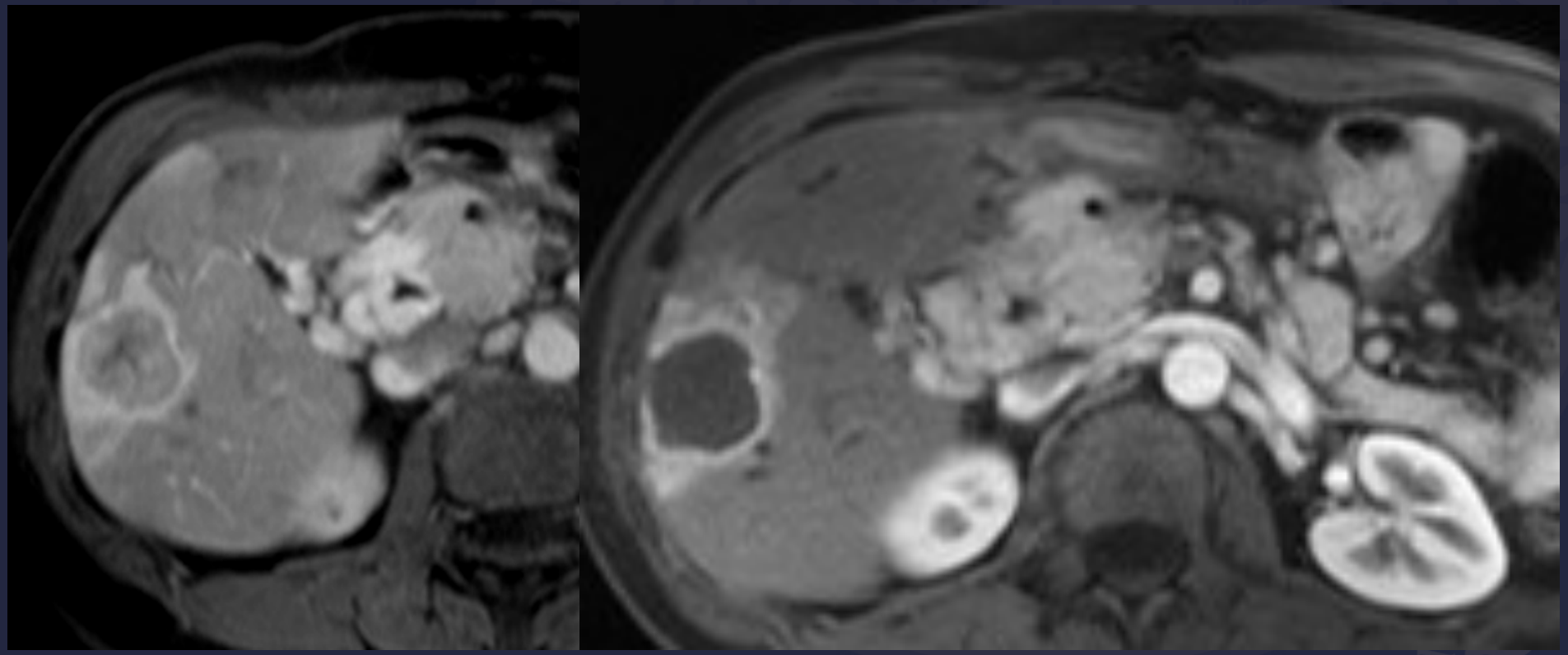


Pre Tx



Post Tx

SPINCTEROTOMY



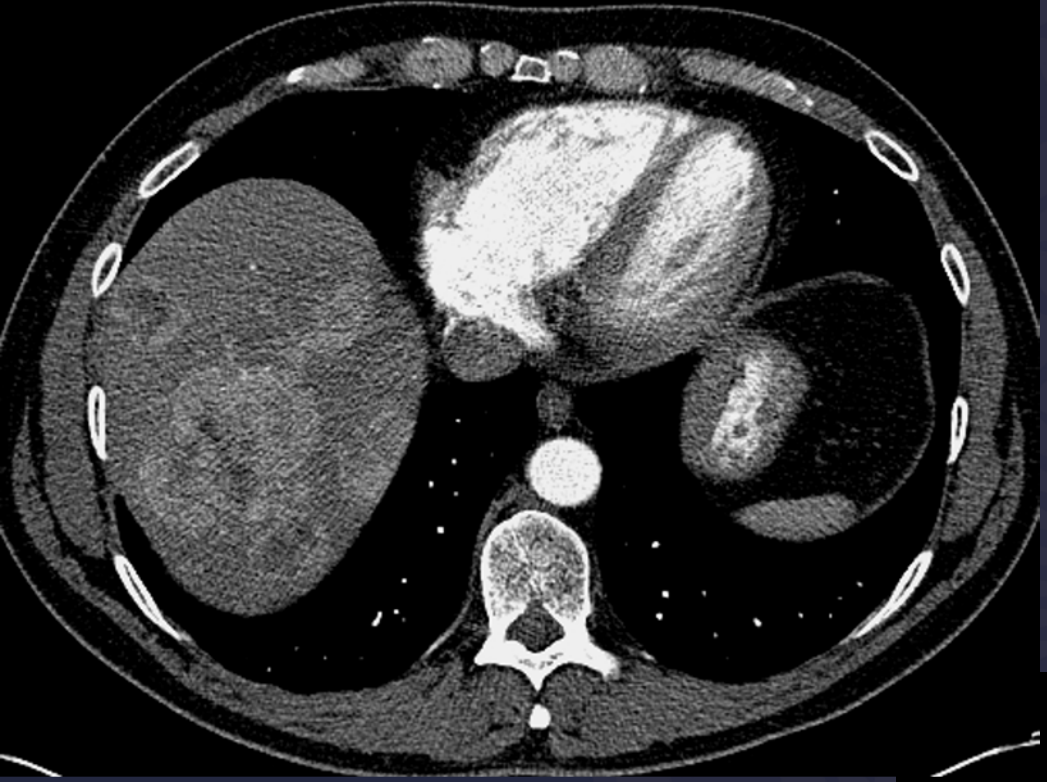
Y-90 with bilioenteric anastomosis

- 16 patients
  - 24 y-90 resin radioembolization
  - Treated with Levo/Flagyl
    - 2 days prior 14 days after
  - Bowel prep the day prior
  - 0% rate of hepatic abscess
  - (similar cTACE cohort with same pretreatment algorithm)
    - 23% (3/13) patients, one fatal

Cholopranee A. CVIR 2014 July (epub ahead of print)

REVERSING THE ORDER OF RESECTION

Pt with met islet Reverse Resection!



Transarterial Chemoembolization vs Radioembolization for Neuroendocrine Liver Metastases: A Multi-Institutional Analysis

Michael E Egger, MD, MPH, FACS[1], Emily Armstrong, BS[2], Robert CG Martin II, MD, PhD, FACS[1], Charles R Scoggins, MD, MBA, FACS[1], Prejesh Philips, MD, FACS[1], Manisha Shah, MD[3], Bhavana Konda, MD, MPH[3], Mary Dillhoff, MD, FACS[2], Timothy M. Pawlik, MD, MPH, PhD, FACS[2], Jordan M Cloyd, MD[2]

Methods

- A retrospective review of all patients with NELM at two academic medical centers undergoing transarterial therapies from 2000-2018 was performed.
- Postoperative morbidity, radiographic response according to RECIST criteria, and long-term outcomes were compared between patients who underwent TACE versus TARE.

Transarterial Chemoembolization vs Radioembolization for Neuroendocrine Liver Metastases: A Multi-Institutional Analysis

Michael E Egger, MD, MPH, FACS[1], Emily Armstrong, BS[2], Robert CG Martin II, MD, PhD, FACS[1], Charles R Scoggins, MD, MBA, FACS[1], Prejesh Philips, MD, FACS[1], Manisha Shah, MD[3], Bhavana Konda, MD, MPH[3], Mary Dillhoff, MD, FACS[2], Timothy M. Pawlik, MD, MPH, PhD, FACS[2], Jordan M Cloyd, MD[2]

Results:

- Among 248 patients with NELM, 197 (79%) received TACE while 51 (21%) received TARE.
- Patients who underwent TACE were more likely to have carcinoid syndrome, larger tumors, and have higher chromogranin A levels,
- There was no difference in tumor differentiation, primary site, bilobar disease, or synchronous presentation.
- Nearly all TARE treatments (92%) were performed as an outpatient while 99% of TACE patients spent at least one night in the hospital.
- There were no differences in overall morbidity (TARE 13.7% vs TACE 22.6%, p = 0.17), grade III/IV complications (5.9% vs 9.2%, p=0.58), or 90-day mortality.

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Table 2: Periprocedural Outcomes after Transarterial Chemoembolization vs Transarterial Radioembolization among Patients with Neuroendocrine Liver Metastases

Outcome	TARE (n=51)	TACE (n=197)	p Value
Length of stay, d, median (IQR)	0 (0, 0)	1 (1,1)	<0.0001
Any complication, n (%)	7 (13.7)	44 (22.6)	0.17
Major complication, n (%)	3 (5.9)	18 (9.2)	0.58
30-day mortality, n (%)	1 (2.0)	6 (3.1)	1.0
90-day mortality, n (%)	5 (9.8)	10 (5.2)	0.21
Laboratory, median (IQR)			
Bilirubin change, mg/dL	0 (-0.3, +0.1)	+0.4 (+0.1, +0.8)	<0.0001
Platelet change, $10^3/\mu L$	-29 (-78, +19)	-42 (-82, -4)	0.31
INR change	+0.1 (-0.1, +0.3)	+0.2 (+0.1, +0.3)	0.07
Creatinine change, mg/dL	-0.1 (-0.2, 0)	+0.1 (0, +0.2)	<0.0001
% chromogranin change	-16 (-64, +49)	-43 (-77, -4)	0.07
Radiographic			
% change in size, median (IQR)	-9 (0, -27)	-19 (-6, -34)	0.051
RECIST response, n (%)			0.0002
Complete response	2 (4.4)	5 (3.6)	
Partial response	9 (19.6)	37 (26.6)	
Stable disease	27 (58.7)	92 (66.2)	
Progressive disease	8 (17.4)	5 (3.6)	

IQR, interquartile range; INR, international normalized ratio; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; RECIST, response evaluation criteria in solid tumors.

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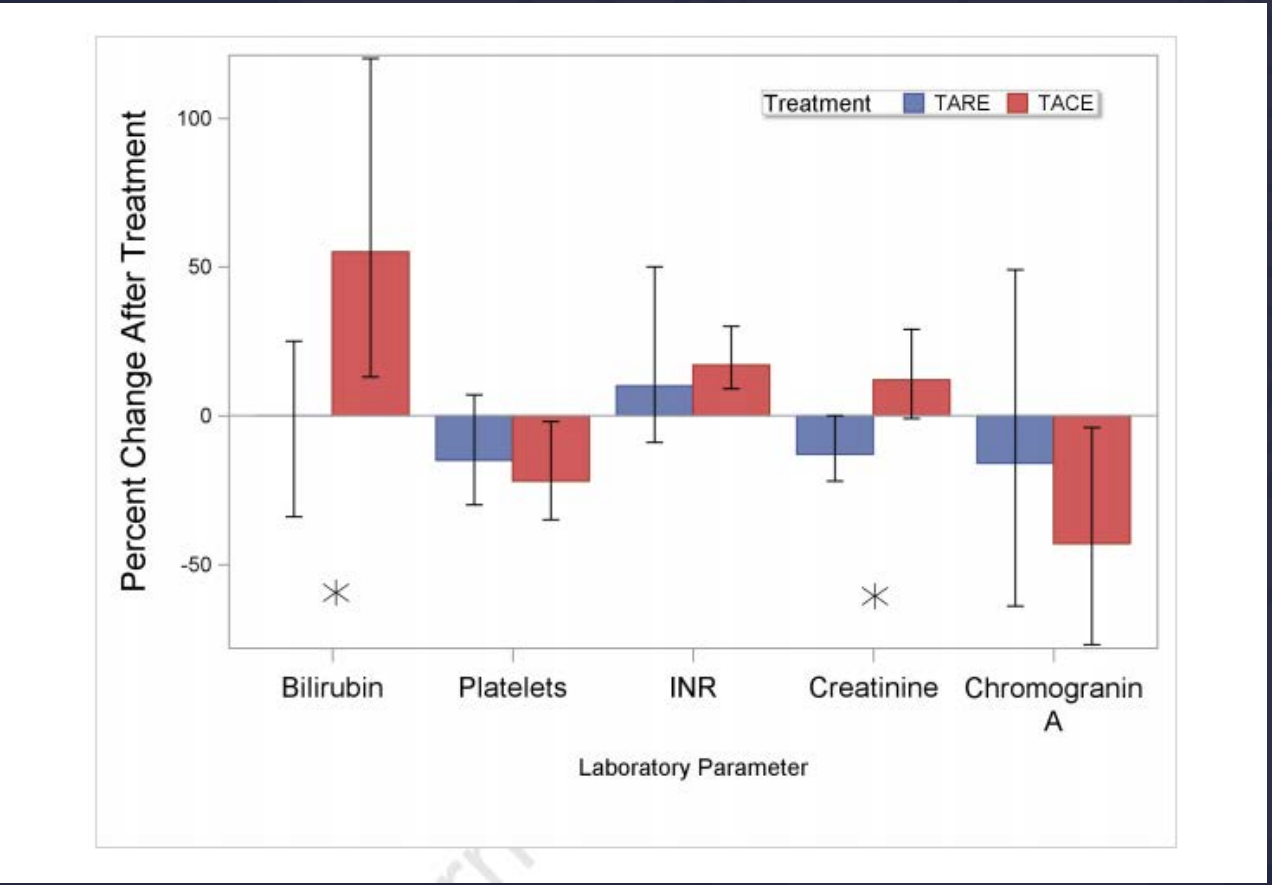

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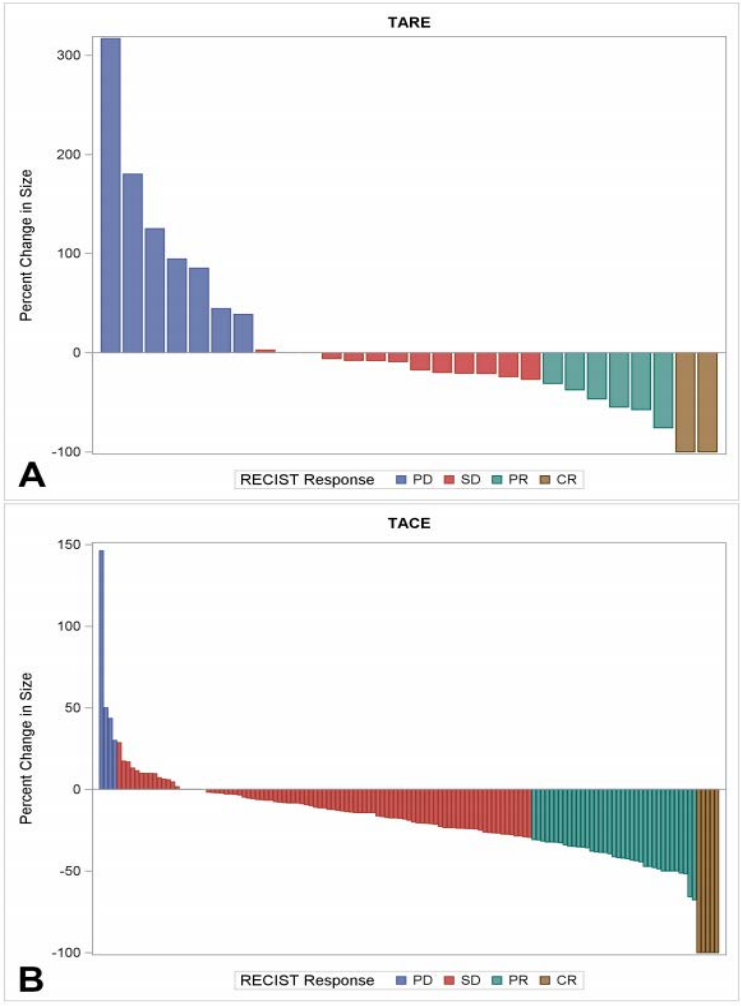

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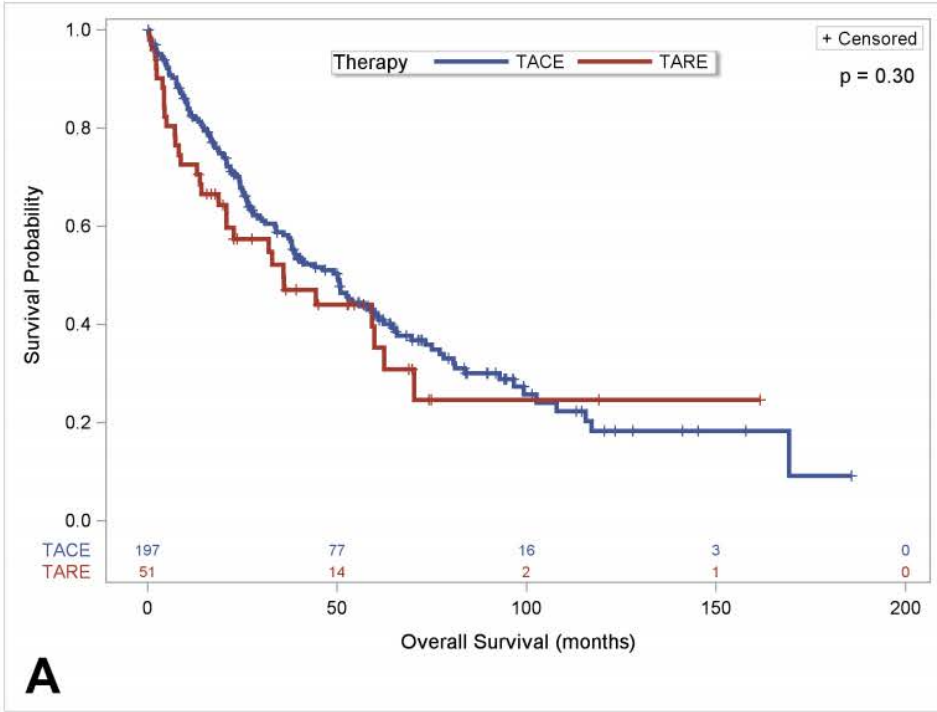
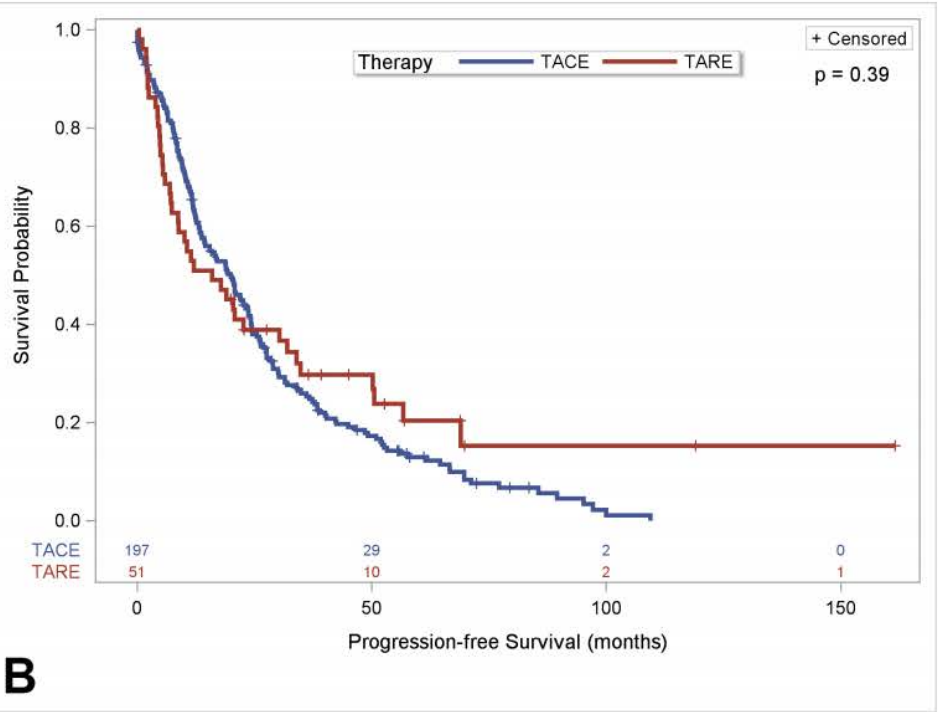
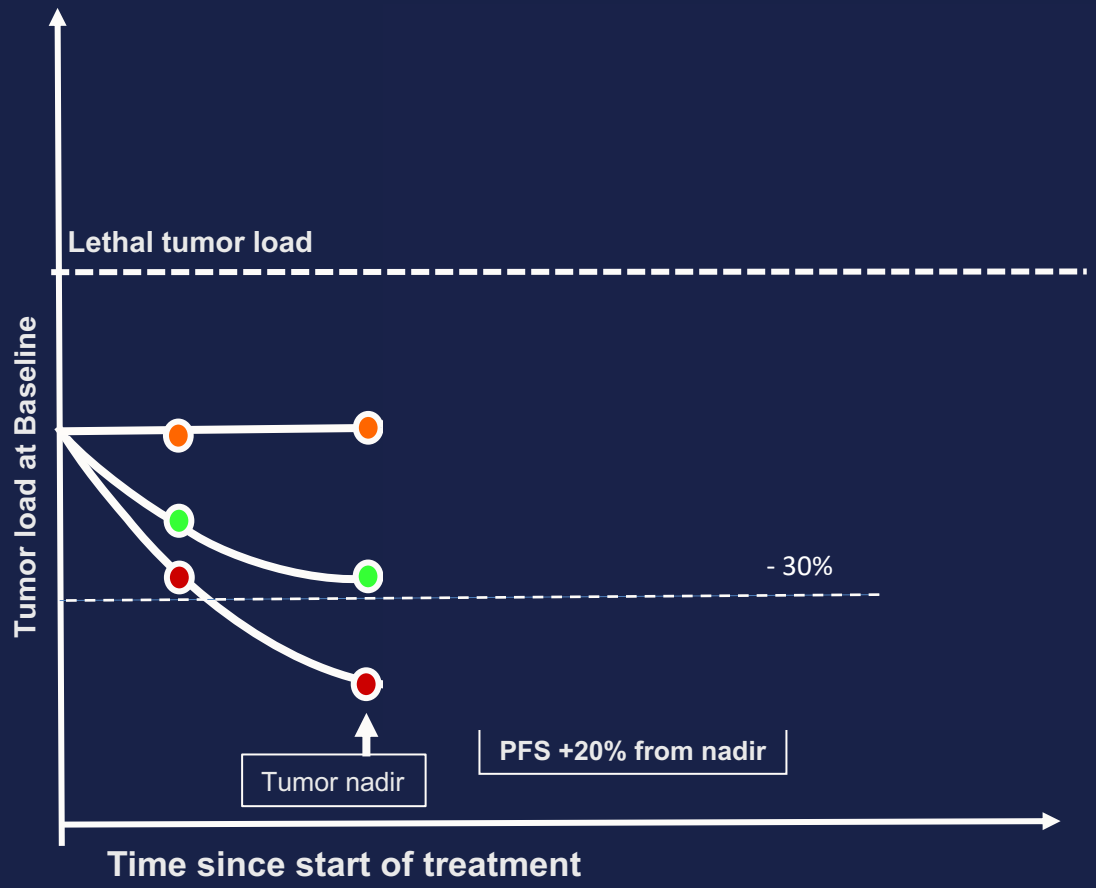




Why does response matter? Related to PFS

-for any given PFS, highest RR yields lowest tumor burden



Conclusion-IR perspective

- Level of evidence is limited: surgery, ablation, embolization
- If PR is sought, locoregional therapies provide the highest PR rates
  - Bulk symptoms
- “Limited extrahepatic disease” is heterogeneous term
  - Pattern of progression varies in the liver and extrahepatic sites
  - Still strong rationale to perform LRT if liver dominant disease
- Radiation works
  - Known for 20 years
  - Lu177! Also caused lymphopenia
  - Cost of Y90 versus Lu177?
  - Toxicities followed for median 14 months from NEJM...chronic toxes?
  - OS from NETTER-1 looks like it may converge at 3-4 years. Same as Y90.
- RETNET trial- randomized study comparing bland, cTACE and DEBTACE
  - HPFS