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# Liver-directed therapies for patients with metastatic NET

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# Hepatic (liver) metastases in NE

- Only <30 cases of primary hepatic NE tumors reported
- However, 5-40% of all NE tumors eventually spread to the liver, depending on organ of origin
- When NE spreads, liver is the most common site, and metastases are frequently liver-only or liver-dominant
- Hepatic metastases are a major source of morbidity (symptoms, disability) and mortality (death)
- Controlling the growth of hepatic metastases can prolong survival and improve quality of life

# Liver-directed therapies

- It does not always make sense to treat the whole body
- Limit side effects by treating only where tumors are recognized
- Surgery, radiation therapy work this way
- More options available now with improvements in imaging technologies, devices:
  - Thermal ablation
  - Image-guided radiotherapy
  - Catheter-based methods (embolization, chemoembolization, radioembolization)

# Ablation

- Heat

  - Microwave (MWA)

  - Radiofrequency (RFA)

  - (Laser interstitial thermal therapy) (LITT)

  - High-intensity focused ultrasound (HIFU)

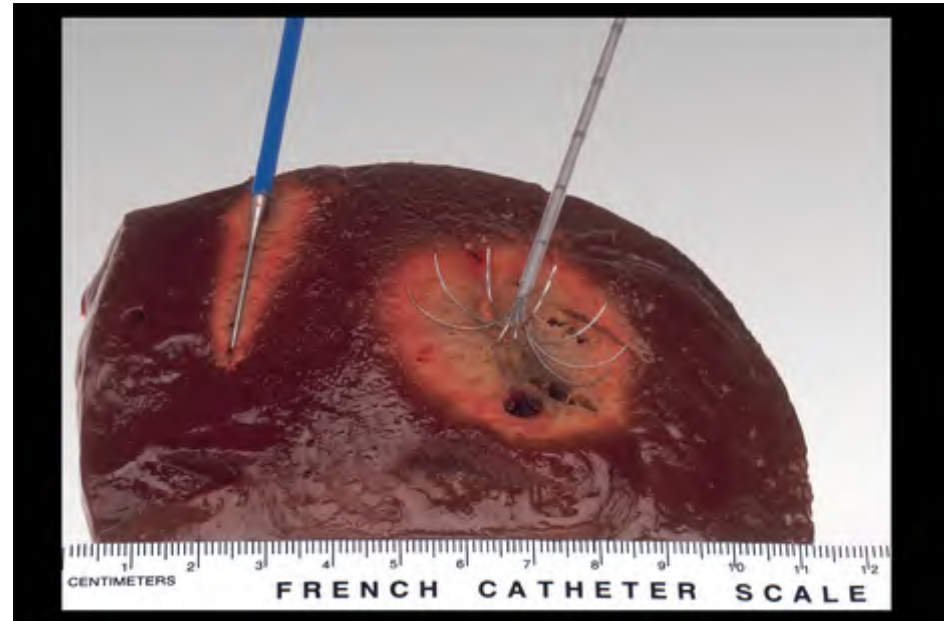
- Cold

  - Cryoablation

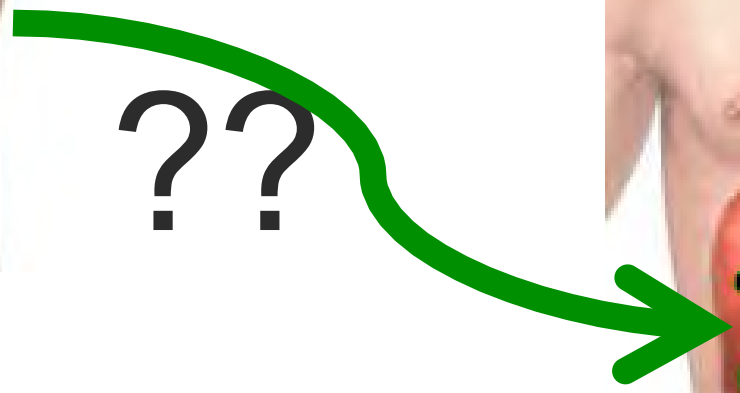
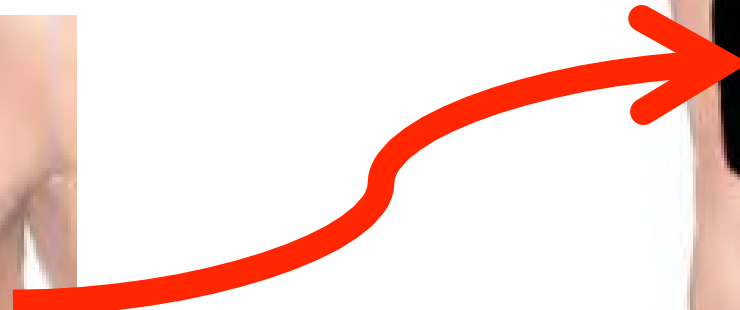
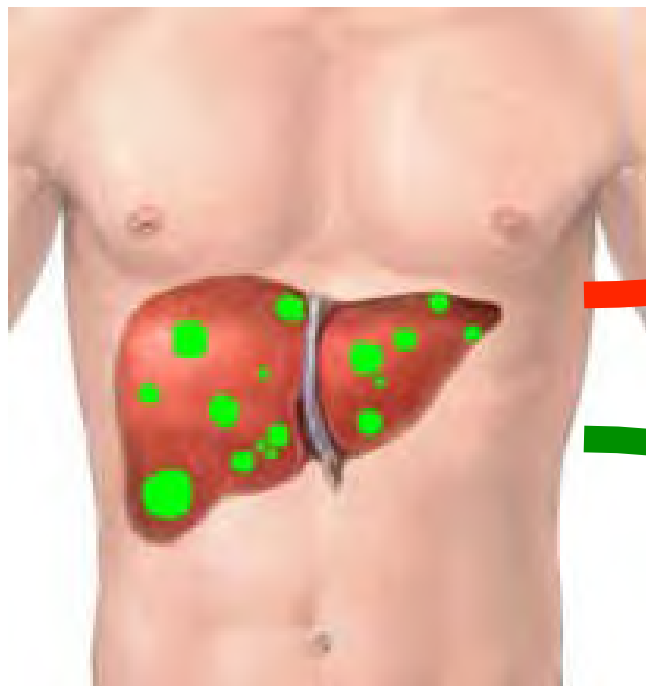
- Electrocutation

  - Irreversible electroporation (IRE)

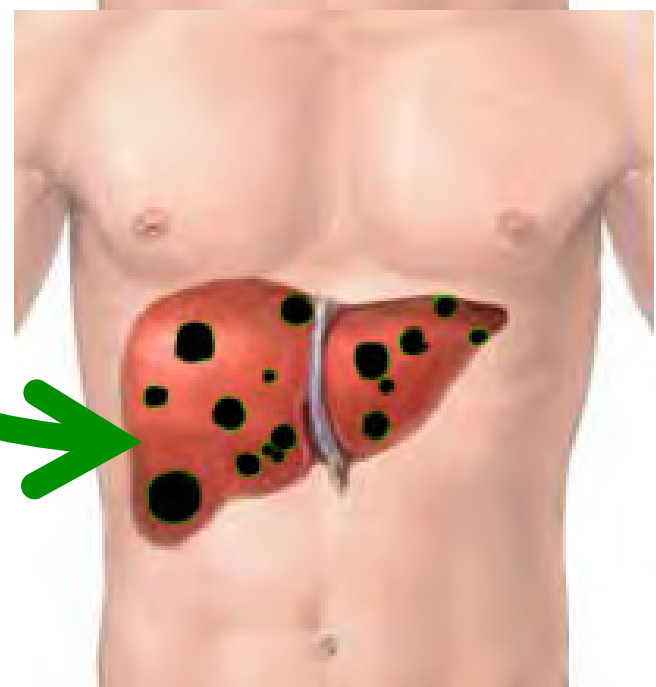
- Best suited to 1-2 lesions, < 3 cm diameter



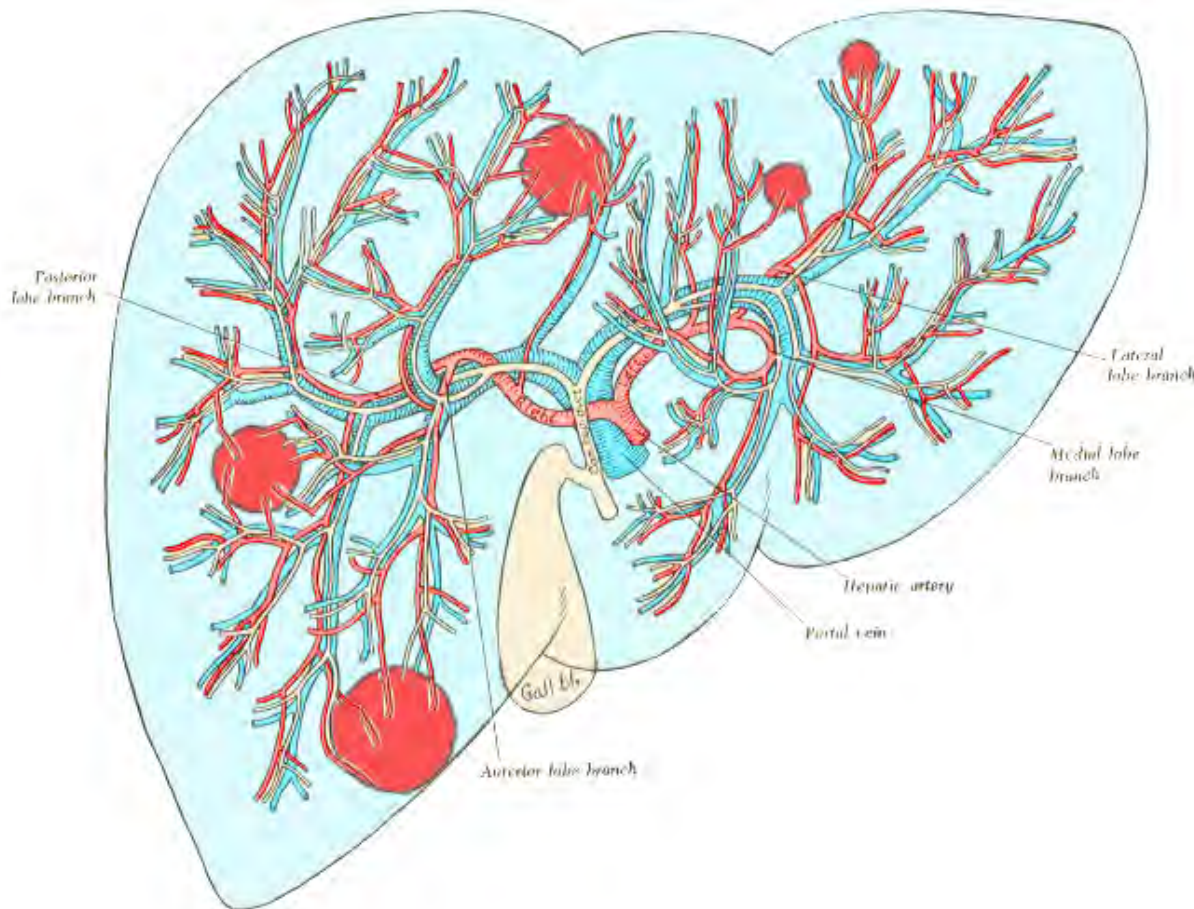
# Limit collateral damage



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# Dual blood supply



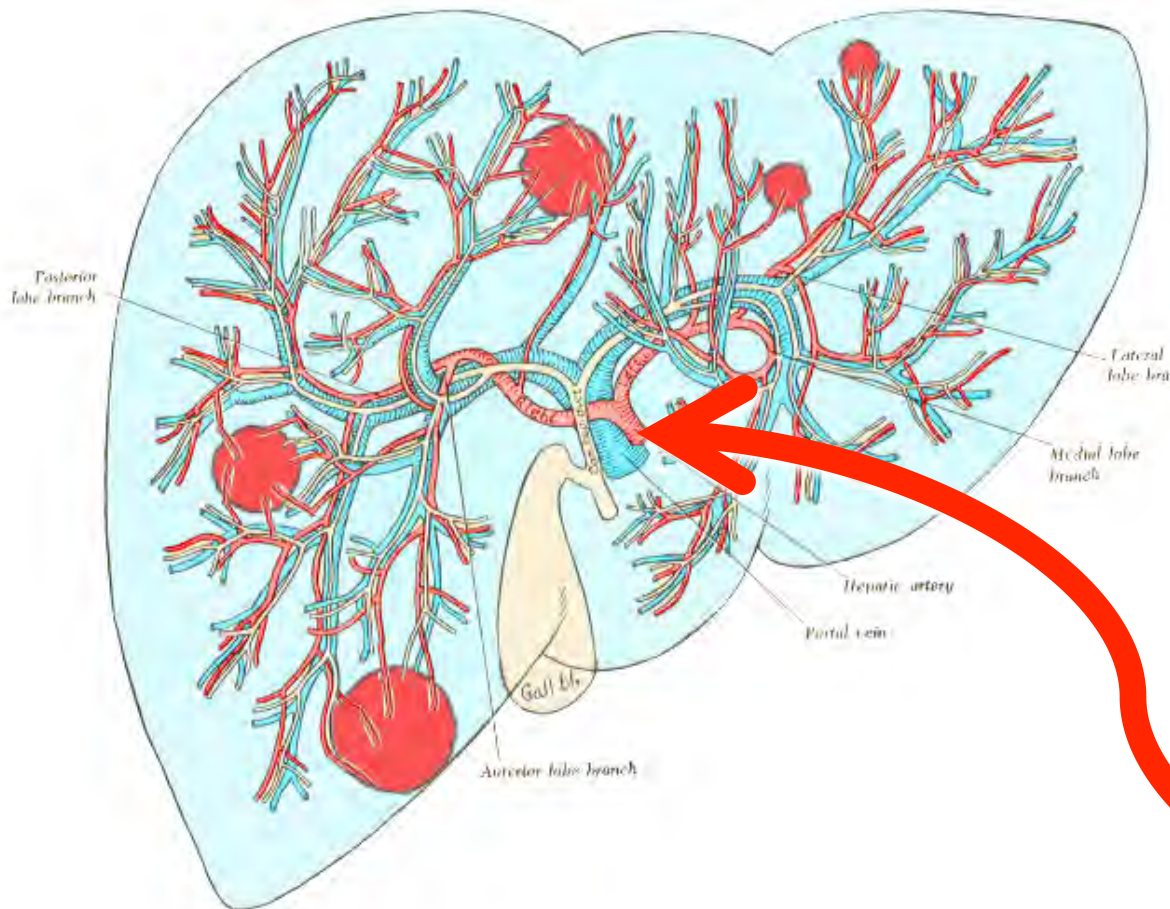
- Liver normally receives 70% of its blood from portal vein, 30% from hepatic artery
- Tumors receive >90% of their blood from hepatic artery

At the Cal entrance



At the Stanford entrance

# Give cancer-killing stuff into the artery



- Chemoinfusion
- Chemoembolization
- Radioembolization
- Bland embolization
- Chemosaturation





# Less popular options

- Hepatic arterial chemoinfusion
  - Performed through temporary catheter, percutaneous port, or surgically-implanted pump with reservoir
  - Delivers higher amount of chemo to liver than to rest of body
  - Benefit difficult to prove
- Bland embolization
  - Injection of mechanical blockers of arterial blood flow, like medical grade dust or sand
  - Starves tumors of blood, nutrition, oxygen
  - It works, but has potentially severe side effects (pain, nausea, fever), and most believe combined methods work better
  - Trials underway, but accrual slow

# Transarterial Chemo-Embolization (TACE)

## ■ Technique

- Injection of concentrated chemotherapy mixed with sticky oil and embolization material
- Newer method of drug-eluting microspheres (tiny sponge balls)

## ■ Rationale:

- High local dose of chemotherapy
- Prolonged dwell time
- Ischemia (lack of blood, oxygen, and nutrients)
- Limited liver and systemic toxicity

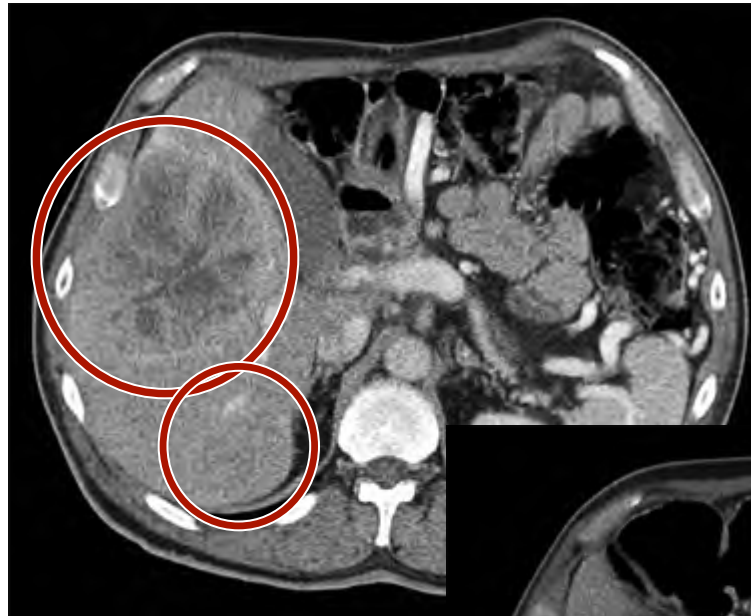
# Level I Evidence:TACE (HCC only)

- Llovet et al. (Lancet 2002; 359:1734)
  - Survival: TACE (82%, 63%) > embo (75%, 50%) > supportive (63%, 27%)
  - Hazard ratio 0.47
- Lo et al. (Hepatology 2002; 35:1164)
  - Survival: TACE (57%, 31%, 26%) > supportive (32%, 11%, 3%)
  - Hazard ratio 0.49
- No good proof for NE, anecdotal evidence for 30 years

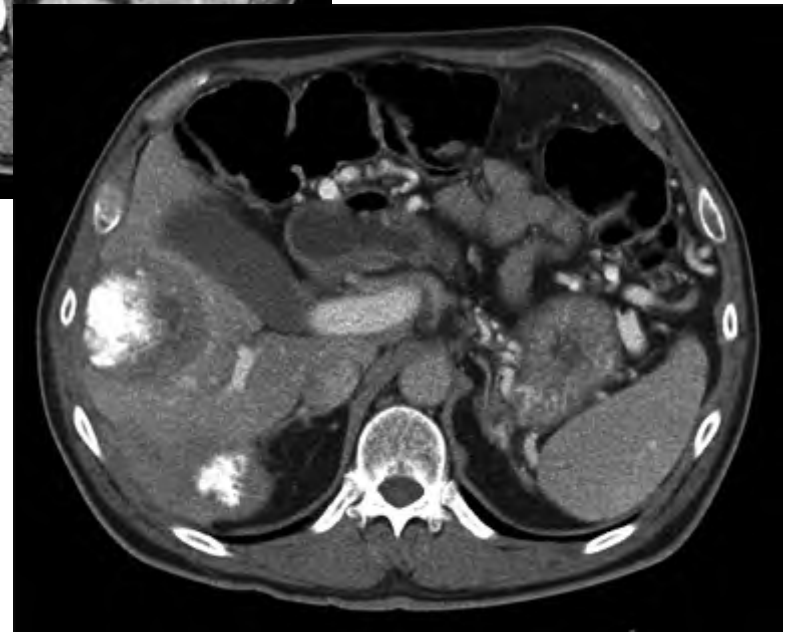


# Example of NE treated by TACE

- Pretreatment



- 4 months post



# Radioembolization (TARE)

- $^{90}\text{Y}$ trium: pure  $\beta$  emitter (.9367 Mev)
- Average tissue penetration 2.5 mm, maximum penetration 11mm
- Neutron bombardment of  $\text{Y}^{89}$ , decays to  $\text{Zr}^{90}$
- $T_{1/2} = 64 \text{ h}$

A periodic table of elements with a red arrow pointing from the top-left towards the element Yttrium (Y) in the transition metal block. The arrow points to the space between Yttrium (Y) and Zirconium (Zr) in the 5th period, indicating the decay path from  $\text{Y}^{89}$  to  $\text{Zr}^{90}$ .

1																	2
3	4											5	6	7	8	9	10
11	12											13	14	15	16	17	18
19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
55	56	57	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86
87	88	89	104	105	106	107	108	109	110								
		58	59	60	61	62	63	64	65	66	67	68	69	70	71		
		Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu		
		Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr		

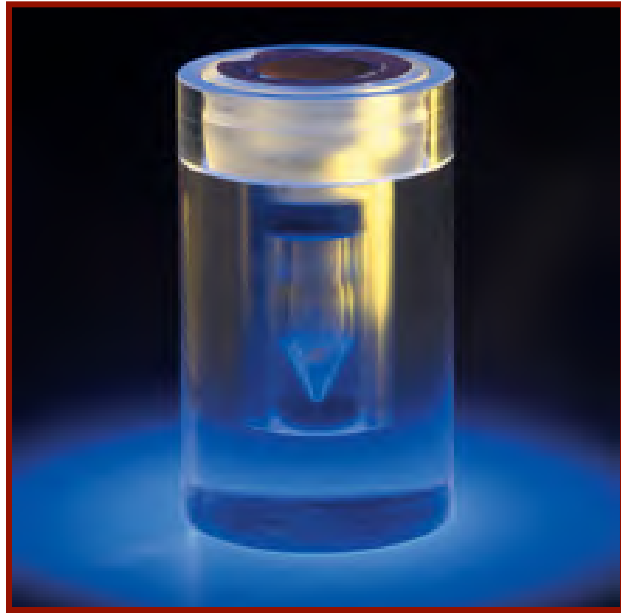
# Rationale

- Liver is radiosensitive (~30 Gray max; VOD, RILD)
- Tumors may be resistant (some require 60-80 Gray to be killed). Above 80 Gray, everything is affected.
- Arterially administered beads preferentially lodge in tumors – whatever is thirstiest gets the most radiation



# $^{90}\text{Y}$ trium formulations

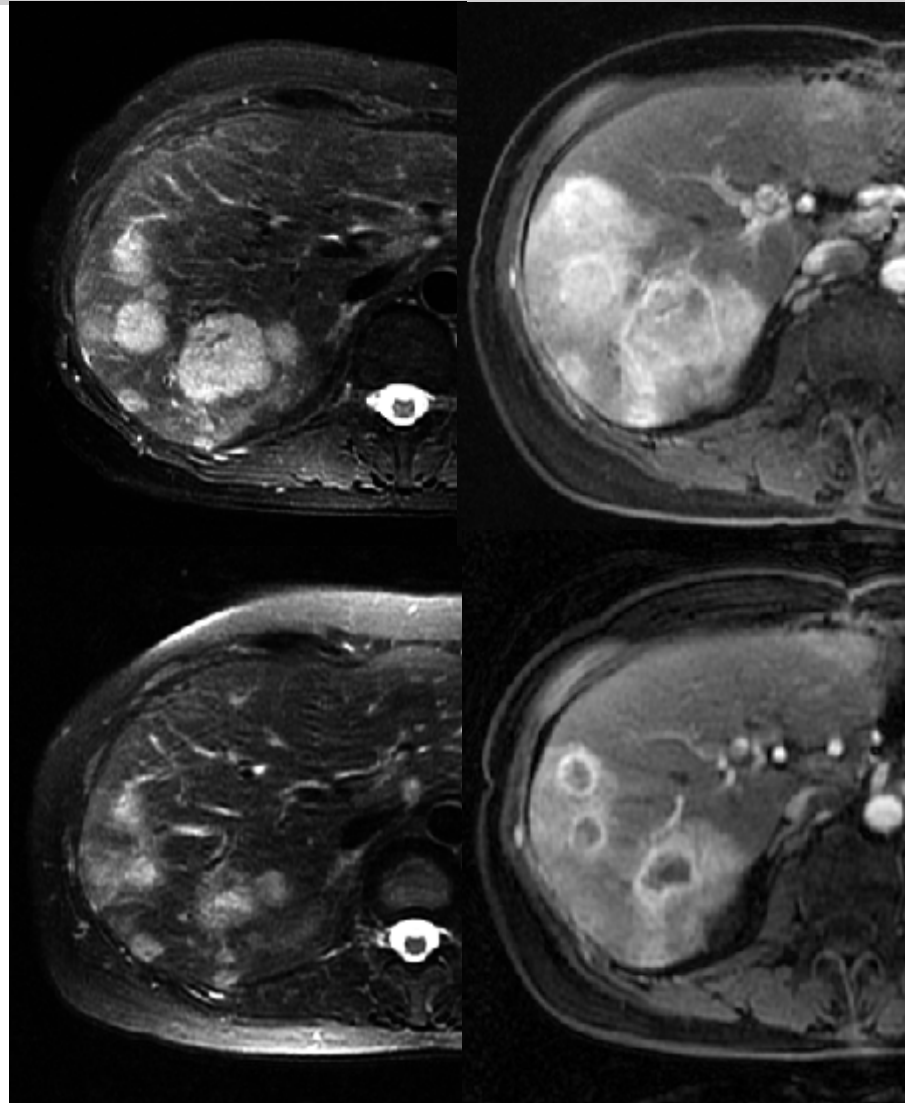
- SIR-Spheres (SIRtex, Australia)
  - Resin microspheres 25-35  $\mu\text{m}$
  - FDA PMA-approved 2002 for CRC with FUdR HAI



- TheraSpheres (BTG/Nordion, Canada)
  - Glass microspheres 20-30  $\mu\text{m}$
  - FDA-approved 1999 as HDE for HCC

# Metastatic NE treated by TARE

Pre



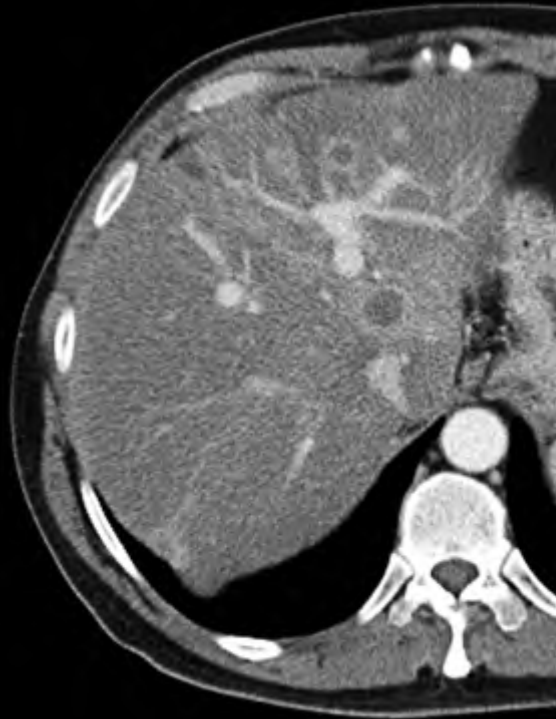
3 months post



# Metastatic NE treated by TARE



Pre



3 mos



19 mos

# How to choose?

- Side effects very similar (fatigue, lack of appetite, some pain and nausea, lasting 1-4 weeks)
- Evidence of effectiveness also very similar
  - Kill a majority of tumor cells in a majority of patients, but difficult to predict. Time gained depends on rate of growth.
- TARE is more expensive, and is designed to be a one (or two) time treatment
- If one does not work or stops working, switch
- Most patients opt for TARE first – slightly easier recovery, longer duration of benefit

# Published literature

- Meta-analysis of TARE:
  - ORR: 48%
  - DCR: 85%
  - Median OS: 29 months

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## **The Efficacy of Hepatic <sup>90</sup>Y Resin Radioembolization for Metastatic Neuroendocrine Tumors: A Meta-Analysis**

Zlatko Devcic<sup>1</sup>, Jarrett Rosenberg<sup>2</sup>, Arthur J.A. Braat<sup>3</sup>, Tust Techasith<sup>1</sup>, Arjun Banerjee<sup>1</sup>, Daniel Y. Sze<sup>1</sup>, and Marnix G.E.H. Lam<sup>1,3</sup>

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# PRRT +/- TARE

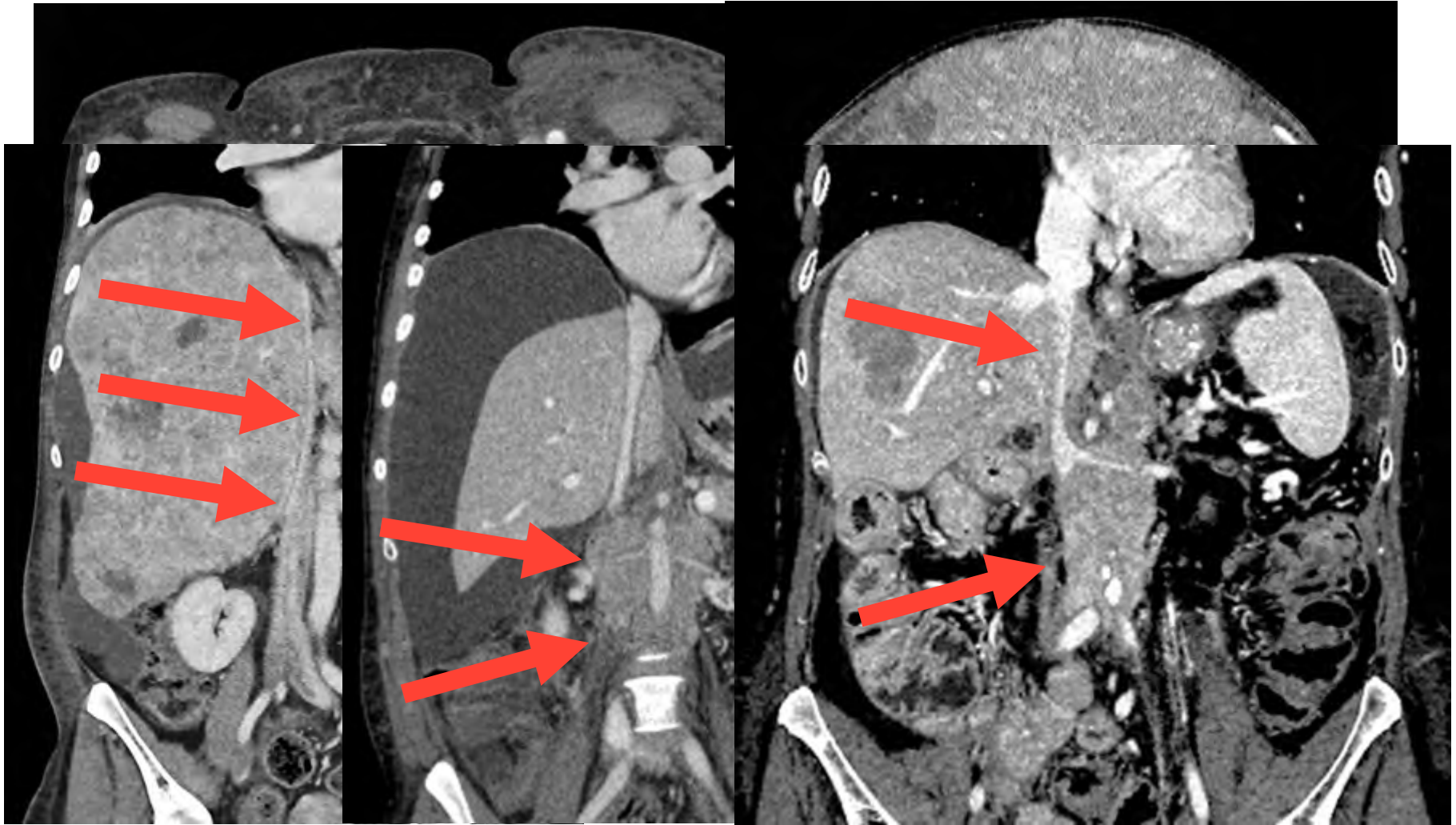
- Both cause collateral radiation damage to the liver
- 3 papers showing safety in 23, 20, 1 patients who received TARE after failed PRRT
- Unpublished reports of patients who went into fatal liver failure after receiving both – no good way to predict liver radiation exposure, risk
- TARE results in higher dose to liver tumors, PRRT treats disease outside of the liver
- Work in progress: inject PRRT agent into the liver

# Treating vascular blockages

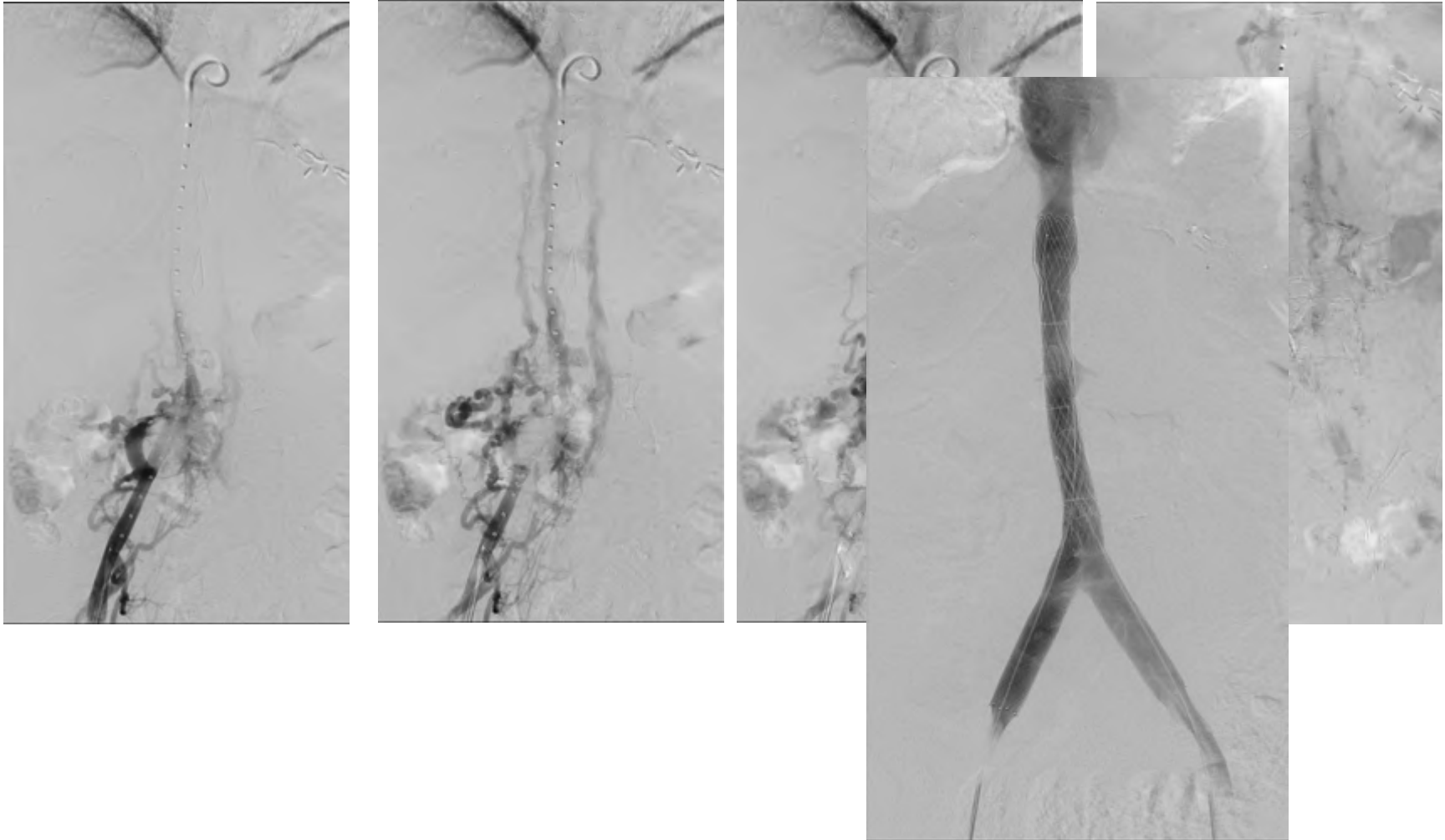
- Many patients with liver and lymph node metastases develop swelling of the feet and legs (peripheral edema) and fluid accumulation in the abdomen (ascites)
- May be in part due to blockage of blood vessels:
  - IVC (inferior vena cava)
  - Portal vein



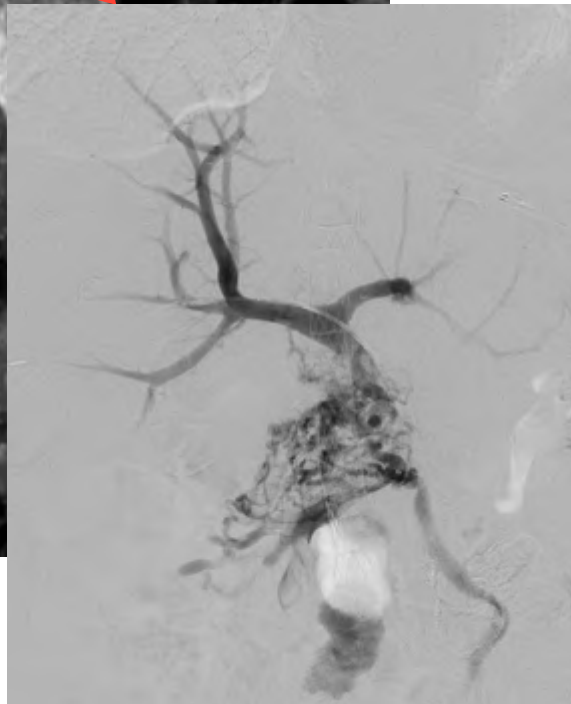
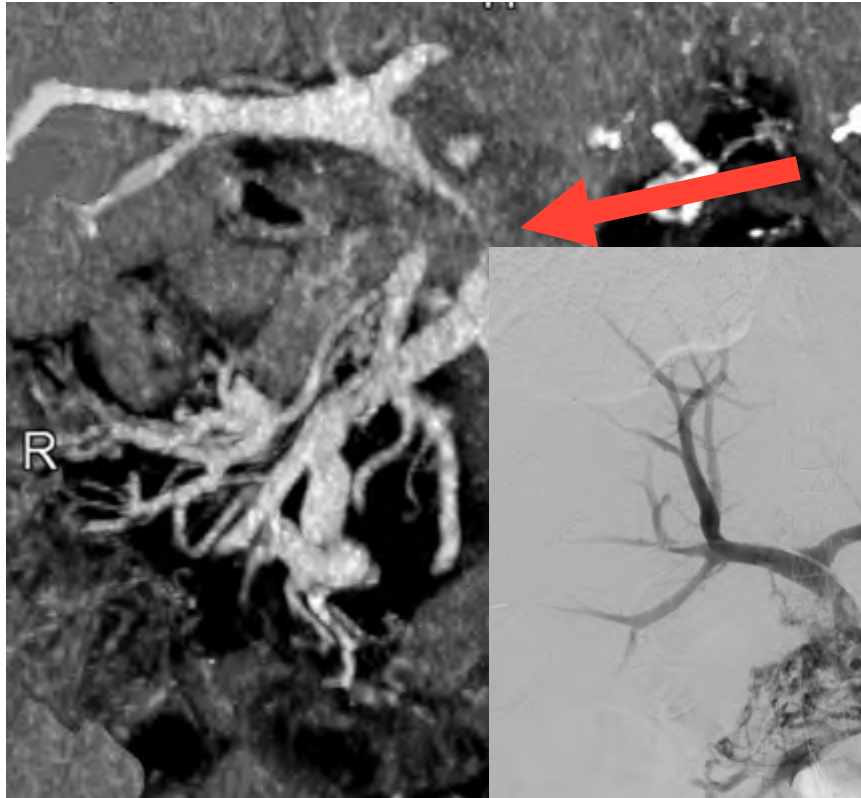
# Inferior vena cava (IVC)



# Inferior vena cava (IVC)



# Portal vein



Big blood vessels we can fix.  
Small (lymphatic obstruction, cirrhosis, etc.) not so much



# Conclusions

- Cancer (especially NET) is not an automatic death sentence, even after spreading to the liver, and can be treated as a chronic disease.
- Although many cancers including NET are spread systemically, liver tumors are responsible for significant morbidity and mortality.
- Spatially targeted methods to attack liver metastases (chemoembolization, radioembolization), though not curative, result in substantial benefit.
- Most treatments are “off label,” and may require a fight with your insurance company.
- Blocked plumbing can also be reopened



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