My Approach to Neuroendocrine Tumor

Ghassan El-Haddad, MD

Associate Member, Interventional Radiology and Cancer Physiology

Moffitt Cancer Center and Research Institute

Associate Professor, Interventional Radiology, and Oncologic Sciences

University of South Florida

Disclosures

- Consulting: Novartis, Canon medical systems, Boston Scientific corporation, Curium pharma, Terumo medical corporation, Bayer

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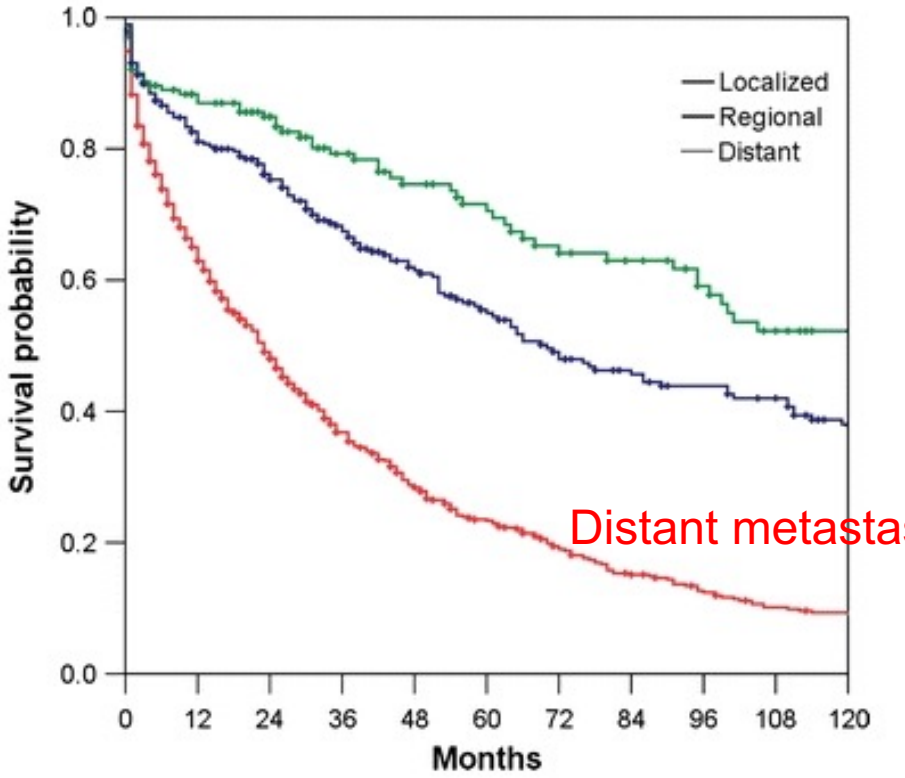
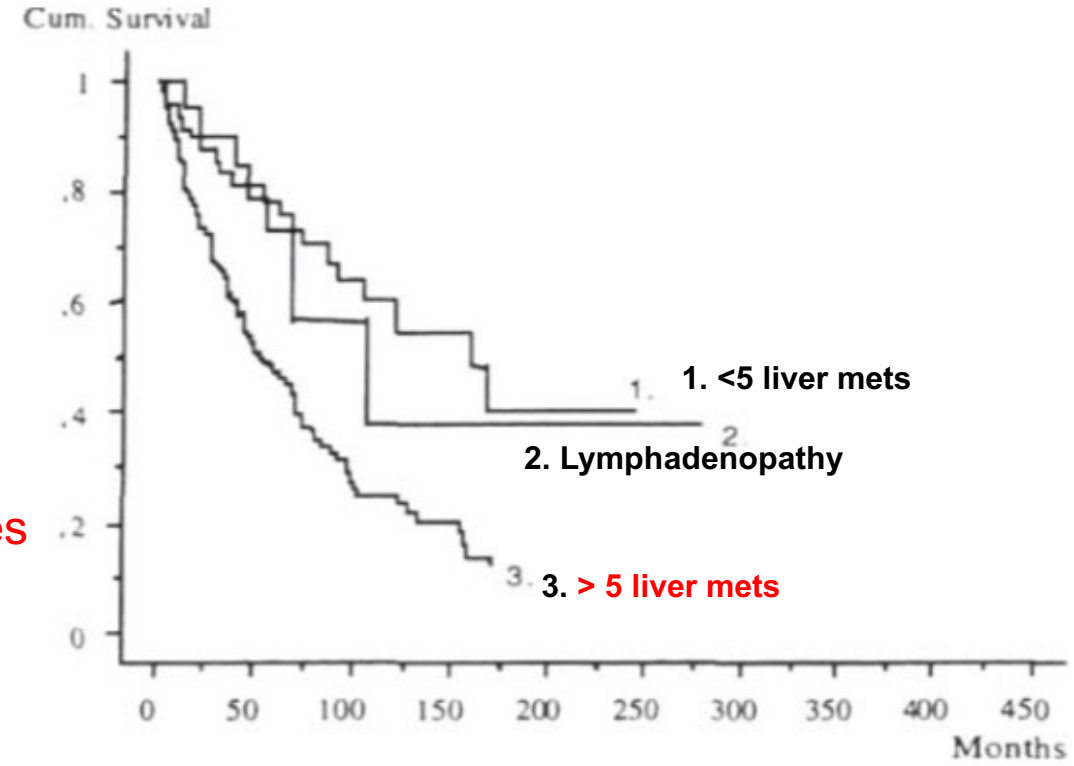
Impact of NET Liver metastases

Pancreatic NET



Distant metastases

Carcinoid



1. <5 liver mets

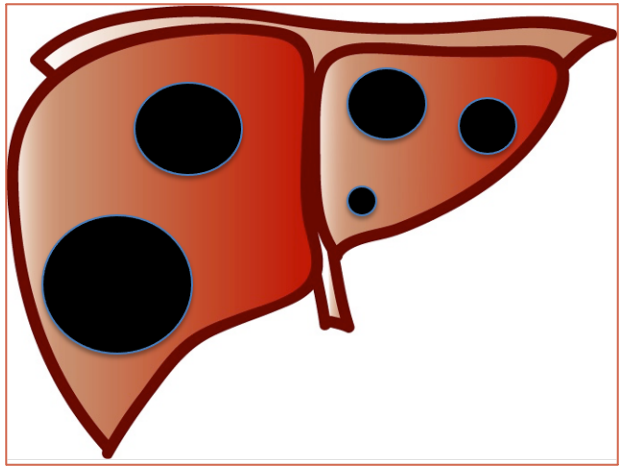
2. Lymphadenopathy

3. > 5 liver mets

Yao et al. Ann Surg Oncol. 2007 Dec; 14(12): 3492–3500.
Janson ET, et al. Ann Oncol. 1997 Jul;8(7):685-90.

Metastatic NET

- Peptide Receptor Radionuclide Therapy (PRRT)



- Embolotherapy
  - TAE
  - TACE
  - TARE

TAE: Bland embolization
TACE: Chemoembolization
TARE: Radioembolization
ORR: Overall response rate

Embolotherapy for liver dominant mNET
TAE/TACE/TARE

- Symptomatic, progressive, or bulky hepatic metastases
- ORR~50% (67% carcinoids, 35% pancreatic neuroendocrine tumors)
- Median time-to-progression ~ 12 to 18 months
- ~80% with hormonal syndromes experience symptomatic responses

TAE: Bland embolization
TACE: Chemoembolization
TARE: Radioembolization
ORR: Overall response rate

Shah MH, et al. J Natl Compr Canc Netw. 2018;16(6):693-702.
Strosberg JR, et al. Pancreas. 2017;46(6):707-14.
Pavel M, et al. Neuroendocrinology. 2016;103(2):172-85.
Knigge U, et al. Surgeon. 2008;6(4):232-9.
Gupta S, et al. Cancer. 2005;104(8):1590-602

Which embolotherapy to choose?

Randomized Embolization Trial for NeuroEndocrine Tumor Metastases To The Liver (**RETNET**) trial

- Objective: estimate duration of Hepatic Progression Free Survival
  - Bland Embolization
  - Lipiodol Chemoembolization

(*Drug-Eluting Bead Chemoembolization: excluded after safety report*)

https://clinicaltrials.gov/ct2/show/NCT02724540

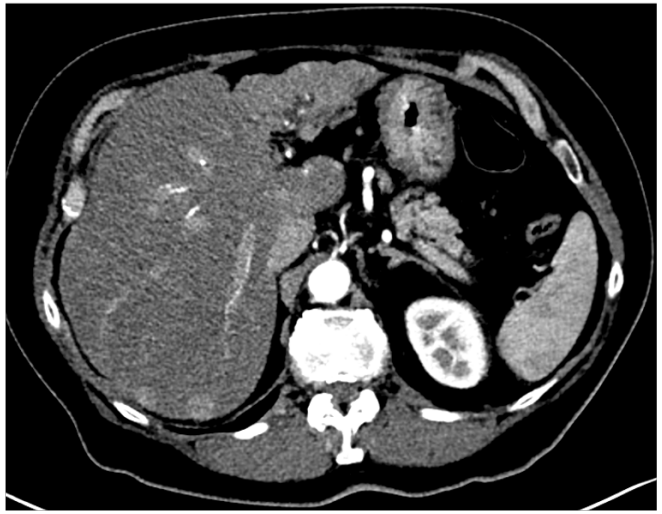
- Single-arm Phase 2 trial of DEB-TACE in NETs closed early: 7/13 (58%) subjects developed bilomas or liver abscesses
- Prospective French trial of 20 subjects: hepatic necrosis in five patients (25%)
- Retrospective studies showing higher rates of biliary complications

Bhagat N, et al. Cardiovasc Intervent Radiol 36:449-59, 2013
de Baere T, et al. J Vasc Interv Radiol 19:855-61, 2008
Guiu B, et al. J Hepatol 56:609-17, 2012
Joskin J, et al. Cardiovasc Intervent Radiol 38:372-80, 2015

Radioembolization induced chronic liver disease

- Ascites
- Liver failure
- Pseudocirrhotic appearance
- Can develop 6 months post TARE
- Concern for bilobar mNET treatment

70-year-old woman with metastatic ileal carcinoid



1/9/13
111.6 Gy Y90 glass microspheres Left lobe

11/3/16
Bland embolization Right

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

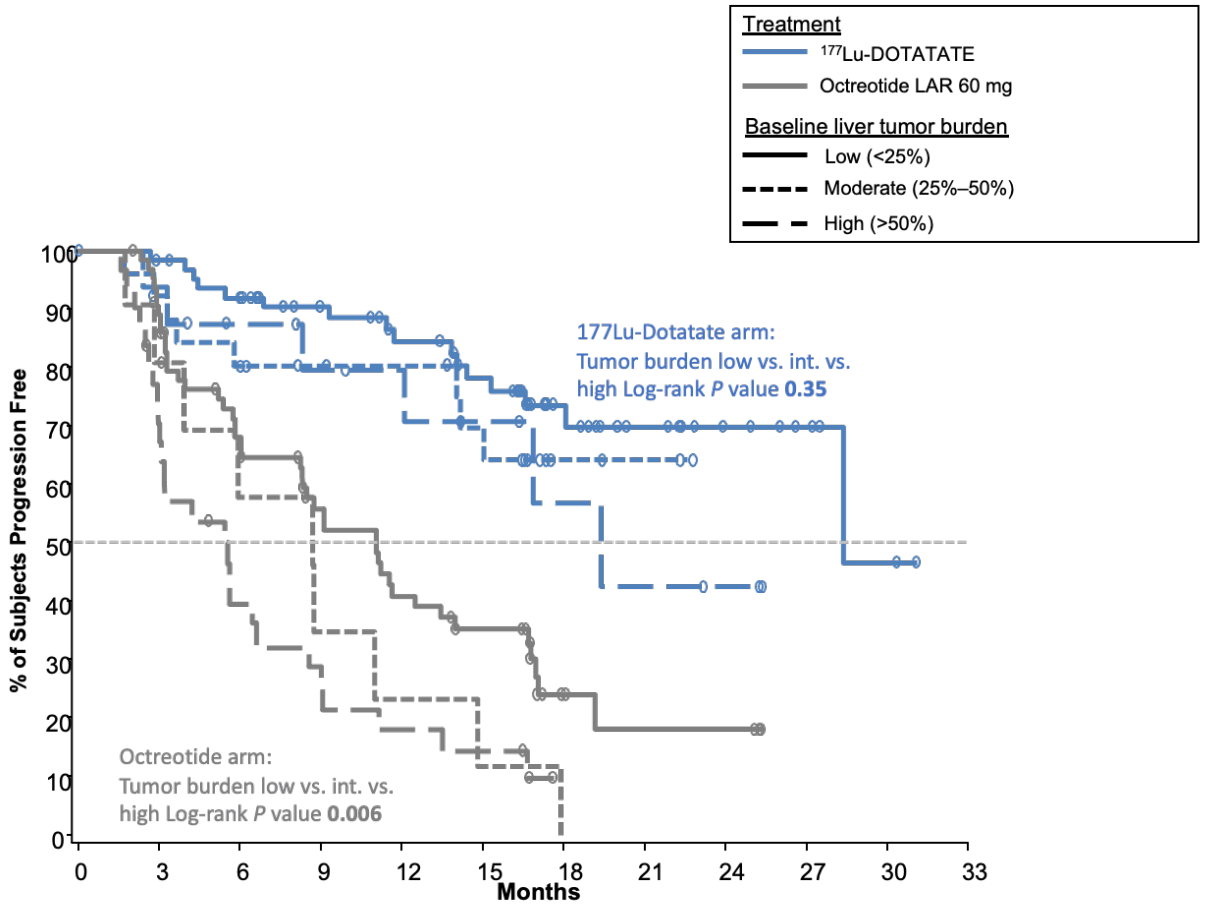
Peptide Receptor Radionuclide Therapy (PRRT)

- Lu-177 DOTATATE approved 1/26/18, SSTR–positive GEP-NETs
- Based on NETTER-1 and data from ERASMUS Medical Center
- Mainly used for WD G1/G2 NET, G3 (ki-67%<55%) who failed or who cannot tolerate chemotherapy
- SSTR-positive bronchial NET
- Long PFS, 30-40 months, improved QOL
- Relatively low toxicity, <1% liver dysfunction
- ORR NETTER-1: 18%

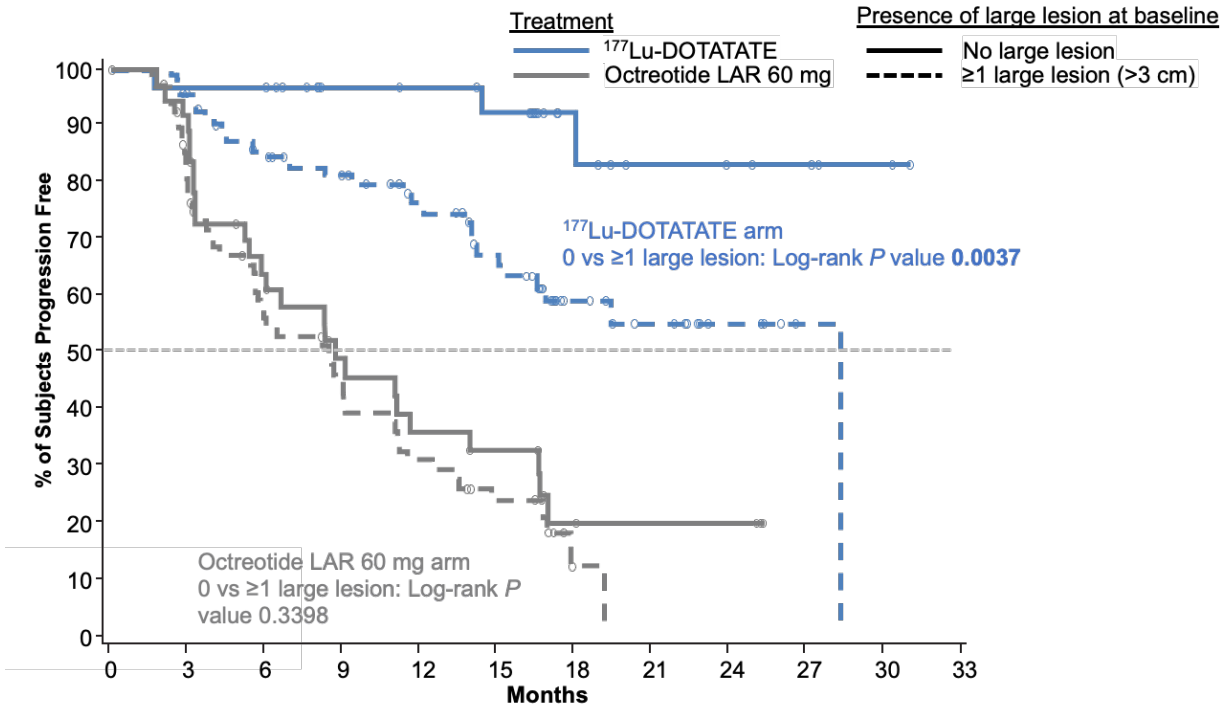
- SSTR, somatostatin-receptor.
- GEP, Gastroenteropancreatic
- WD, well differentiated
- QOL, Quality of life

Strosberg et al.N Engl J Med. 2017;376(2):125-135.
Brabander et al. Clin Cancer Res. 2017;23(16):4617-4624.
Hicks et al. Neuroendocrinology. 2017;105(3):295-309.
Strosberg J, et al. J Clin Oncol. 2018 Sep 1;36(25):2578-2584.
Bodei et al. Eur J Nucl Med Mol Imaging. 2015;42:5.

PFS by Baseline Liver Tumor Burden

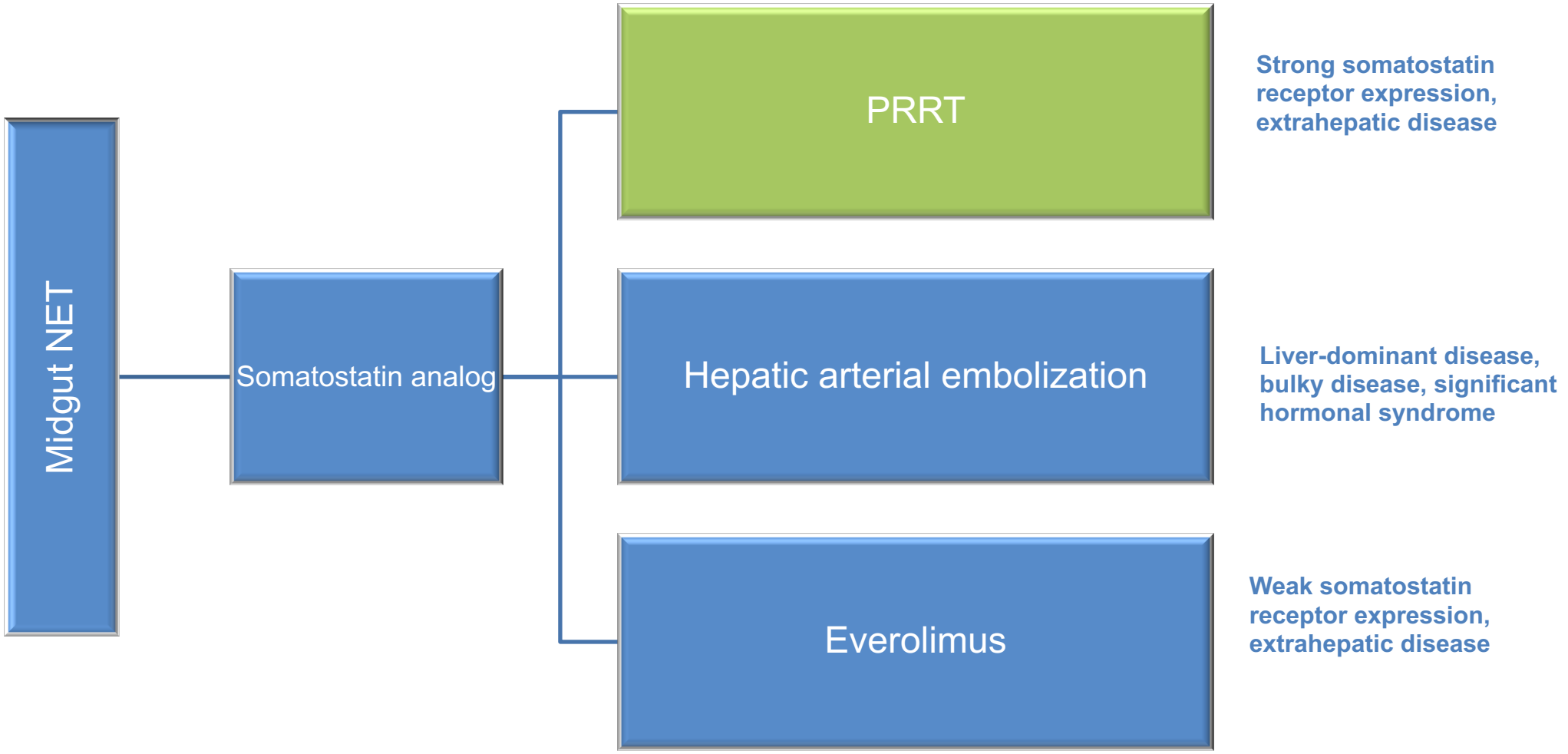


PFS Stratified by Presence of a Large Lesion at Baseline



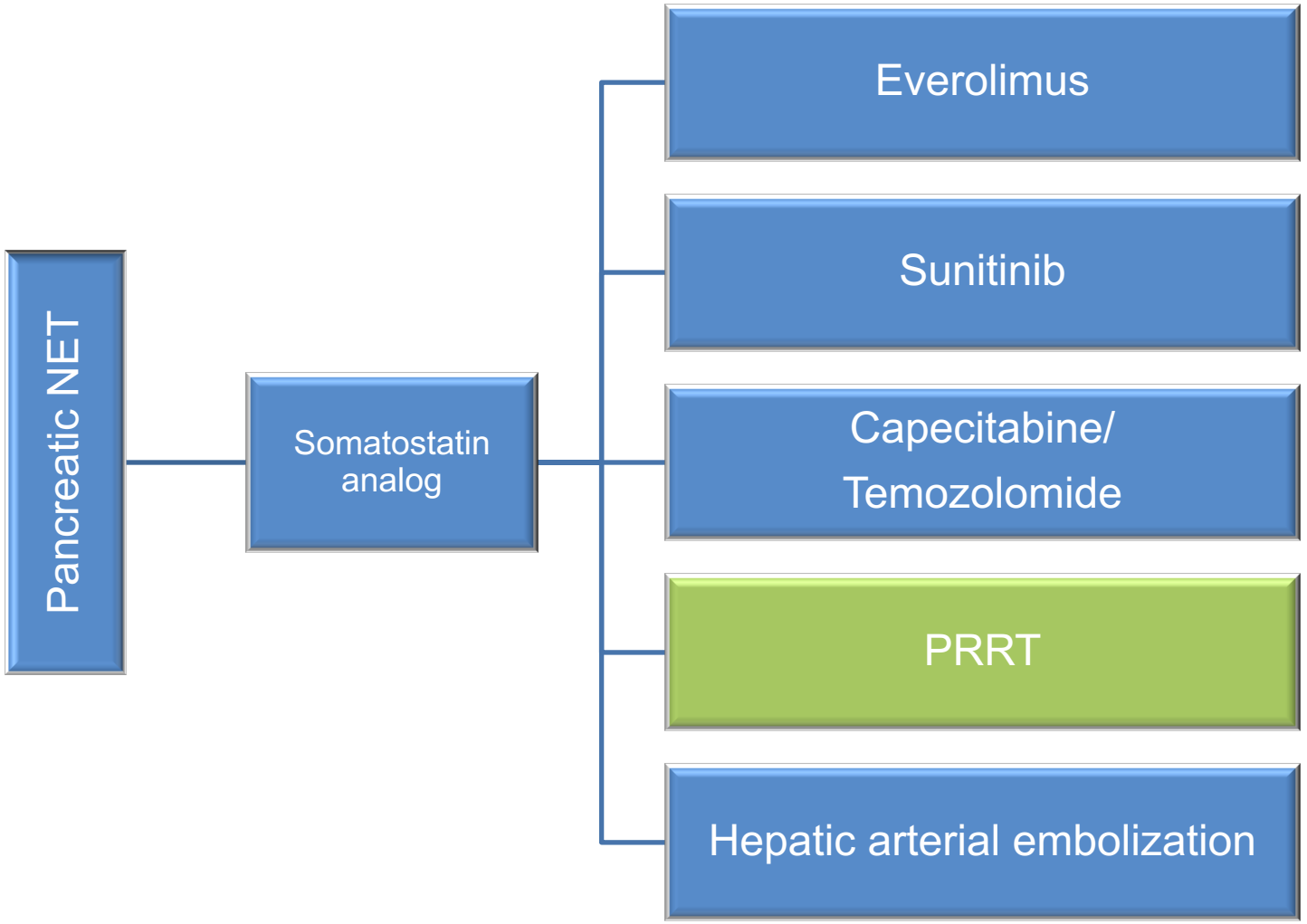
Strosberg J, et al. *Eur J Nucl Med Mol Imaging*. 2020;47(10):2372-2382.

Midgut NET



PRRT, peptide receptor radiotherapy.

Pancreatic NET



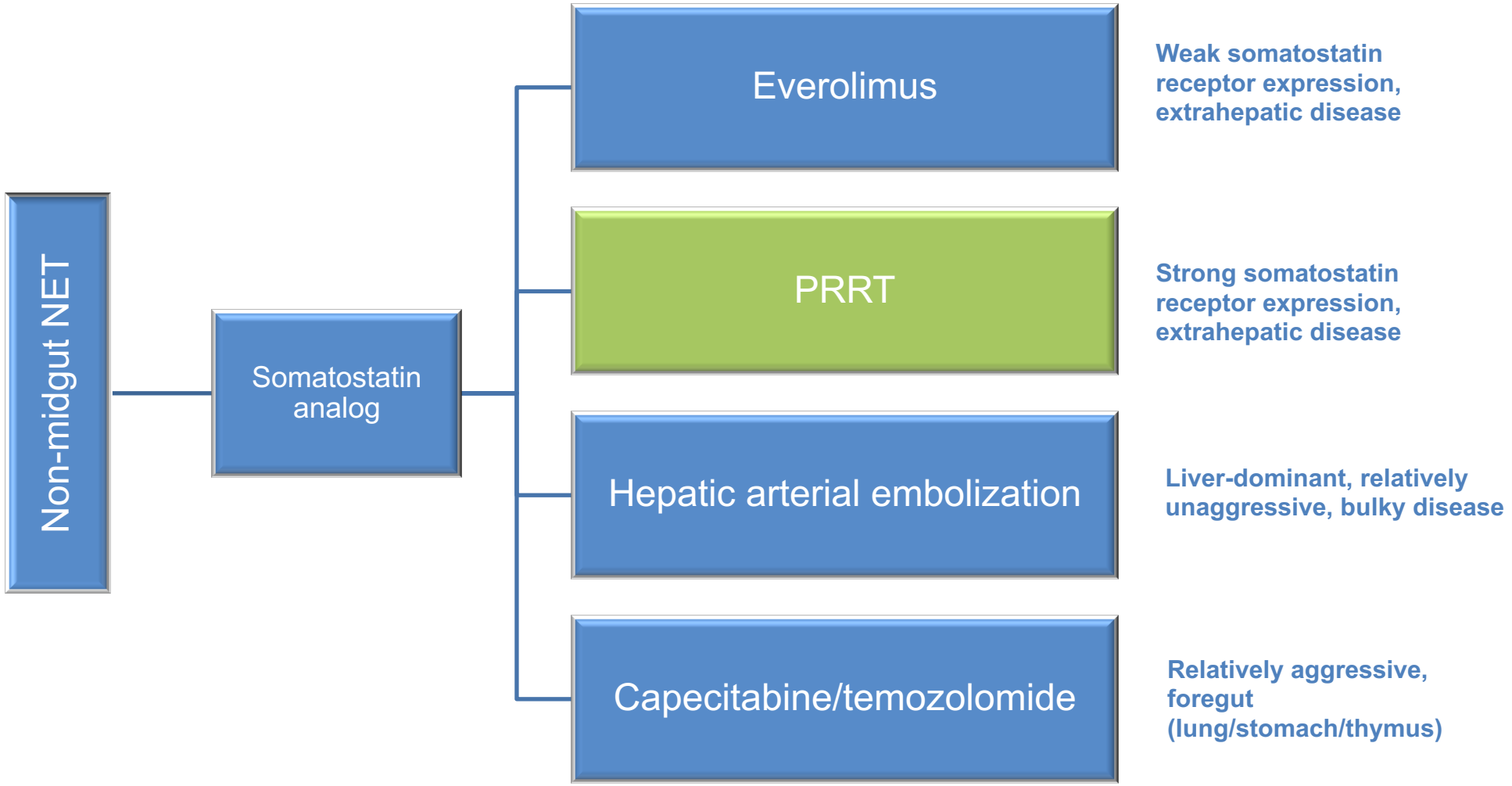
Weak somatostatin receptor expression, extrahepatic disease

Relatively aggressive disease

Strong somatostatin receptor expression, Extrahepatic disease

Liver-dominant, relatively unaggressive, bulky disease

Non-midgut GI NET



GI, gastrointestinal.

Midgut NET

43-year-old diagnosed with small bowel carcinoid in July 2007 after abdominal cramping.
5/2007: resection of SB tumor and root of mesentery tumor

5/2008: two measurable liver lesions
- RFA. Sandostatin LAR

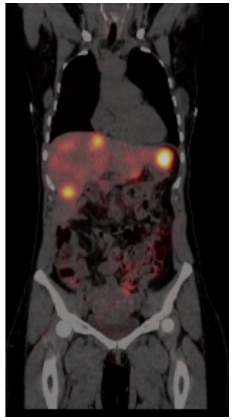
10/2009: liver disease progression
- Everolimus

11/2010: progression of liver lesions
- Hepatic bland embolization

11/8/10

Delay in progression by about 2 years

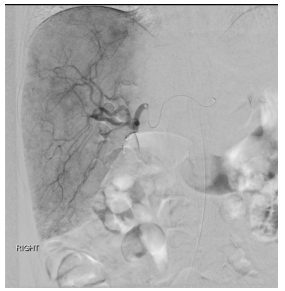
01/2013: progression of liver metastases
- Lu-177 DOTATATE PRRT



4/10/13

Delay in progression by about 6 years

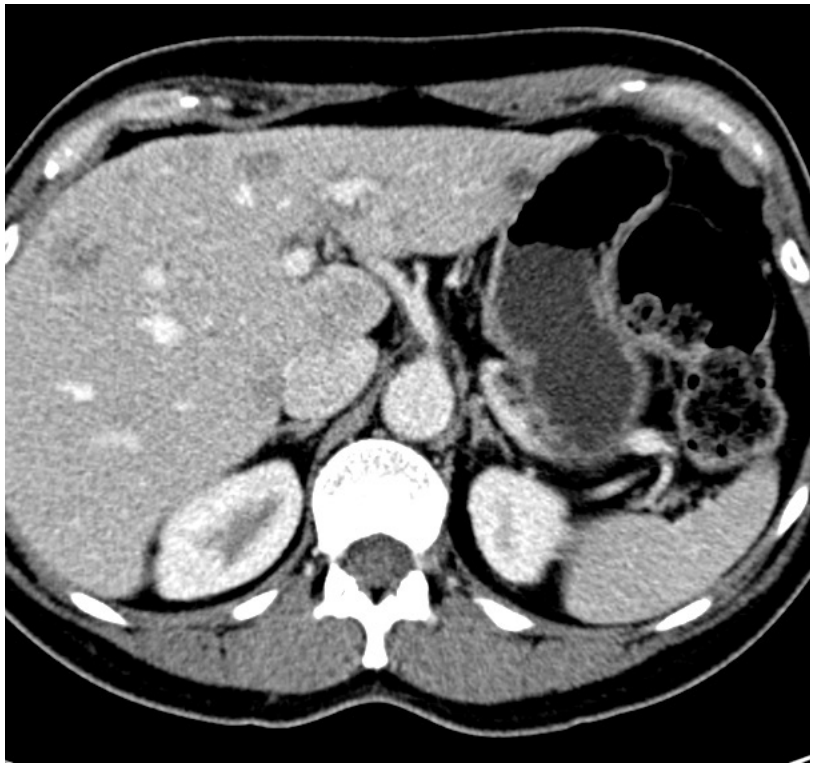
12/2018: liver progression
- Hepatic bland embolization



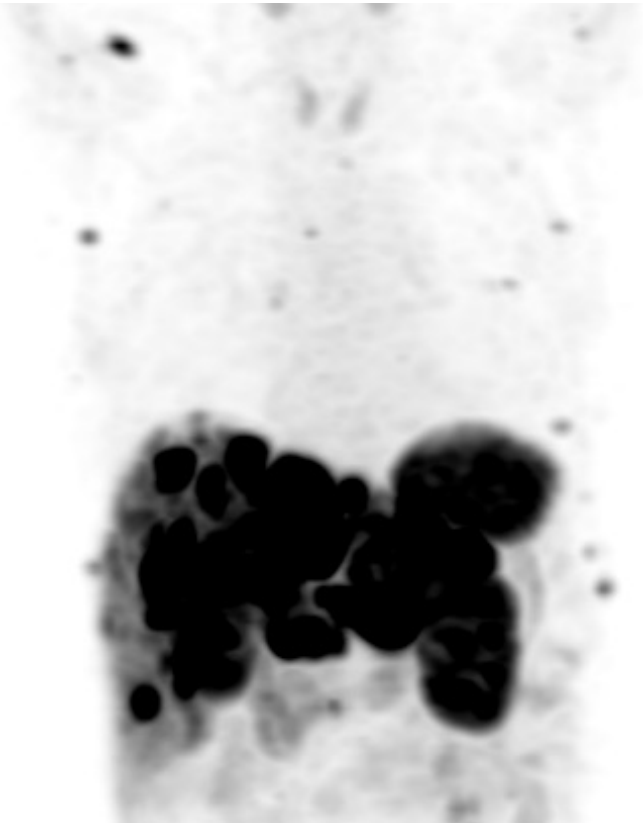
01/12/18

Progression 10 months after repeat HAE

10/2/18



12/3/18



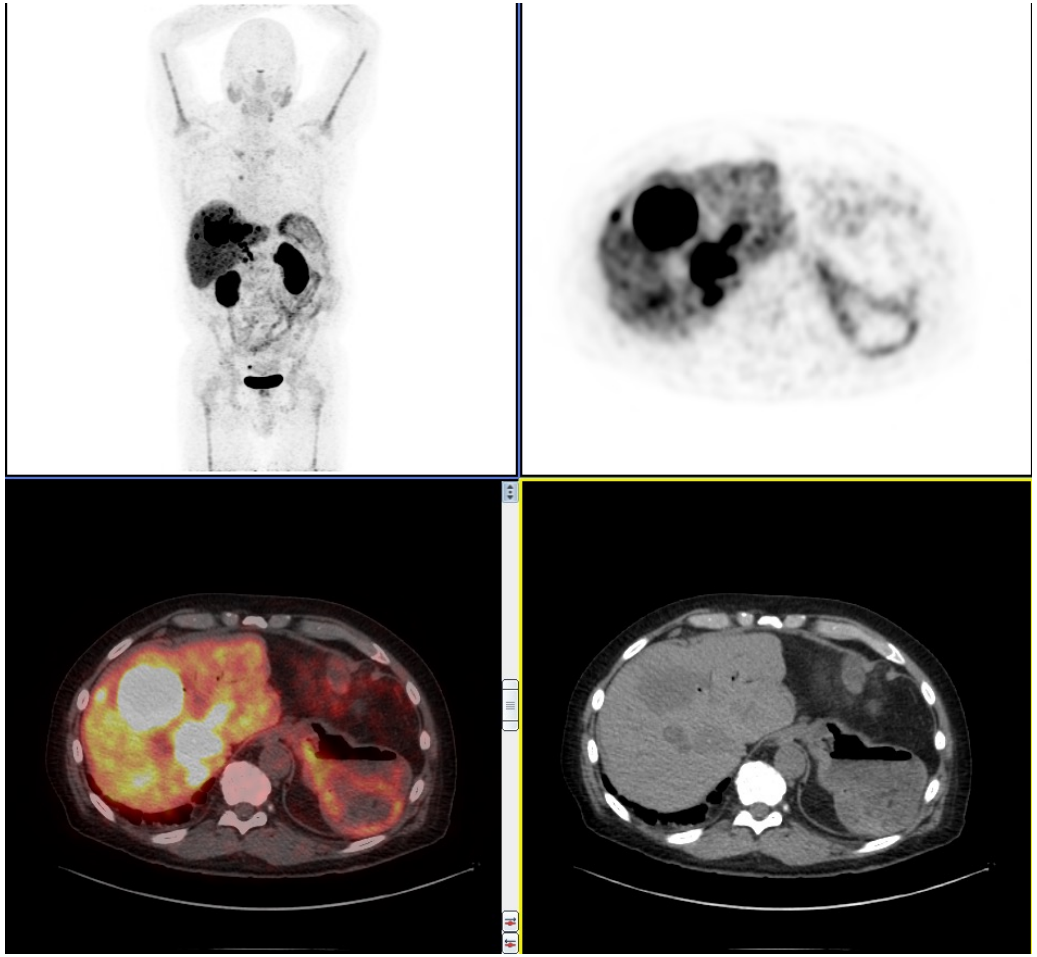
Sequencing of liver embolotherapy and PRRT

- Limited data on liver toxicity
- In NETTER-1 >80% of patients had liver metastases. 16% of patients who received Lutathera received TACE, TARE or TAE with low toxicity
- Early data conflicting
- Concern about long-term radioembolization hepatotoxicity
  - multicenter retrospective study ^{90}Y TARE after PRRT, 44 patients 58 TARE of which **55% whole liver**. Median of a year after PRRT, RECIST 1.1 at 3 months, ORR was 16% and disease control rate 91%. Three patients developed REILD and one died 20 weeks after TARE

Riff BP, et al. Clin Nucl Med. 2015;40(11):845-850.
Strosberg et al.N Engl J Med. 2017;376(2):125-135.
Hamiditabar et al. Clin Nucl Med. 2017;42(11):822-828.
Su et al. J Vasc Interv Radiol 2017; Nov 28:1520–1526
Tomozawa, et al. J Vasc Interv Radiol. 2018 Jun;29(6):858-865.
Braat A, et al. Cardiovasc Intervent Radiol. 2020;43(2):246-253
Sikaria D, et al. CIRSE 2020.

PRRT or Embolization?

- 72 y old man with metastatic WD G3 pNET diagnosed in 2009
- 1 ½ year on SSA
- Cap/Tem in 2014
- Bilobar TAE in Feb/Mar of 2017
- FOLFOX September 2017 for rapid progression in liver with poor tolerance
- Carbo/etoposide
- Total pancreatectomy and ablation of liver metastases 7/2018 complicated by hepatic abscess needing hepatic drain that caused an empyema leading to thoracotomy
- Progressed and received PRRT in 2019
- Imaging mid 2021 progression in the liver
- Chronic fatigue and recent anemia. Bone marrow biopsy was done demonstrating myelodysplastic syndrome



Delayed toxicity of PRRT

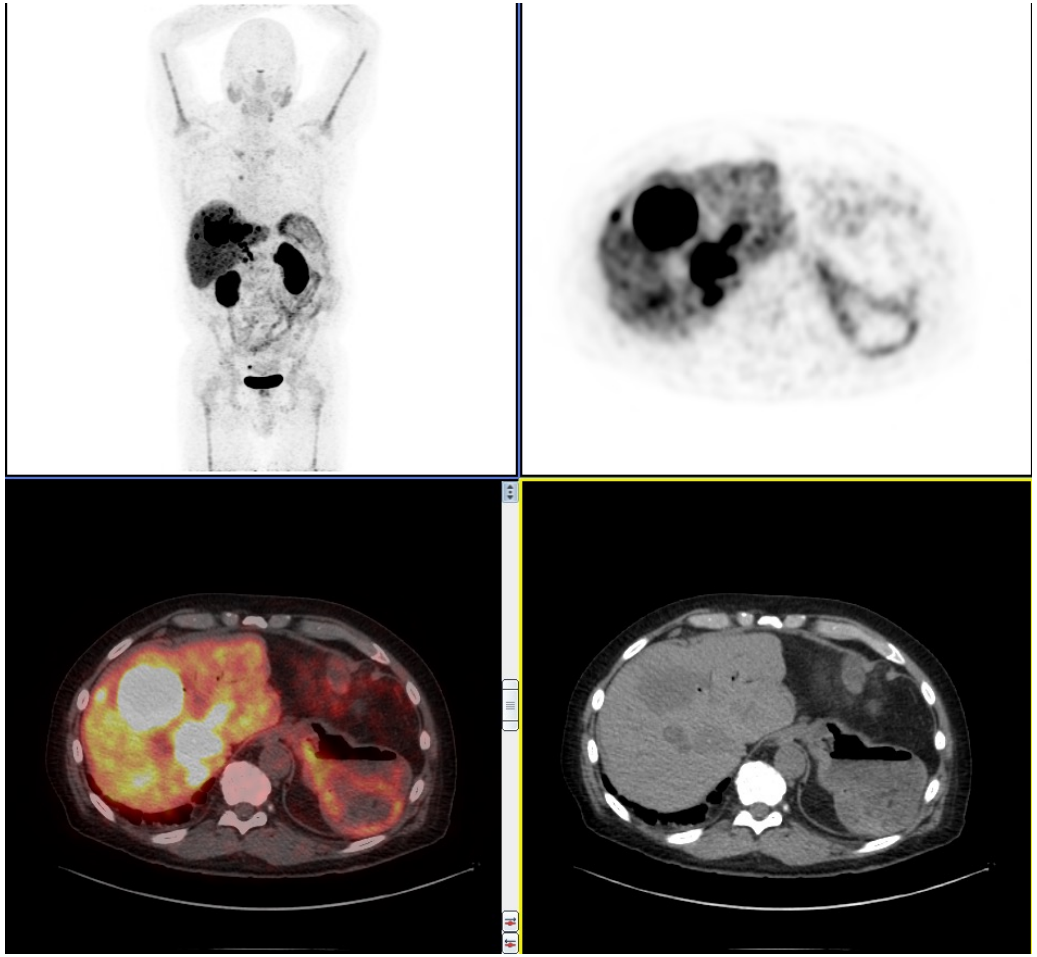
- **Myelodysplastic Syndrome/Acute Myeloid Leukemia:**
- **1.5%** (9/582) of patients developed **MDS**, (**median 28 months** after treatment)
- **0.7%** (4/582) of patients developed **AML** (**median 55 months** after treatment)

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

Brabander T *et al. Clin Cancer Res* 2017;23(16):4617–24.

Which embolotherapy?

- Previous biliary instrumentation/surgery risk of hepatic infection
- TARE (about 8%) <TAE/TACE (about 20%) despite broad-spectrum antibiotic coverage
- Y90 glass microspheres appear to carry 6.9 times risk than resin microspheres



Cholapranee A, et al. Cardiovasc Intervent Radiol 2015;38(2):397–400.
Devulapalli KK, et al. (90)Y Radioembolizatio*Radiology*. 2018;288(3):774-781

Selection of embolotherapy

- In general, we use TAE as first-line embolotherapy, especially for indolent disease
- Maybe a role for TACE for pNET, more chemosensitive
- TARE for high-grade tumors (more radiosensitive)or if failed other embolotherapy, portal vein thrombosis, and Radiation segmentectomy/lobectomy

Singla S, et al. J Gastrointest Oncol 7:441-8, 2016.

Conclusion

- Role for both embolotherapy and PRRT
- Individualize therapy:
  - tumor characteristics (location, extent, mitotic rate and/or ki-67, functionality)
  - prior surgery, systemic therapy, comorbidities
  - patient preference/access to care
- Sequencing has not been well established
- Attention to long-term toxicities
- Need for high-level evidence from comparative clinical studies