Case #4: How aggressive should we be on metastasectomies for NETs?

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Surgical Management of NET Liver Metastases

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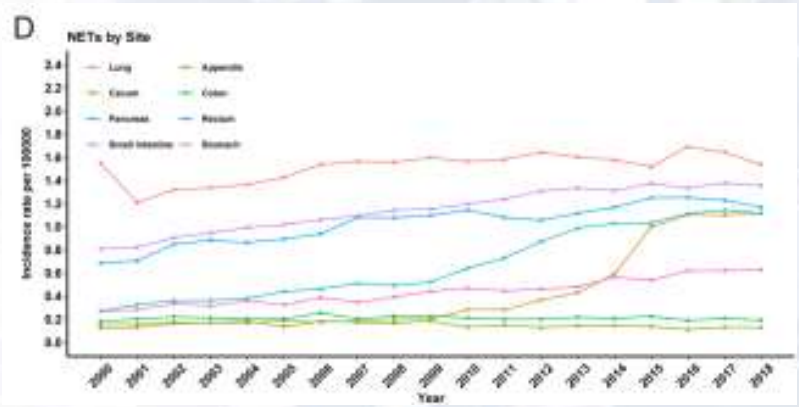
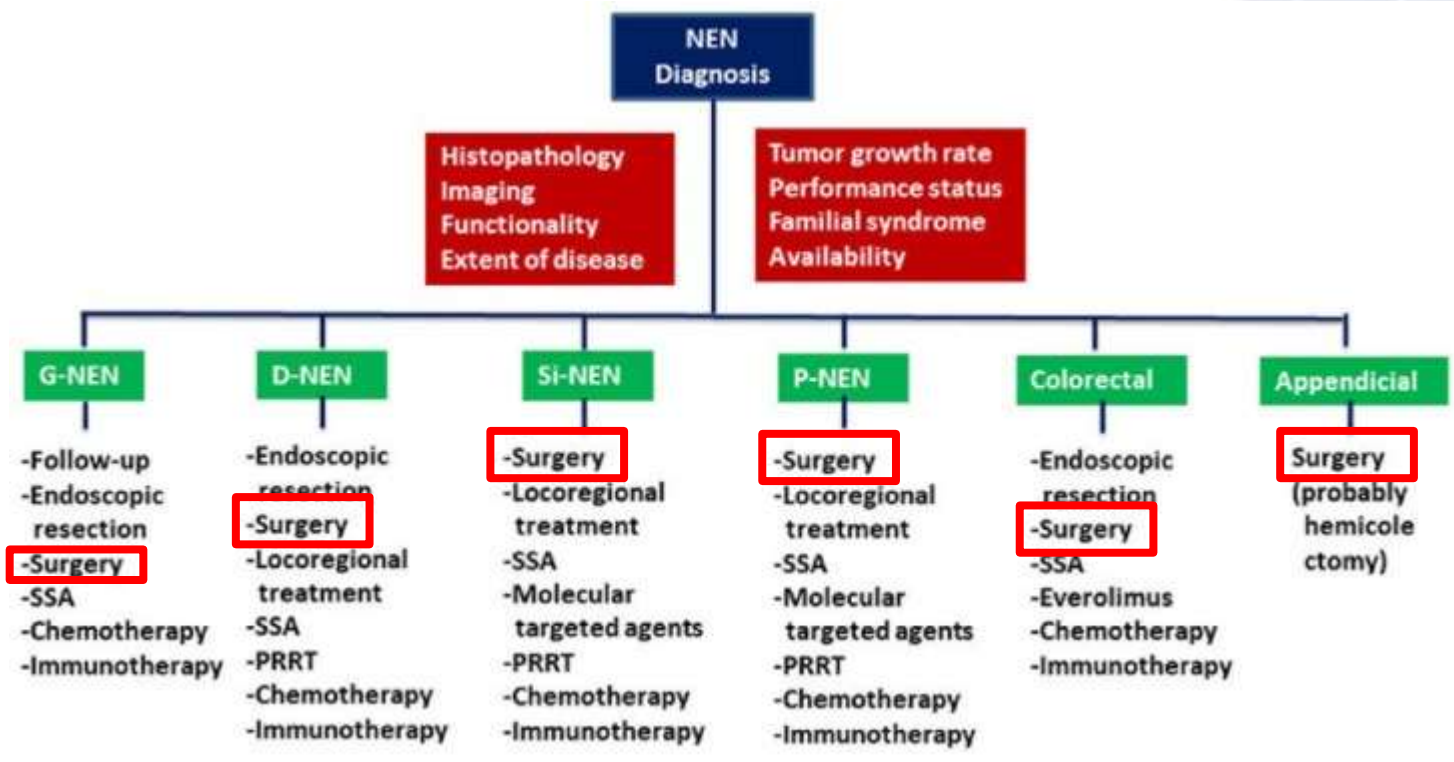
Neuroendocrine Tumors

- Diverse group of tumors
  - Most commonly rise from the gastroenteropancreatic structures (GEP)
  - Functional vs. nonfunctional



- Incidence increasing over time
  - In US incidence has increased >6 fold over last 4 decades

Neuroendocrine Tumors- Treatment



Tsoli M, et al. Current best practice in the management of neuroendocrine tumors. Ther Adv Endocrinol Metab. 2018 Oct 31

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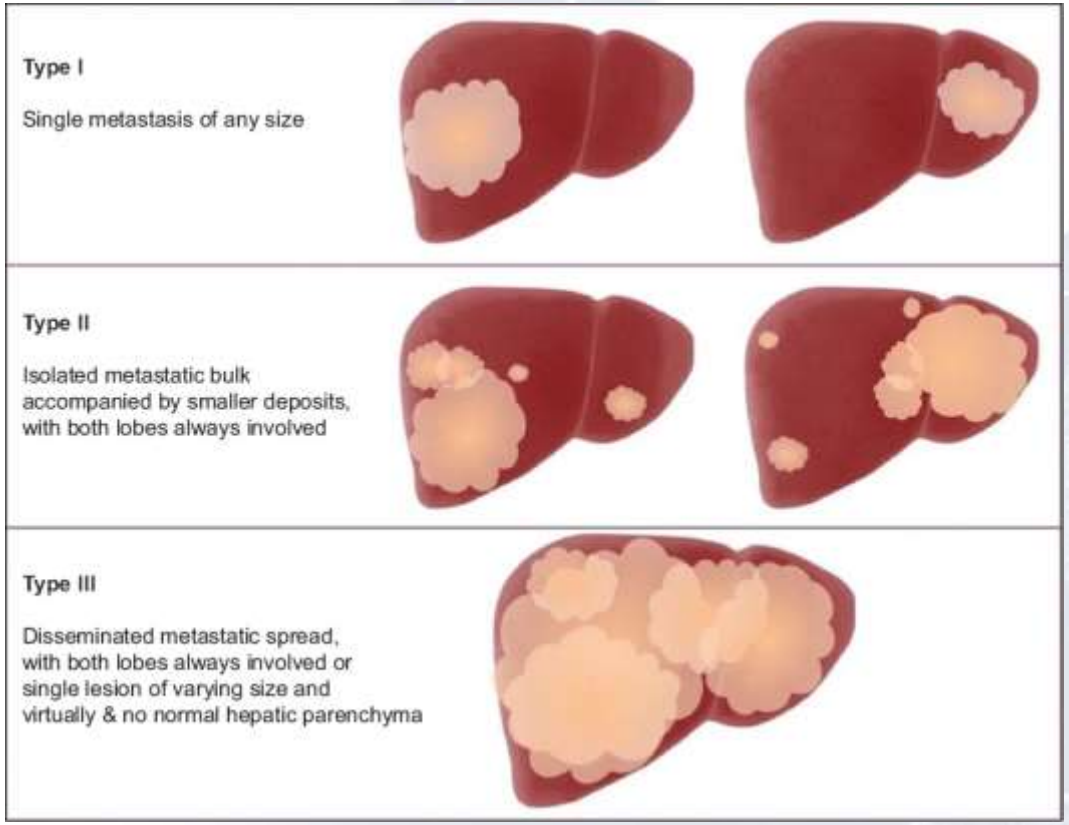
Neuroendocrine Tumors- Treatment

- Liver is the most common site of metastases
- 50-90% of GEP NET patients have liver metastases
  - Pancreatic and small intestine most likely



Endocr Connect. 2023 Nov 23;12(12):e230331
Machairas et al. Currently available treatment options for neuroendocrine liver metastases. Ann Gastro 2021.

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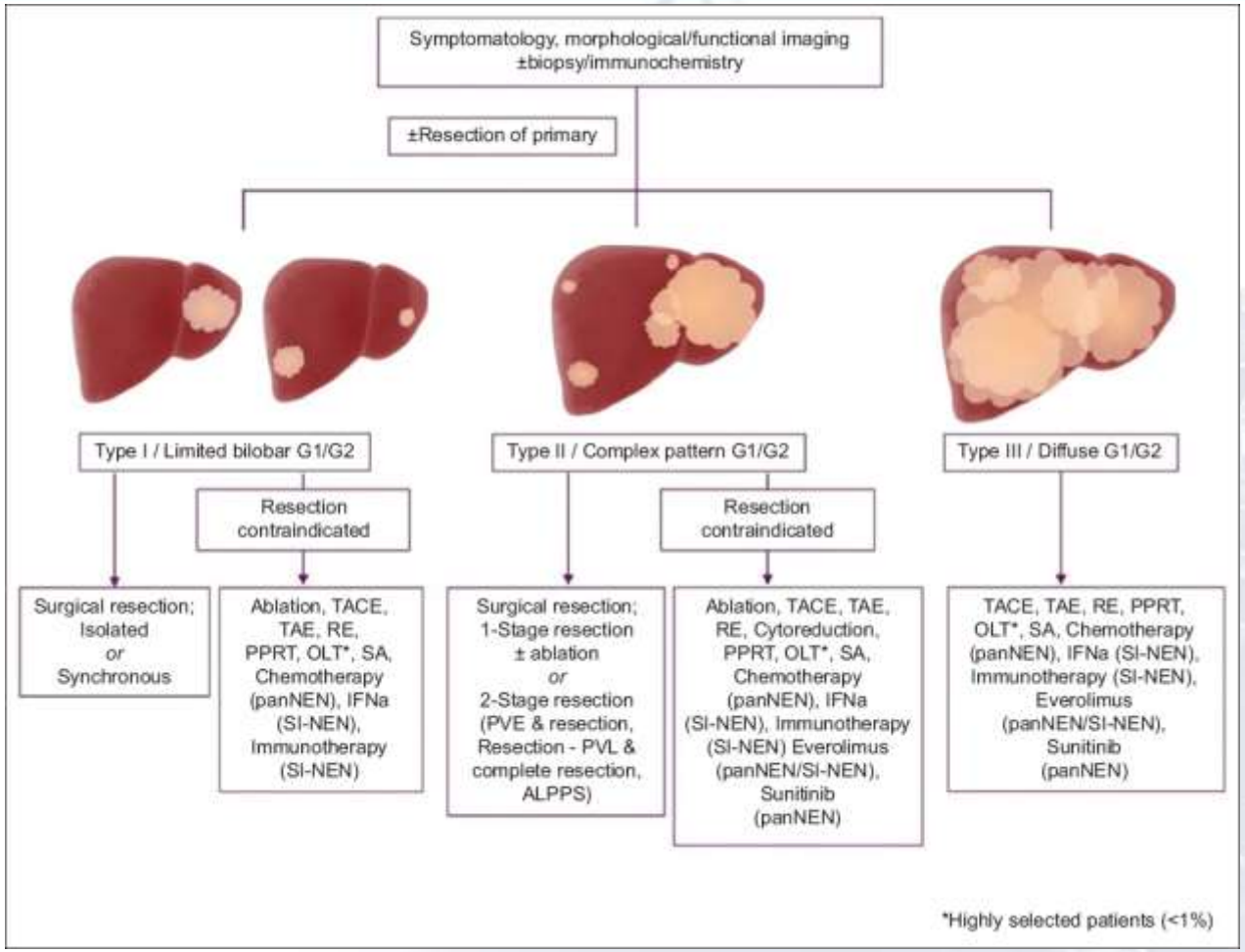
NCCN Guidelines

- Resection of recurrent locoregional disease, isolated distant metastases, or a previously unresectable tumor that has regressed should be considered for selected patients with adequate performance status.

NCCN Guidelines. https://www.nccn.org/guidelines/guidelines

Surgical Considerations for NELM

- Accurately determine the extent of metastases
- Is it technically resectable?
- Is there enough future liver remnant (FLR)?-→ VOLUMETRICS
  - Need at least 30%



Machairas et al. Ann Gastro Jan 2021

Surgical Outcomes for NELM

Author; Year [Ref]	Type of study, Origin	Number of patients (n)	Well-differentiated (%)	Primary tumor location (%)			R0/R1 resection (%)	OS (%)			DFS (%)		
				GI	Pancreas	Other		1-year	3-year	5-year	1-year	3-year	5-year
Sahara 2019 [27]	Multicenter, US	521	65	42.7	42	15.3	76/24	NA	56	43.7	79	56	43.7
Masui 2020 [28]	Single-center, Japan	26	88.4	0	26	0	58/42	NA	NA	83.3	NA	NA	NA
Ruzzenente 2017 [29]	Multicenter, Italy	238	81.9	NA	35.3	NA	NA/NA	NA	NA	67.1	NA	NA	NA
Mayo 2010 [30]	Multicenter, International	339	58	40	40	20	54/22	92	81	74	57	24	6
Saxena 2011 [31]	Single-center, Australia	74	70	51	32	17	38/27	90	73	63	68	32	21
Frilling 2009 [13]	Single-center, Germany	23	100	35	35	30	100/0	100	100	100	NA	NA	96
Hibi 2007 [32]	Single-center, Japan	21	NA	19	29	52	NA/NA	94	75	41	NA	NA	NA
Reddy 2007 [33]	Single-center, US	33	NA	NA	NA	NA	70/3	93	75	68	50	32	NA
Sarmiento 2003 [34]	Single-center, US	170	NA	56	31	13	NA/NA	95	74	61	71	32	16
Chamberlain 2000 [35]	Single-center, US	34	NA	35	50	15	NA/NA	94	83	76	NA	NA	34
McEntee 1990 [49]	Single-center, US	37	NA	65	35	0	NA/NA	93	80	59	NA	NA	NA

OS, overall survival; DFS, disease-free survival; NA, not available; GI, gastrointestinal

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Machairas et al. Ann Gastro Jan 2021

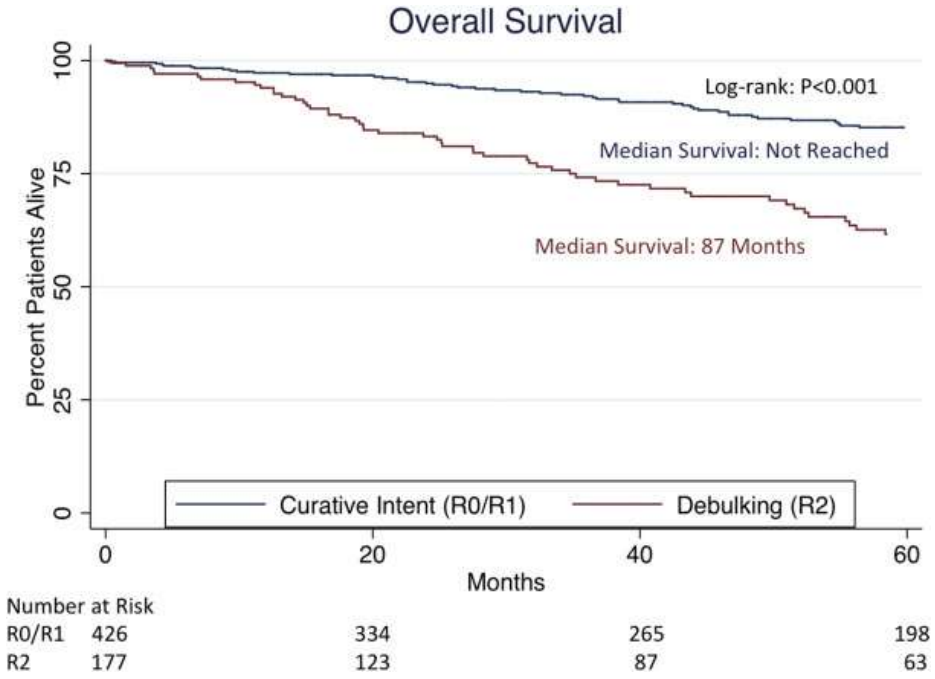
Cytoreduction/Debulking

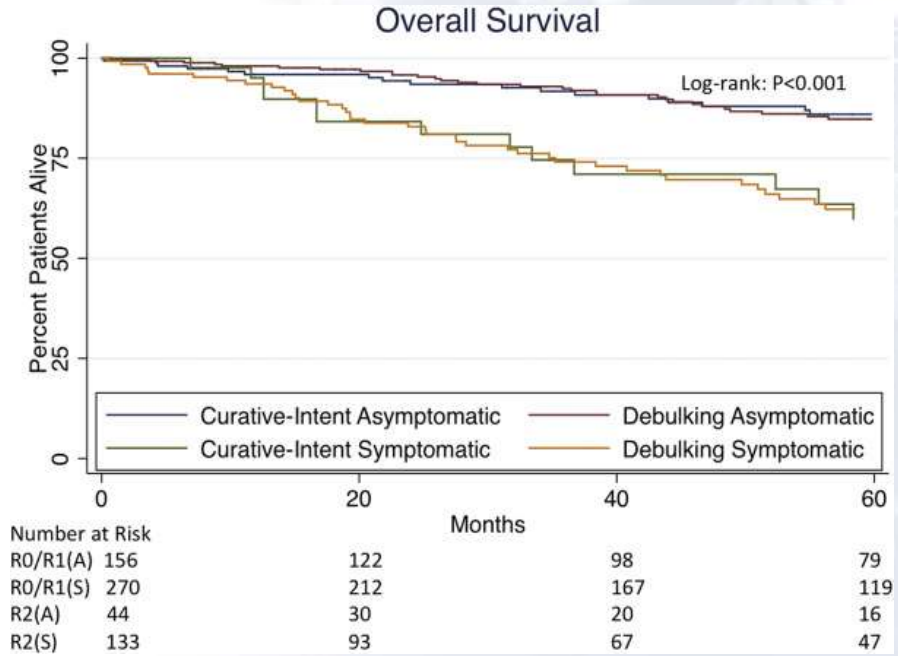
- Only 10-20% are able to be resected to R0
- Initially explored by Mayo clinic in 1990
  - 37 patients, 20 with palliative resection
  - 50% complete relief of symptoms→ lasted ~ 1 year

1. Tsoli M, Chatzellis E, Koumarianou A, Kolomodi D, Kaltsas G. Current best practice in the management of neuroendocrine tumors. Ther Adv Endocrinol Metab 2019;10:2042018818804698.
2. Gurusamy KS, Pamecha V, Sharma D, Davidson BR. Palliative cytoreductive surgery versus other palliative treatments in patients with unresectable liver metastases from gastro-entero-pancreatic neuroendocrine tumours. Cochrane Database Syst Rev 2009;2009:CD007118.
3. McEntee GP, Nagorney DM, Kvols LK, Moertel CG, Grant CS. Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 1990;108:1091-1096.

Cytoreduction/Debulking: Does it change survival?

- International multicenter study
  - 612 patients with NELM who underwent liver directed therapy
  - 179 patients who underwent R2/cytoreductive surgery mainly for symptomatic disease
  - median 5-year OS of 60.7% months (R2) vs. 85.2% (R0/R1)





Ejaz A, Reames BN, Maithel S, et al. Cytoreductive debulking surgery among patients with neuroendocrine liver metastasis:a multi-institutional analysis. HPB (Oxford) 2018;20:277-284.

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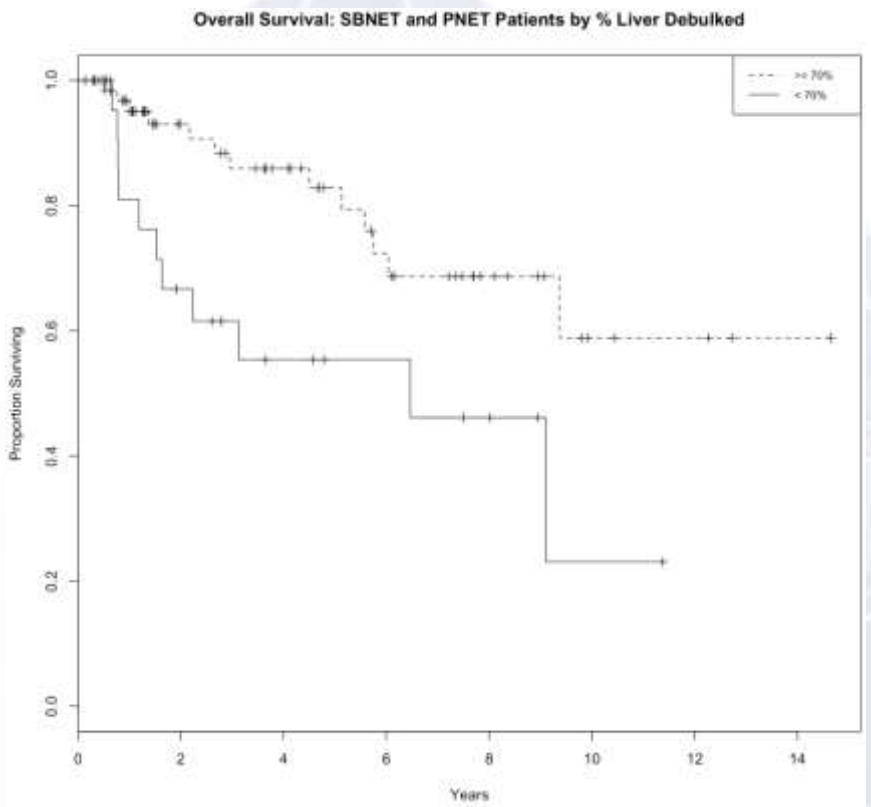
Cytoreduction/Debulking: How much do you need to debulk?

- Matter of debate: initially 90%
- More recently, some suggest 70%

- Single US institution
  - >70% of NELM reduction was associated with significantly higher OS and progression-free survival (PFS)
  - 70% threshold for patients with carcinoid NELM demonstrated a 5-year disease-specific survival of 90%



1. Maxwell JE et alLiver-directed surgery of neuroendocrine metastases:What is the optimal strategy?Surgery 2016;159:320-333.
2. Graff-Baker AN et al. Expanded criteria for carcinoid liver debulking:Maintaining survival and increasing the number of eligible patients. Surgery 2014;156:1369-1376.

Cytoreduction/Debulking: How much do you need to debulk?

- NCCN Guidelines:
  - “Cytoreductive surgery of >90% of metastatic disease may provide symptomatic relief, prevent future symptoms, and improve progression-free survival for patients with functioning tumors. This strategy is particularly appropriate for patients with relatively indolent metastatic small bowel NETs, and less appropriate for patients in whom rapid progression of disease is expected after surgery. Patients who are symptomatic from hormonal syndromes, such as carcinoid syndrome, typically derive palliation from cytoreductive surgery.”

Transplant

- The Milan group:
  - 42 highly selected patients underwent OLT vs. 46 who received local treatments
  - OLT patients increased OS compared to non-OLT patients at 5 and 10 years, with 97.2% vs. 50.9% and 88.9% vs. 22.4%, respectively (P<0.001)

Milan	• Age <55 years • Confirmed histology of low-grade neuroendocrine tumors (G1/G2) with or without the presence of syndrome • Primary tumor drained by the portal system (pancreas and intermediate gut: from distal stomach to sigmoid colon) already removed with a curative resection (removal of all extra-hepatic tumor deposits prior to OLT) • Involvement of <50% hepatic parenchyma • Good response to therapies/stable disease during the pre-OLT period (at least 6 months)
ENETS	• Young patients (<55 years) • Well-differentiated NEN (G1/G2) with Ki67 proliferation index ≤10% • Involvement of <50% hepatic parenchyma or <75% in cases with refractory hormonal symptoms • Primary tumor removed prior to OLT (at least 6 months) • Stable disease for at least 6 months • Robust exclusion of extrahepatic disease by optimized staging (cross-sectional and functional imaging) • Low serum total bilirubin
UNOS	• Age <55 years • Primary tumor drained by the portal system • Involvement of <50% hepatic parenchyma • Resected primary tumor and all extra-hepatic tumor deposits • Good response to therapies/stable disease during the pre-OLT period (minimum of 6 months) • No extrahepatic disease, bilobar NELM, not amenable to resection

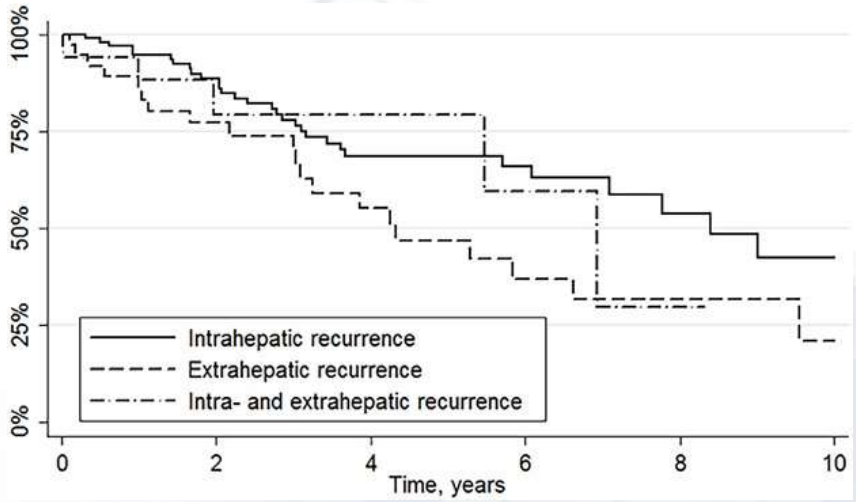
OLT, orthotopic liver transplantation; NELM, neuroendocrine liver metastases; ENETS, European Neuroendocrine Tumor Society;

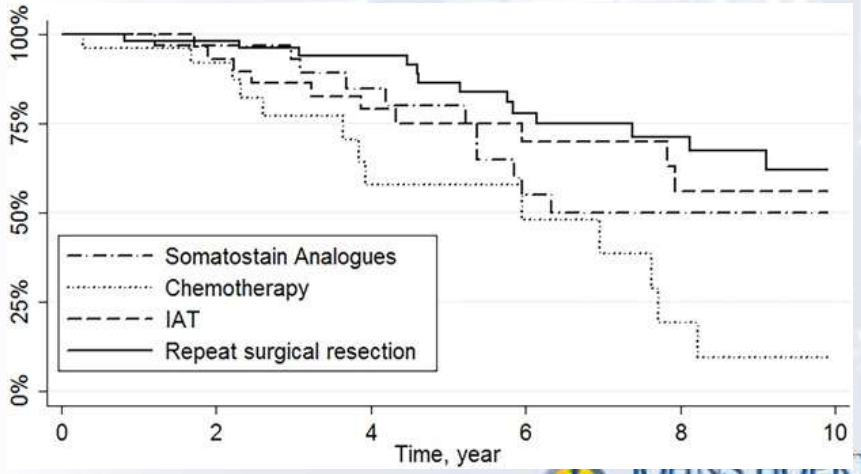
NET, neuroendocrine tumor; UNOS, United Network For Organ Sharing

1. Lerut J,, et al. Secondary non-resectable liver tumors:A single-center living-donor and deceased-donor liver transplantation case series. Hepatobiliary Pancreat Dis Int 2019;18:412-422.
2. Grossman EJ, Millis JM. Liver transplantation for non-hepatocellular carcinoma malignancy:indications, limitations, and analysis of the current literature. Liver Transpl 2010;16:930-942
3. Mazzaferro V,, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. Am J Transplant 2016;16:2892-2902..

Surgery for Recurrent NELM

- Recurrence rates 65-90%
- Retrospective multinational cohort:
  - 322 patients underwent resection for NELM
    - 65% with liver only recurrence
    - Repeat liver resection 43.8% vs. somatastatin analog, cytotoxic chemotherapy or intra-arterial therapy
    - 10 year OS:
      - Surgery 60.3%
      - Intra-arterial therapy 52.0%
      - Somatastatin analog 45.9%



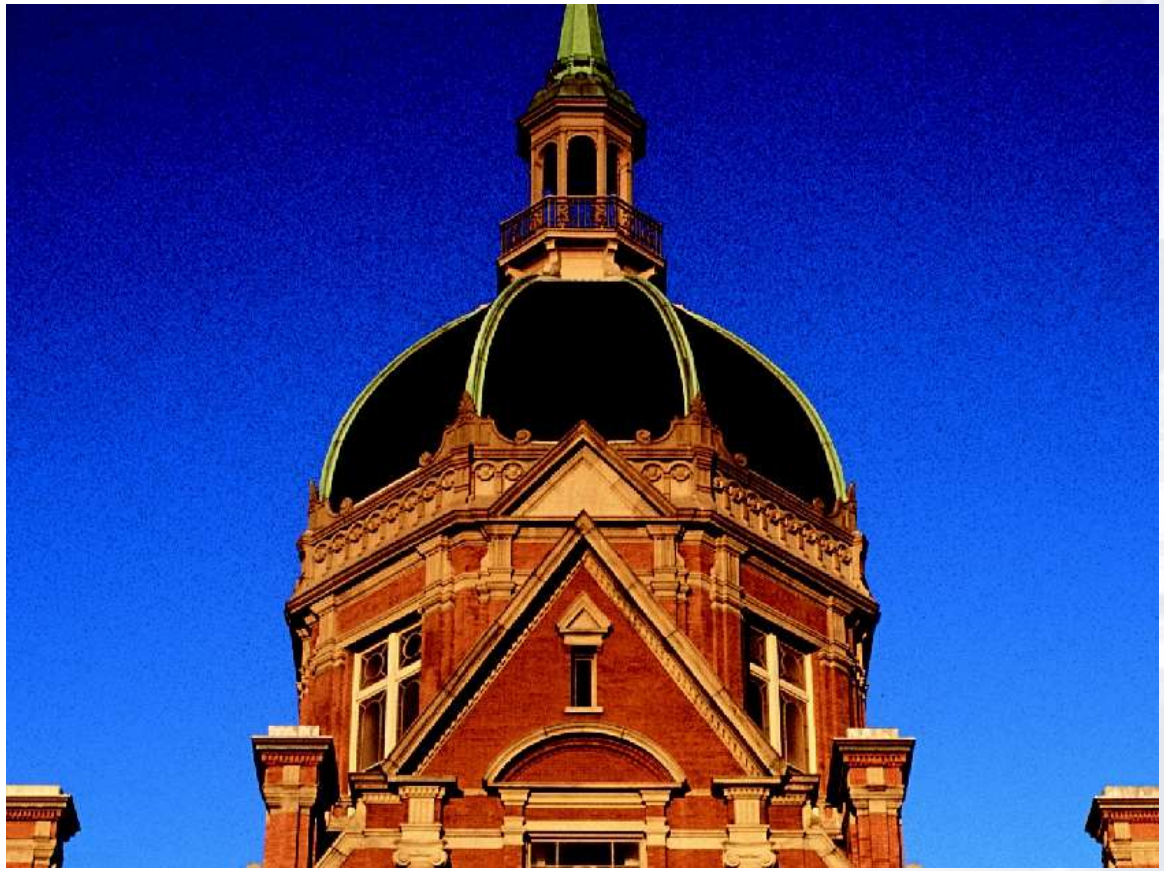


Spolverato G et al. Management and outcomes of patients with recurrent neuroendocrine liver metastasis after curative surgery: An international multi-institutional analysis. J Surg Oncol. 2017 Sep;116(3):298-306.

Conclusions

- Surgery is only curative intent option for NELM
- Most appropriate for WD/G1 with adequate FLR where R0 resection is possible
- Liver transplant may be an option for very select patients

Thank You



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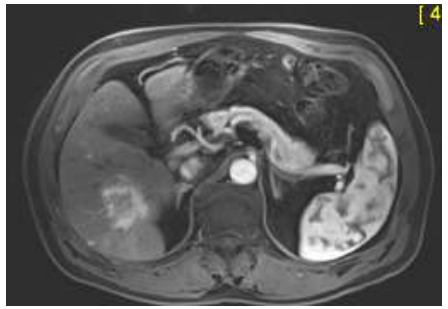

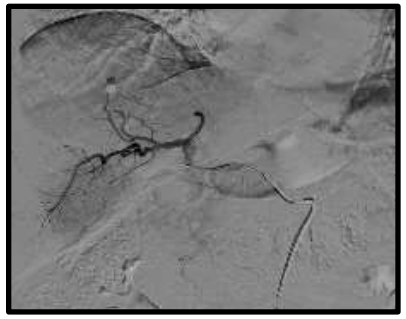

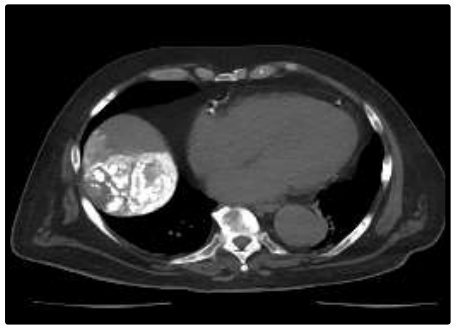

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NET Liver Metastases
Liver directed therapy

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Executive Vice Chair

Associate Professor of Radiology

Johns Hopkins Medicine

NET Liver Metastases: goals

- Choices of IR therapies:
  - Thermal Ablation
  - Intra-arterial (TAE, TACE, TARE)
- How should you choose?
- Outcomes
- What's on the horizon: Histiotrypsy

NET Liver Metastases

- Grading system important
- Liver mets occur in 50-90% NET patients
- Most common site of progression, major determinant of survival and symptoms/ QoL
- long-term survival after resection ~50%, but R0 resection not feasible most
- If not controlled, results in death due to liver failure

IR local therapies: considerations

- NET liver mets may be hormonally active/functional or not
- Palliating symptoms appropriate even with extra-hepatic disease
- If liver disease control: most G1/G2 good prognosis, long standing patient
- preservation of liver function paramount
- Some may have surgery: biliary enteric anastomosis: liver abscess risk

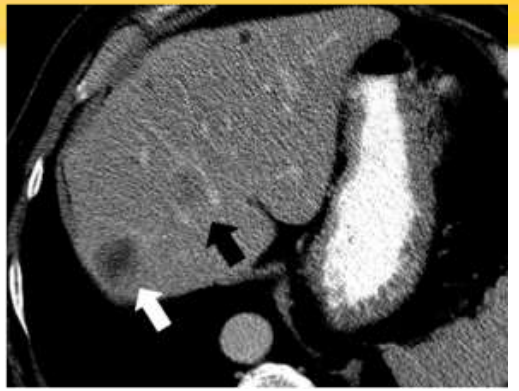
Chen JX, Wileyto EP, Soulen MC. Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET): study protocol for a randomized controlled trial. Trials. 2018 Jul 17;19(1):390.

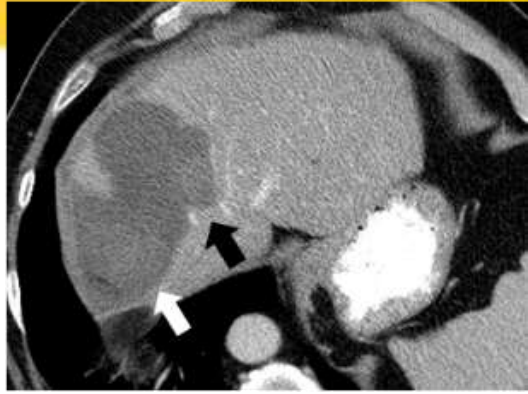
IR Local therapies

- Does it control symptoms? 75%
- Does it debulk liver tumors? Imaging response
  ORR 55-60%
- How durable is the response?
  Liver PFS 18 months G1, 12 months G2
- How safe is it?
  SAE 6.5%; Mortality 0-2%

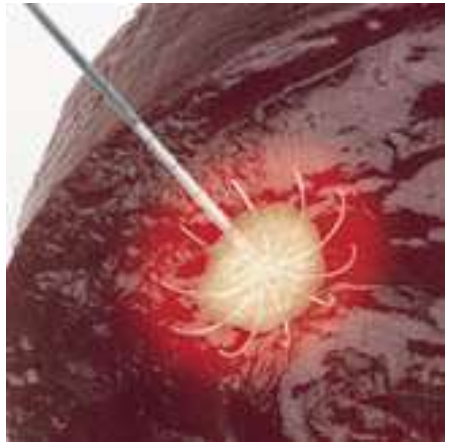
Chen JX, Wileyto EP, Soulen MC. Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET): study protocol for a randomized controlled trial. Trials. 2018 Jul 17;19(1):390.

NET Liver Ablations





- Microwave, RFA, Cryoablation
- Proven curative in early stage HCC and CRC mets; alternative to surgery
- Critical to get R0 ablation with adequate margins
- In combination with surgery, other local therapies, systemic therapies
- But tendency of NET to present with numerous liver lesions
- 5-year OS ~53% with 22% local recurrence
- 95.3% (41/43) treated tumors showed a CR at mean of 2.1 years
- CR in 31.6% and PR in 36.8%
- Complications profile minor, carcinoid crisis and abscesses higher risk in those without an intact sphincter of Oddi



Gillams A, et al. Radiofrequency ablation of neuroendocrine liver metastases: the middlesex experience. Abdom Imaging. 2005;30(4):435–41.

1Vogl TJ, et al. Liver metastases of neuroendocrine carcinomas: interventional treatment via transarterial embolization, chemoembolization and thermal ablation. Eur J Radiol. 2009;72(3):517–28.

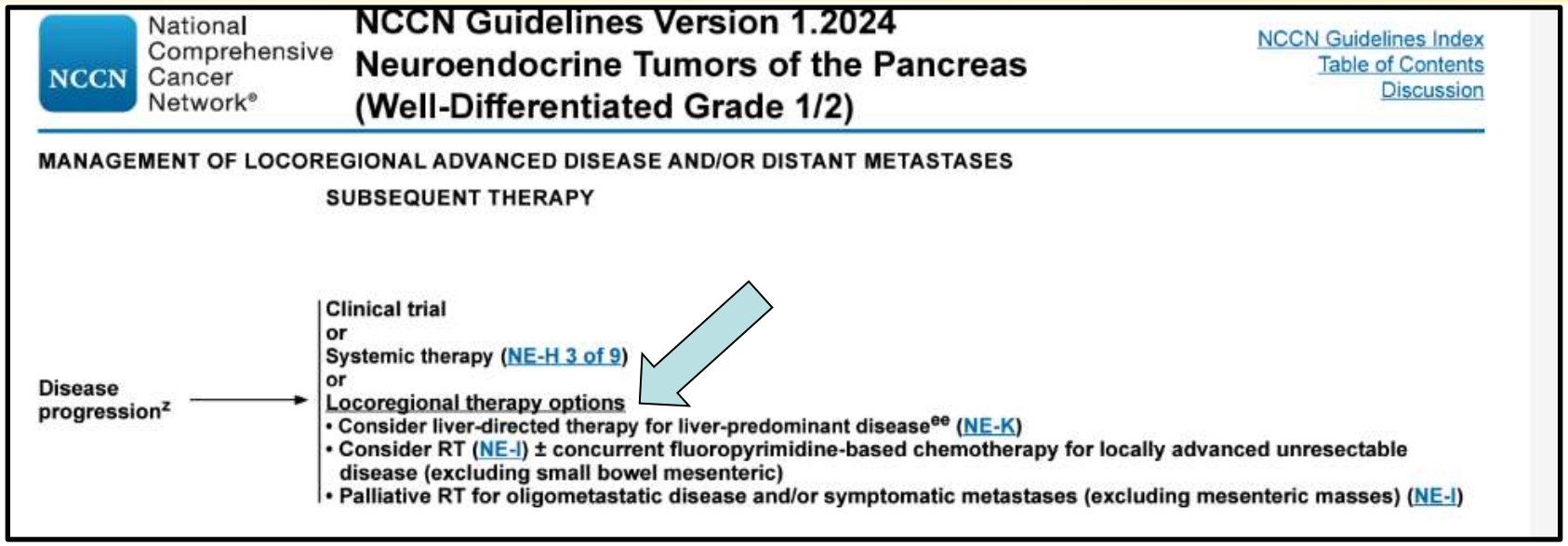
Frilling A, et al. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol. 2014;15(1):e8–21.

Hellman P, et al. Radiofrequency tissue ablation using cooled tip for liver metastases of endocrine tumors. World J Surg. 2002;26(8):1052–6.

IA Liver directed Therapies

Therapy	Approach	Features
TAE: bland embolization	Embolic agents (microspheres, gelatin particles, Lipiodol)	Diffuse, multifocal, bilobar; lower risk of AE's, post embolic syndrome
TACE	Chemo (most common Doxorubicin) and embolic agent	Diffuse, bilobar, More AE's than TAE, similar outcomes
DEB-TACE	Chemo eluted into microspheres, used in HCC	Diffuse, bilobar, less chemo AE's, higher biliary ischemia
TARE	Microspheres loaded with Y90 radioactive isotope; localized radiation	Previous HJ surgery, CBD instrumentation; risk of radiation to normal liver

Criss CR, et al. Liver-Directed Locoregional Therapies for Neuroendocrine Liver Metastases: Recent Advances and Management. Curr Oncol. 2024 Apr 5;31(4):2076-2091.


National Comprehensive Cancer Network®
NCCN Guidelines Version 1.2024
Neuroendocrine Tumors of the Pancreas
(Well-Differentiated Grade 1/2)
NCCN Guidelines Index
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Discussion
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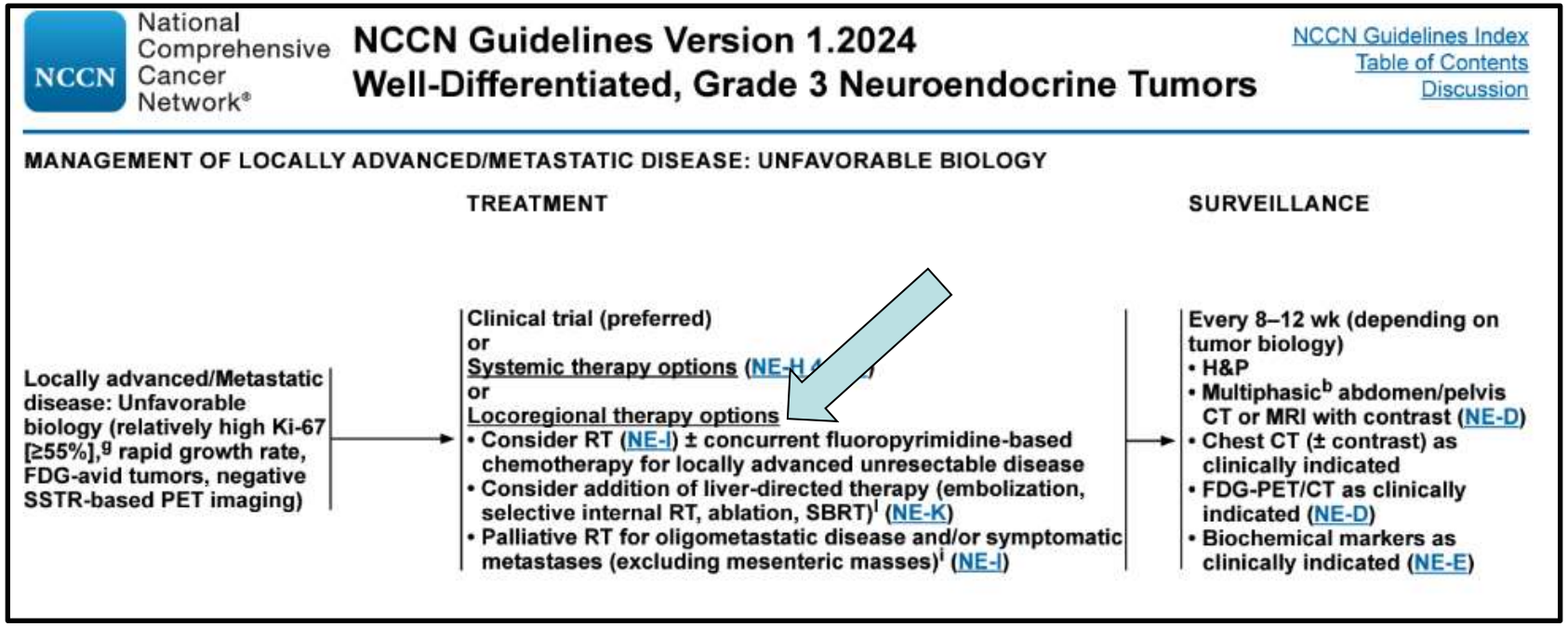
Disease progression[z]
Clinical trial
or
Systemic therapy (NE-H 3 of 9)
or
Locoregional therapy options
• Consider liver-directed therapy for liver-predominant disease[ee] (NE-K)
• Consider RT (NE-I) ± concurrent fluoropyrimidine-based chemotherapy for locally advanced unresectable disease (excluding small bowel mesenteric)
• Palliative RT for oligometastatic disease and/or symptomatic metastases (excluding mesenteric masses) (NE-I)


National Comprehensive Cancer Network®
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Well-Differentiated, Grade 3 Neuroendocrine Tumors
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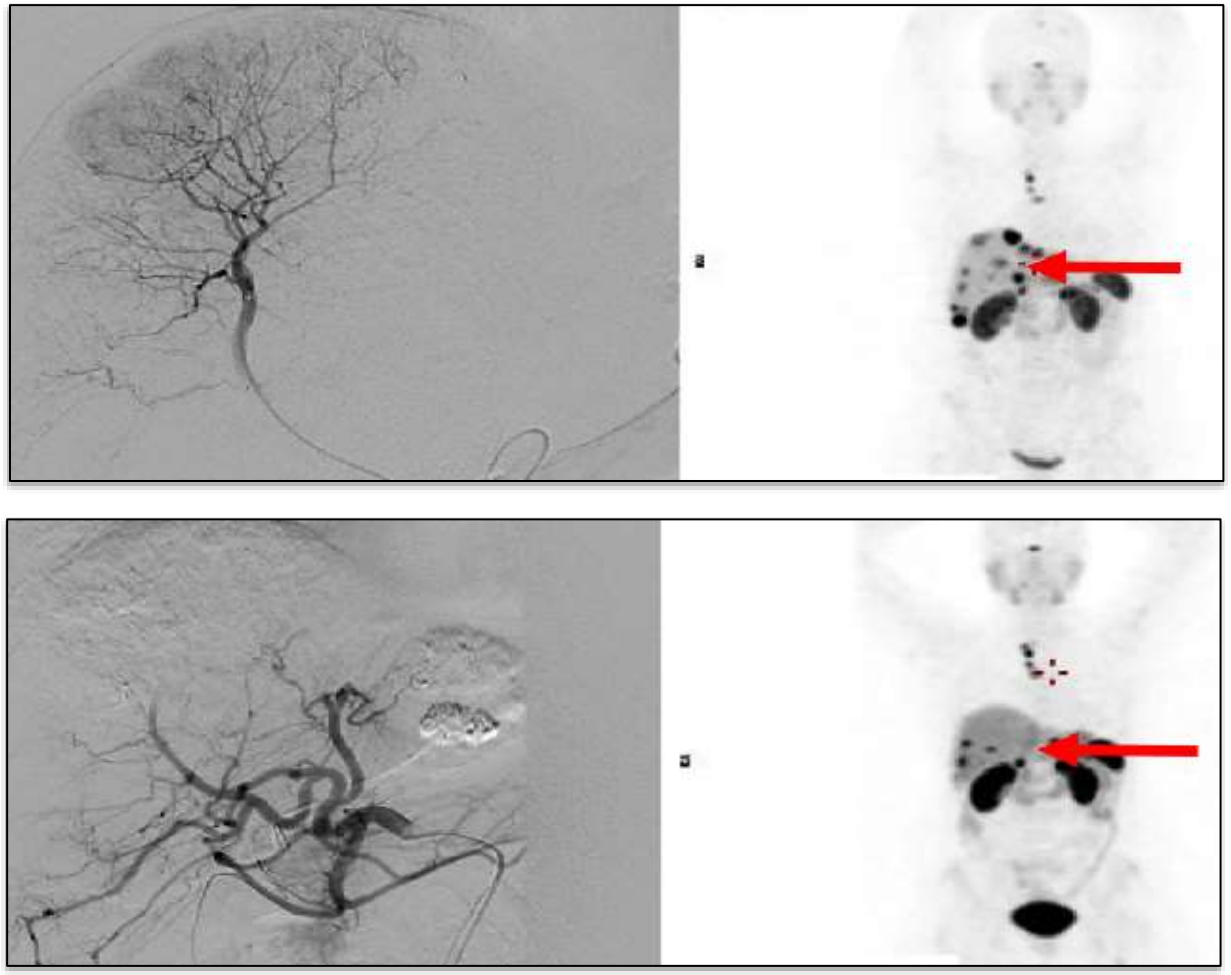
MANAGEMENT OF LOCALLY ADVANCED/METASTATIC DISEASE: UNFAVORABLE BIOLOGY
TREATMENT
SURVEILLANCE
Locally advanced/Metastatic disease: Unfavorable biology (relatively high Ki-67 [≥55%],[g] rapid growth rate, FDG-avid tumors, negative SSTR-based PET imaging)
Clinical trial (preferred)
or
Systemic therapy options (NE-H
or
Locoregional therapy options
• Consider RT (NE-I) ± concurrent fluoropyrimidine-based chemotherapy for locally advanced unresectable disease
• Consider addition of liver-directed therapy (embolization, selective internal RT, ablation, SBRT)[i] (NE-K)
• Palliative RT for oligometastatic disease and/or symptomatic metastases (excluding mesenteric masses)[i] (NE-I)
Every 8–12 wk (depending on tumor biology)
• H&P
• Multiphasic[b] abdomen/pelvis CT or MRI with contrast (NE-D)
• Chest CT (± contrast) as clinically indicated
• FDG-PET/CT as clinically indicated (NE-D)
• Biochemical markers as clinically indicated (NE-E)

Bland Embolization TAE

- Variety of agents used published
- Goal of treating hypervascularity of mets to 2-5 cardiac bat stasis
- Well tolerated, repeatable



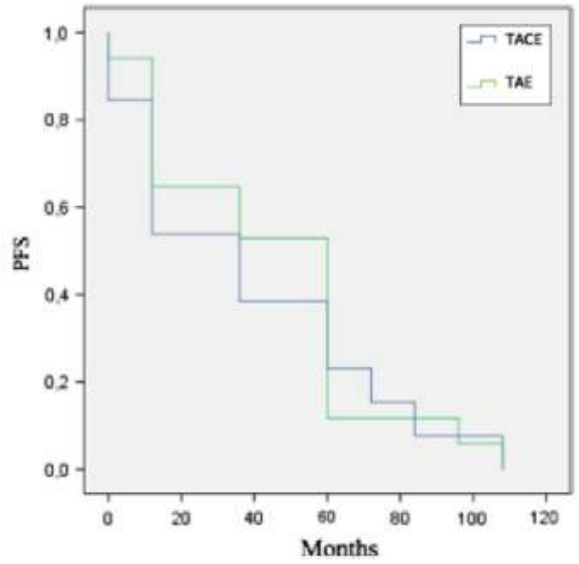
Bland Embolization TAE vs TACE

Endocrine (2014) 47:177–182
DOI 10.1007/s12020-013-0130-9

ORIGINAL ARTICLE

Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors

Francesco Fiore · Michela Del Prete · Renato Franco · Vincenzo Marotta · Valeria Ramundo · Francesca Marciello · Antonella Di Sarno · Anna Chiara Carratù · Chiara de Luca di Roseto · Annamaria Colao · Antongiulio Faggiano



- Small early series Naples group,
- 30 patients gastro-entero-pancreatic NET
- TAE (17) vs TACE (13)
- median PFS 36 months (16.2-55.7 CI), no difference between TAE and TACE.
- AE's: PES 41 % TAE and 61 % TACE.
- Conclusion: T AE and TACE equal ;TAE should be preferred w similar anti-tumor effects but better toxicity profile

Fiore F, et al. Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors. Endocrine. 2014 Sep;47(1):177-82.

Endocrine (2018) 60:499–509
https://doi.org/10.1007/s12020-018-1537-0

ORIGINAL ARTICLE

Hepatic intra-arterial therapies in metastatic neuroendocrine tumors: lessons from clinical practice

S. Grozinsky-Glasberg[1] · G. Kaltsas[2] · M. Kaltsatou[2] · N. Lev-Cohain[3] · A. Klimov[3] · V. Vergadis[4] · I. Uri[1] · A. I. Bloom[3] · D. J. Gross[1]

Received: 18 October 2017 / Accepted: 15 January 2018 / Published online: 30 January 2018

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No difference in outcomes TAE vs TACE

Table 3 Summary of the relevant studies, including our data, regarding tumor response and survival following hepatic-intra-arterial therapies (embolization and chemoembolization) for metastatic neuroendocrine tumors

Nr.	Study	Nr. of patients	Type of tumor	Type of treatment	Drug used	CR (*n*, %)	PR (*n*, %)	SD (*n*, %) (including minimal response)	PD (*n*, %)	PFS/ TTP (median, months)	OS (median, months)	5-year survival (%)
1	Carrasco et al. 1986 [22]	25	intestinal, pancreatic, and lung NETs	TAE	ivalon followed by gel foam	–	17 (68%)	1 (4%)	5 (20%)	–	–	–
2	Ajani et al. 1988 [36]	22	pancreatic NETs	TAE	PVA	–	12 (54%)	–	–	–	34	–
3	Nobin et al. 1989 [37]	8	intestinal NETs	TAE	gel foam	–	3	5	–	–	–	–
5	Ruszniewski et al. 1993 [29]	24	intestinal and pancreatic NETs	TACE	iodized oil followed by doxorubicin and gel foam	2 (8%)	6 (25%)	3 (13%)	–	14	–	–
6	Therasse et al. 1993 [38]	23	intestinal NETs	TACE	iodized oil followed by doxorubicin and gel foam	3 (13%)	6 (24%)	6 (24%)	–	–	24	–
7	Clouse et al. 1994 [39]	20	pancreatic and lung NETs	TACE	iodized oil followed by doxorubicin and gel foam	–	–	–	–	–	24	–
8	Perry et al. 1994 [40]	30	intestinal and pancreatic NETs	TACE	iodized oil followed by doxorubicin and gel foam	–	24 (79%)	4 (13%)	–	–	24	–
9	Wängberg et al. 1996 [41]	40	intestinal NETs	TAE	iodinated contrast medium followed by gel foam	–	17 (43%)	15 (38%)	–	–	–	–
10	Eriksson et al. 1998 [25]	41	intestinal and pancreatic NETs	TAE	iodinated contrast material followed by gel foam	–	14 (34%)	28 (68%)	8 (20%)	–	30	–
11	Diamandidou et al. 1998 [42]	20	intestinal and pancreatic NETs	TACE	microencapsulated cisplatin	–	6 (33%)	8 (44%)	4 (22%)	–	–	–
12	Brown et al. 1999 [43]	35	intestinal and pancreatic NETs	TAE	PVA	–	–	–	–	–	–	54
13	Kim et al. 1999 [44]	30	intestinal and pancreatic NETs	TACE	ivalon followed by cis & doxorubicin (intestinal NETs) or 5-FU & SZT (PNETs) & gel foam	–	11 (37%)	14 (46%)	5 (17%)	–	15	–
14	Dominguez et al. 2000 [28]	15	intestinal and pancreatic NETs	TACE	iodized oil followed by STZ & gel foam	–	8 (53%)	–	–	–	–	–
15	Chamberlain et al. 2000 [7]	33	intestinal, pancreatic, lung and UKO NETs	TAE	PVA	–	–	–	–	–	–	50
16	Roche et al. 2003 [45]	14	intestinal and UKO NETs	TACE	lipiodol followed by doxorubicin & gel foam	–	6 (43%)	6 (43%)	2 (14%)	–	–	–
17	Loewe et al. 2003 [21]	23	intestinal NETs	TAE	lipiodol & cyanoacrylate	4 (18%)	12 (55%)	–	6 (27%)			
18	Gupta et al. 2003 [46]	81	intestinal and pancreatic NETs	TAE or TACE	bland or chemo-embolization	–	46 (67%)	11 (16%)	6 (8.7%)	19		

Table 3 (continued)

Nr.	Study	Nr. of patients	Type of tumor	Type of treatment	Drug used	CR (*n*, %)	PR (*n*, %)	SD (*n*, %) (including minimal response)	PD (*n*, %)	PFS/ TTP (median, months)	OS (median, months)	5-year survival (%)
19	Kress et al. 2004 [47]	26	intestinal, pancreatic and UKO NETs	TACE	lipiodol followed by doxorubicin & gel foam/PVA	–	2 (8%)	14 (54%)	5 (19%)	–	–	–
20	Gupta et al. 2005 [32]	123	intestinal and pancreatic NETs	TAE or TACE	PVA or gelfoam powder/ ± chemotherapeutic agent	–	72 (58%)	43 (35%)	8 (7%)	20	29	22
21	Strosberg et al. 2006 [24]	84	intestinal and pancreatic NETs	TAE	polyvinyl alcohol	–	11 (48%)	12 (52%)			36	–
22	Ruutiainen et al. et al. 2007 [48]	67	NETs	TAE or TACE	polyvinyl alcohol ± cisplatin/ doxorubicin/mitomycin-C, iodized oil	–	33 (50%)	25 (38%)	9 (12%)	6	36	33
23	Ho et al. 2007 [49]	46	intestinal and pancreatic NETs	TAE or TACE	cisplatin–doxorubicin–mitomycin-C mixed with ethiodized oil followed by gel foam	–	15 (46%)	12 (36%)	6 (18%)	–	32	33
24	de Baere et al. 2008 [50]	20	gastroenteropancreatic NETs	TACE	DEB with doxorubicin	–	16 (80%)	3 (15%)	1 (5%)	15	–	–
25	Dong & Carr, 2011 [52]	123	NETs (different origin)	TACE	doxorubicin & streptozotocin followed by gel foam or biospheres	–	76 (62%)	30 (24%)	17 (14%)	–	65	36
26	Fiore et al. 2014 [26]	30	intestinal and pancreatic NETs	TAE or TACE	lipiodol followed by embolizing agents ± epirubicin	–	–	–	–	36	–	–
27	Pericleous et al. 2015 [20]	50	intestinal, pancreatic, lung and UKO NETs	TAE or TACE	contrast followed by gel foam/ PVA ± doxorubicin	–	–	–	–	19	65	–
28	Our study	57	intestinal, pancreatic, lung and UKO NETs	TAE or TACE; SIRT	lipiodol followed by gel foam ± mytomicin/doxorubicin; SIR-Spheres yttrium-90 resin microspheres	–	10 (17%)	46 (78%)	3 (5%)	14	22	–
	Overall	1110	all types of NETs	mainly TAE or TACE	–	9/803 (1%)	423/ 803 (53%)	286/803 (35%)	85/803 (11%)	18	33	38

Grozinsky-Glasberg S, et al. Hepatic intra-arterial therapies in metastatic neuroendocrine tumors: lessons from clinical practice. Endocrine. 2018 Jun;60(3):499-509.

TARE:

- TARE elevated from category 2B to 2A in 2024 NCCN Guidelines
- May be considered for lobar or segmental disease (avoid whole liver)
- TARE well tolerated, vs TAE/TACE
- Long term Radioembolization-induced-liver toxicity (RECHT) may occur in long term survivors, esp if treat bilobar
- No evidence for or against TARE with PRRT

TARE: caution with whole liver; long term

- OHSU JVIR 2018; 29.858-865
  - 52 NET with 12 months Follow up
  - 29% developed findings of cirrhosis and Portal HTN
- Northwestern JVIR 2017;28:1520-1526
  - 54 NETs with 24 months FU
  - 56% whole Liver TARE, developed cirrhosis on imaging
  -41% Ascites, 15% varices
  -21% developed hepatic decompensation (Ascites/GIB, LE edema)
- UPenn JVIR 2019;30:1915-1923
  -13% of 98 patients developed hepatic decompensation in absence of other liver toxicity at mean 2 years FU
  -5 patients died due to RILD

Ann Surg Oncol (2021) 28:1950–1958
https://doi.org/10.1245/s10434-020-09469-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

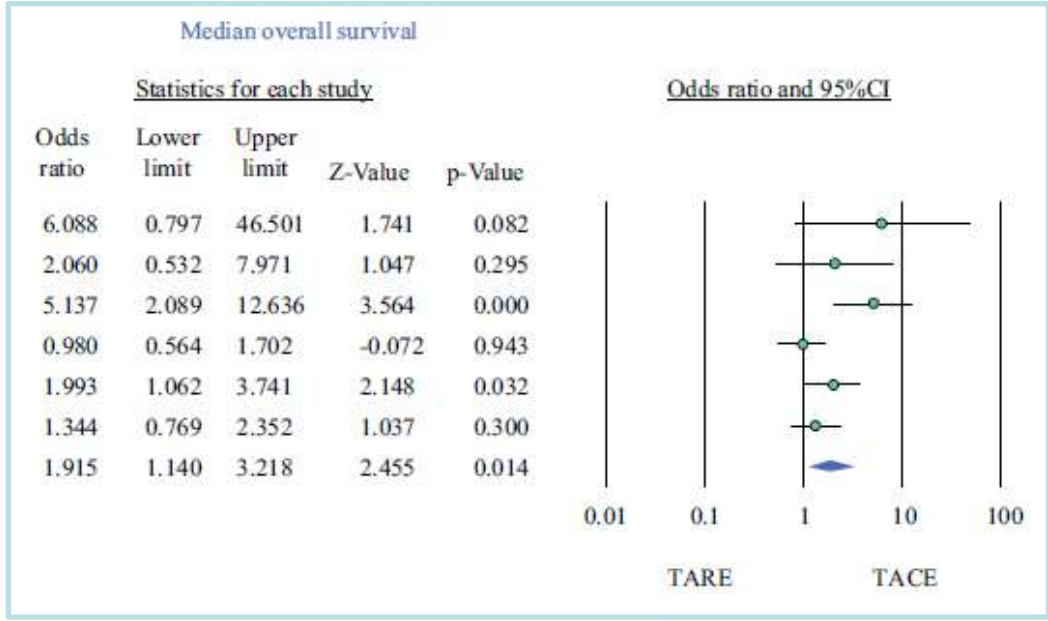
Chemoembolization Versus Radioembolization for Neuroendocrine Liver Metastases: A Meta-analysis Comparing Clinical Outcomes

Lisa Ngo, MPH[1], Ahmed Elnahla, MD[2], Abdallah S. Attia, MD[2], Mohamed Hussein, MD[2], Eman A. Toraih, MSc MD PhD[2,3], Emad Kandil, MBA MD FACS[2], and Mary Killackey, MD[2]

- 344 published studies
- Six eligible cohort studies with a total of 643 patients
- TACE had significantly better OS (odds ratio [OR], 1.92;95% confidence interval [CI] 1.14–3.22,p= 0.014) than those treated with TARE
- No significant differences in hepatic PFS or tumor response were observed (OR, 1.01; 95%CI 0.75–1.35; p= 0.96)
- complication rates were similar (6.9% TACE vs 8.5% of TARE)

TABLE 2 Characteristics of included studies

First author with reference no.	Publication year	Design	Institution	Country
Ozkan F[15]	2013	Retrospective cohort	Single center	Turkey
Engelman ES[16]	2014	Retrospective cohort	Single center	USA
Singla S[18]	2016	Retrospective cohort	Single center	USA
Chen JX[17]	2017	Retrospective cohort	8 Centers	USA
Minh DD[13]	2017	Retrospective cohort	Single center	China, Germany, USA
Egger ME[14]	2020	Retrospective cohort	2 Centers	USA



Ngo L, et al. Chemoembolization Versus Radioembolization for Neuroendocrine Liver Metastases: A Meta-analysis Comparing Clinical Outcomes. Ann Surg Oncol. 2021 Apr;28(4):1950-1958.

Ann Surg Oncol (2021) 28:1950–1958
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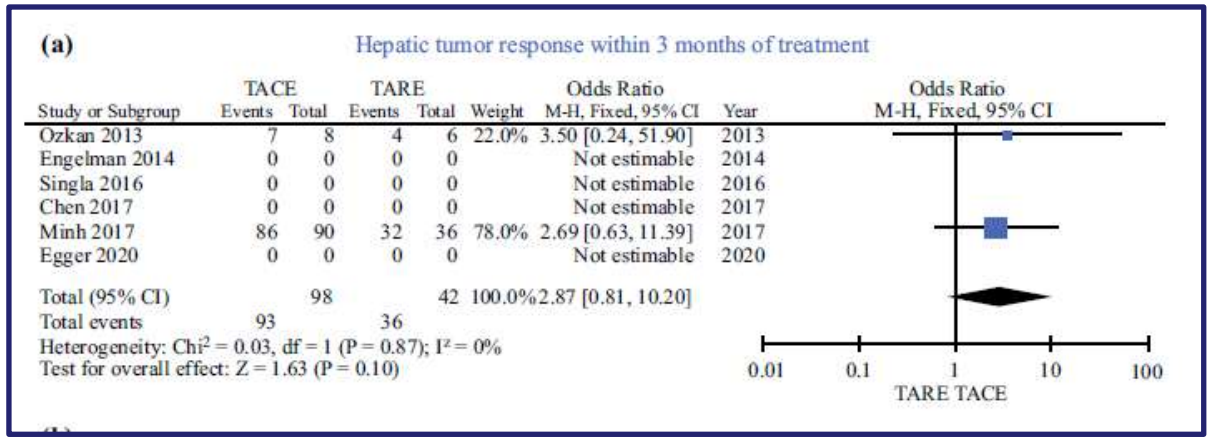
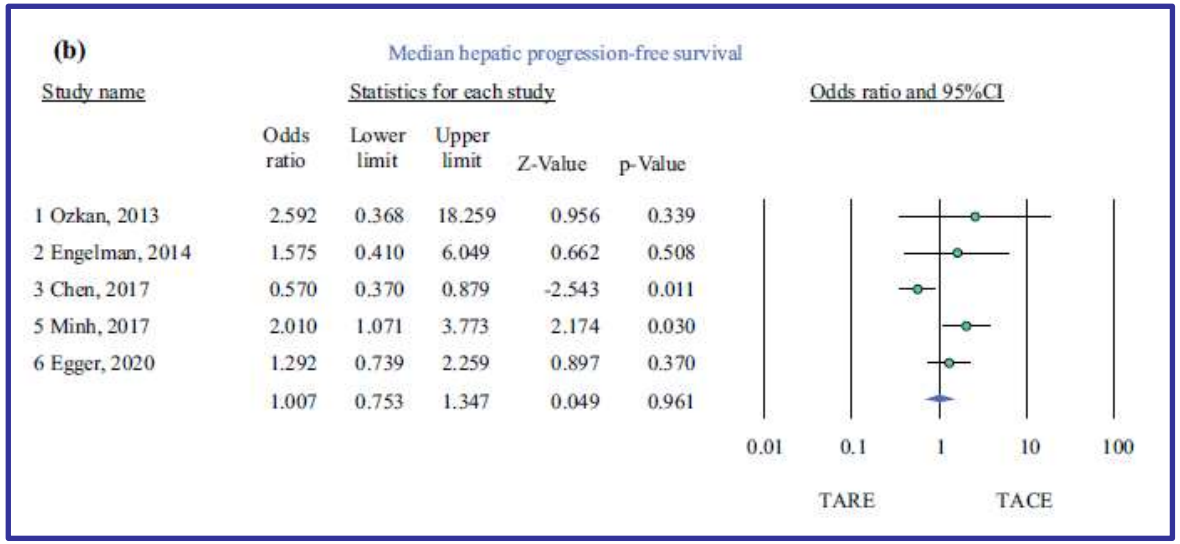
- No significant differences in hepatic PFS or tumor response were observed (OR, 1.01; 95%CI 0.75–1.35; p= 0.96)
- complication rates were similar (6.9% TACE vs 8.5% of TARE)

Conclusions. Despite similar tumor responses,

- OS benefit was associated with TACE compared with TARE
- RCT's needed.





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Chen et al. Trials (2018) 19:390
https://doi.org/10.1186/s13063-018-2782-5

Trials

STUDY PROTOCOL Open Access

Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET): study protocol for a randomized controlled trial

James X. Chen[1], E. Paul Wileyto[2,3] and Michael C. Soulen[1,3,4*]

Study Start (Actual)
2016-03

Primary Completion (Actual)
2024-04

Study Completion (Estimated)
2024-09

Enrollment (Actual)
162

Study Type
Interventional

Phase
Phase 2

Participant Group/Arm	Intervention/Treatment
Experimental: Arm 1 - BE Lobar or segmental bland embolization (BE) with microspheres (50-500 microns) to 2-5 heartbeat stasis.	Device: Bland Embolization • Lobar or segmental bland embolization with microspheres (50-500 microns) to 2-5 heartbeat stasis • Other Names: ◦ BE
Experimental: Arm 2 - TACE Lobar or segmental lipiodol conventional transarterial chemoembolization (TACE). Doxorubicin 50 mg dissolved in 10 mL dilute contrast and emulsified with 10-20 cc iodized oil, followed by 50-500 µm microspheres.	Combination Product: Transarterial chemoembolization • Lobar or segmental lipiodol transarterial chemoembolization. Doxorubicin 50 mg dissolved in 10 mL dilute contrast and emulsified with 10-20 cc iodized oil, followed by 50-500 µm microspheres. • Other Names: ◦ TACE
Experimental: Arm 3 - DEB - CLOSED Lobar or segmental hepatic chemoembolization with DEBDOX (100-300 or 300-500 micron beads loaded with doxorubicin per manufacturer IFU monthly until entire tumor burden is treated.	Combination Product: Drug Eluting Beads Embolization • CLOSED - Lobar or segmental hepatic chemoembolization with DEBDOX (100-300 or 300-500 micron beads loaded with doxorubicin per manufacturer IFU. • Other Names: ◦ DEB

What about DEB-TACE? Currently NO

03:27 PM **Abstract No. 105**

Randomized Embolization Trial for NeuroEndocrine Tumors (RETNET): first safety report

M. Soulen[1], S. White[2], N. Fidelman[3], R. Garcia-Monaco[4], E. Wileyto[5], R. Avritscher[6], G. El-Haddad[7]; [1]University of Pennsylvania, Lafayette Hill, PA; [2]Medical College of Wisconsin, Milwaukee, WI; [3]University of California San Francisco, San Francisco, CA; [4]Hospital Italiano De Buenos Aires, Buenos Aires, Argentina; [5]University of Pennsylvania, Philadelphia, PA; [6]MD Anderson Cancer Center, Houston, TX; [7]Moffitt Cancer Center and Research Institute, Tampa, FL

- DEB arm closed

@ first study review for 4/10 (40%) Grade 3 AE's

2 ICU, 2 permanent biliary injuries, 2 study discontinuation

- Hopkins study 2013
- Phase 1 study of DEBDOX, 5/20 (25%) hepatic necrosis

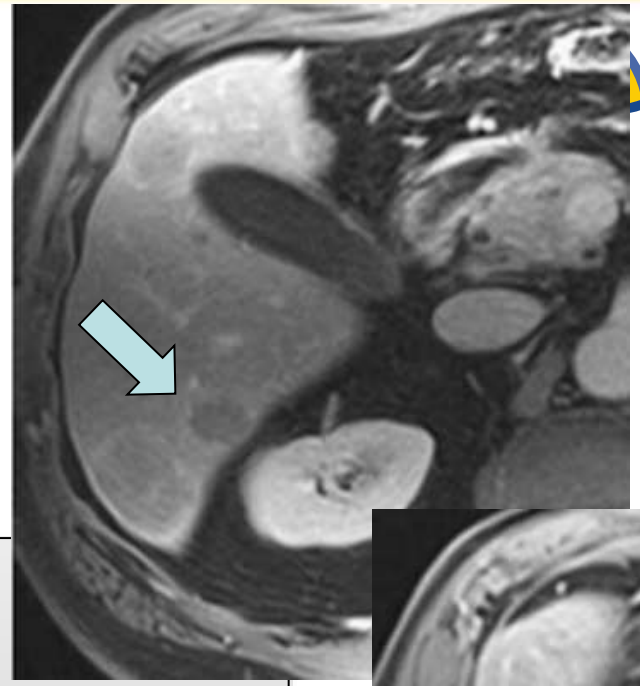
SIR abstract 105, SIR annual scientific meeting 2019

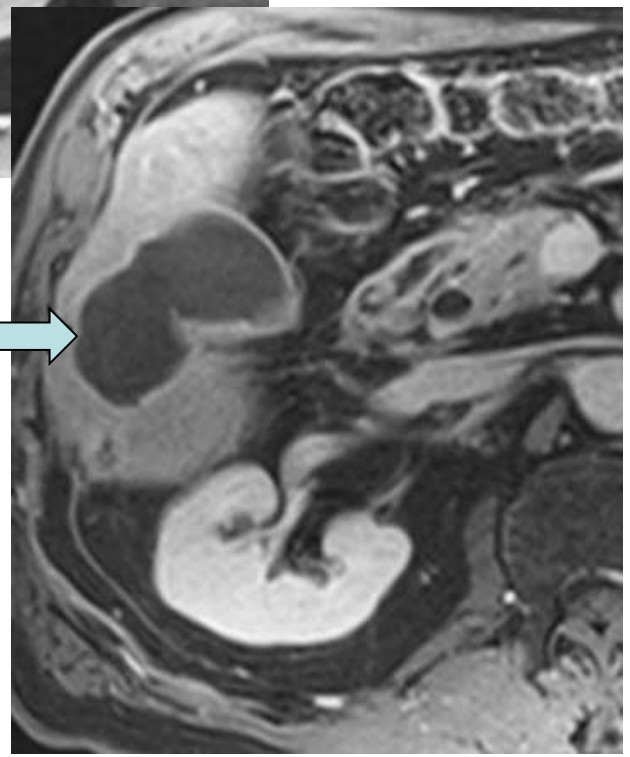
Home > CardioVascular and Interventional Radiology > Article

Phase II Study of Chemoembolization With Drug-Eluting Beads in Patients With Hepatic Neuroendocrine Metastases: High Incidence of Biliary Injury

Clinical Investigation | Published: 22 June 2012

Volume 36, pages 449–459, (2013) Cite this article





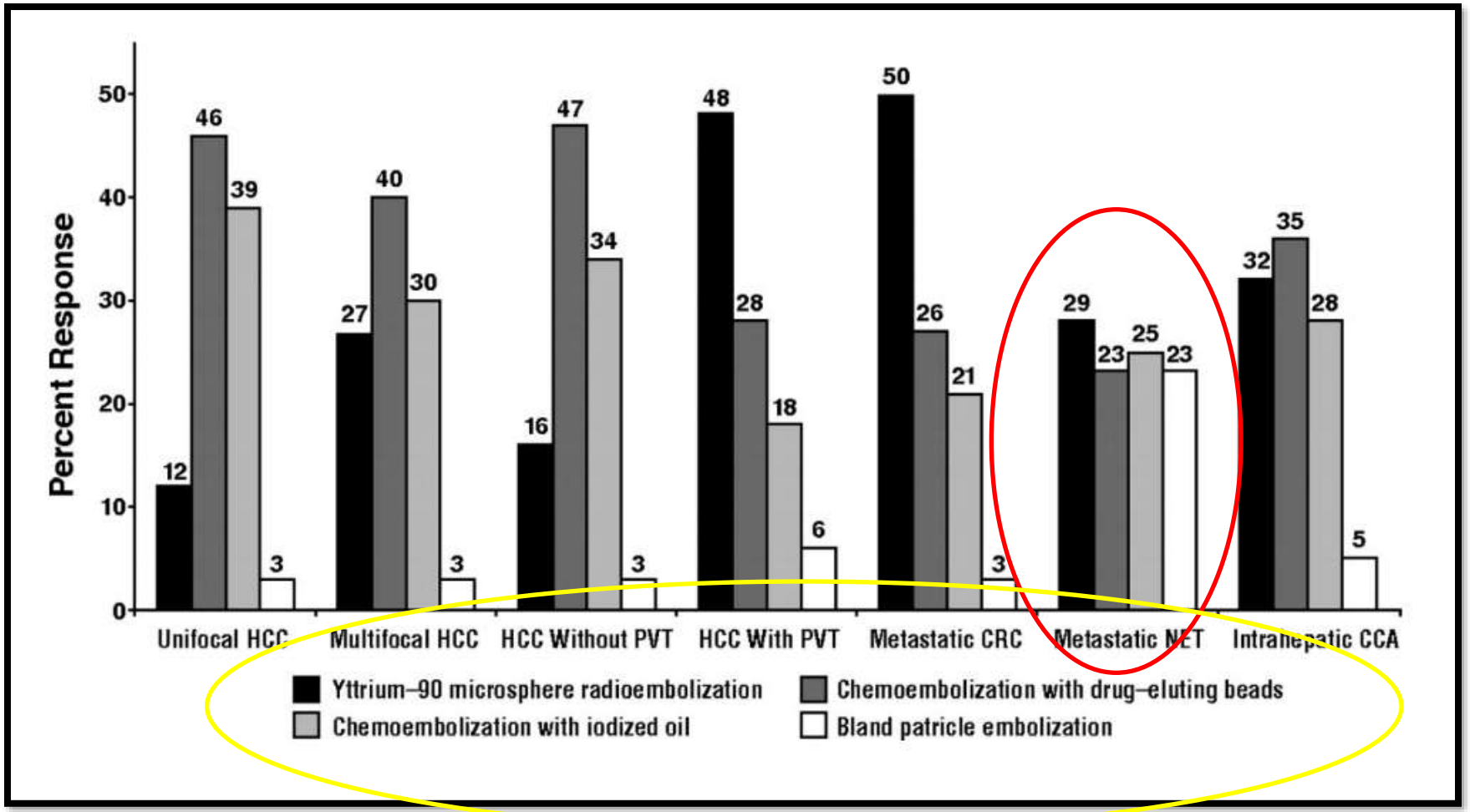
- DEB-TACE in 13 patients.
- At 1 month follow-up, 12 % decrease in tumor ORR 78 %.
- Grade 3/4 toxicities wre fatigue (23 %), ALT(15 %), hyperglycemia (15 %), and abdominal pain (8 %).
- **7 patients developed bilomas (54 %);** all of these patients had multiple small (<4 cm) lesions.
- **Conclusions:** biloma / liver abscess are known risks after TACE, the high incidence in our study population was unexpected and forced interruption of the trial.
- Termination of of the trial.

Bhagat N, et al. Phase II study of chemoembolization with drug-eluting beads in patients with hepatic neuroendocrine metastases: high incidence of biliary injury. Cardiovasc Intervent Radiol. 2013 Apr;36(2):449-59.

AJR

Original Research | Vascular and Interventional Radiology | November 23, 2012

Chemoembolization Practice Patterns and Technical Methods Among Interventional Radiologists: Results of an Online Survey



aba RC. Chemoembolization practice patterns and technical methods among interventional radiologists: results of an online survey. AJR Am J Roentgenol. 2012 Mar;198(3):692-9.

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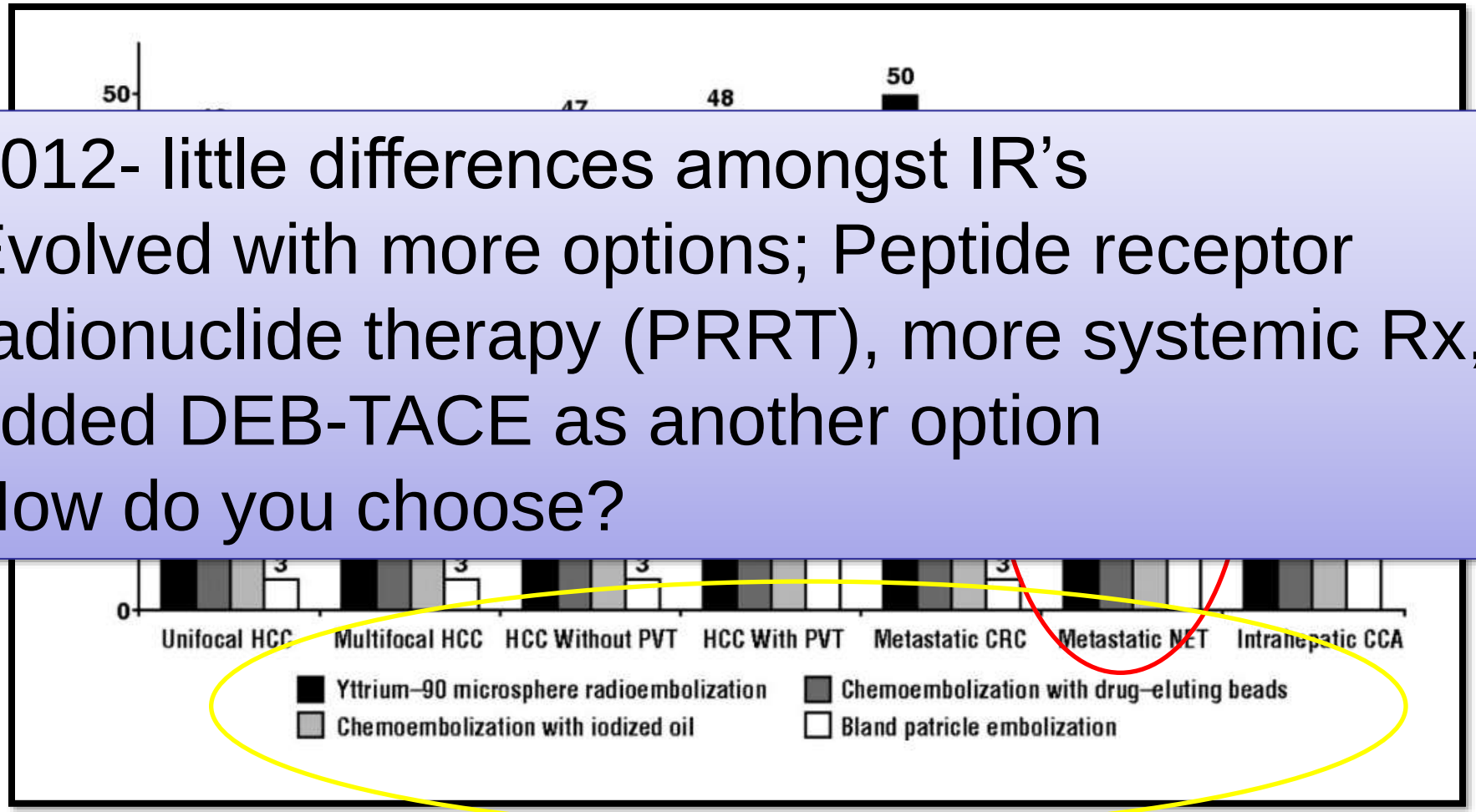
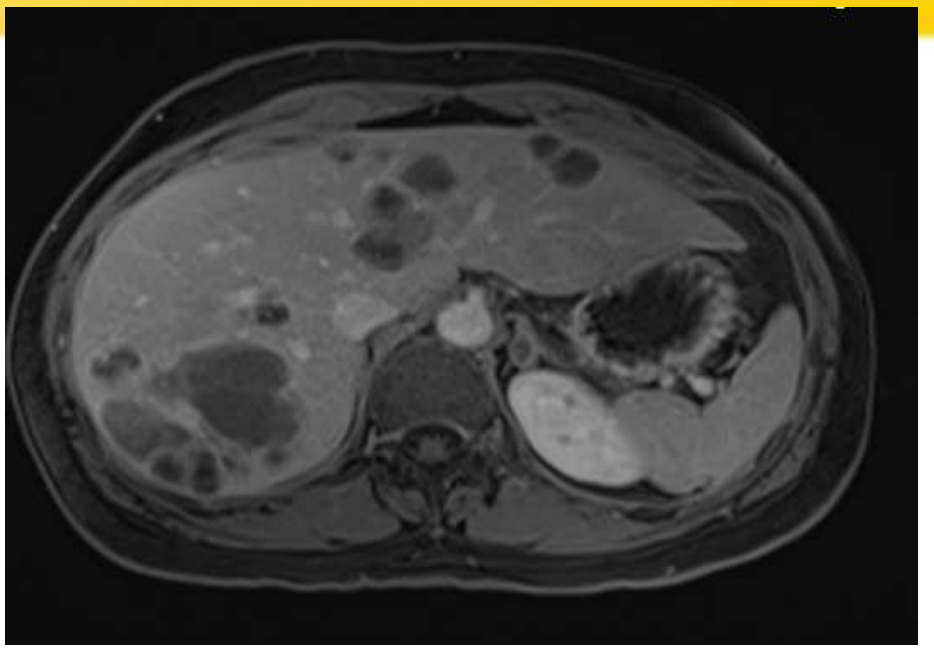


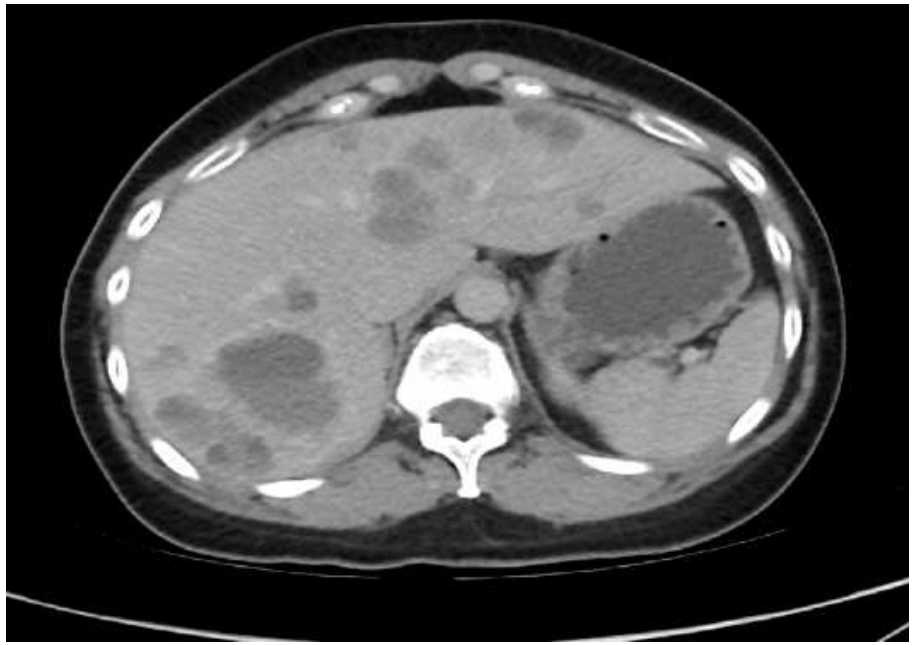
2012- little differences amongst IR's
Evolved with more options; Peptide receptor radionuclide therapy (PRRT), more systemic Rx, and added DEB-TACE as another option
How do you choose?

aba RC. Chemoembolization practice patterns and technical methods among interventional radiologists: results of an online survey. AJR Am J Roentgenol. 2012 Mar;198(3):692-9.

Case in point:

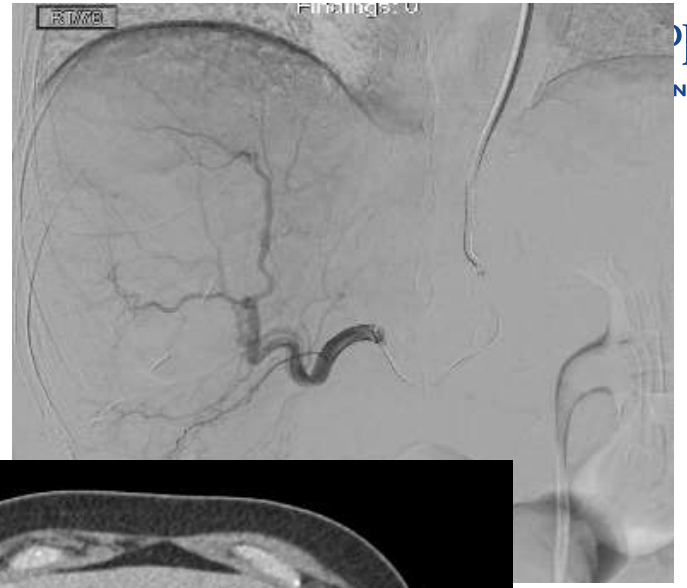
- 52 yr old NET functional with carcinoid
- From out of state, 4 hours away- wife of a ED doctor; 2017
- Young family, 3 young children <10
- Referred for bulk and symptoms, PS ECOG 2 (flushes, diarrhea)
- Very pessimistic; rapid liver progression over 1 year, talked about palliative care/ not seeing her children grow up

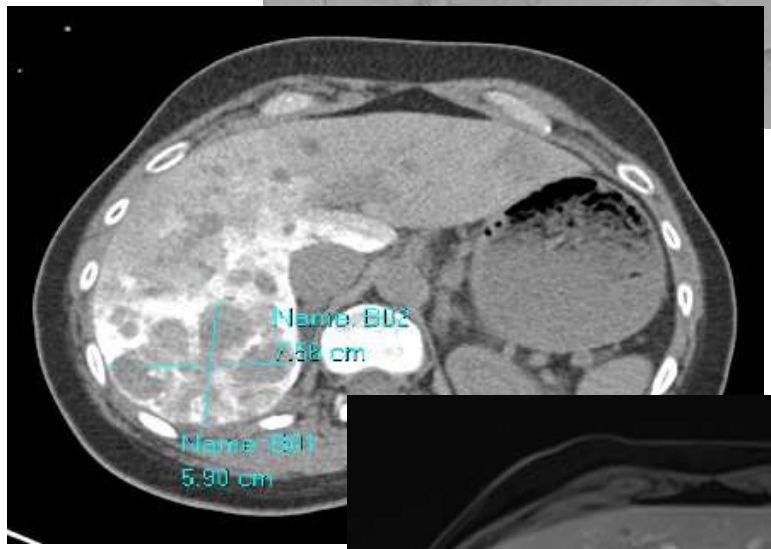


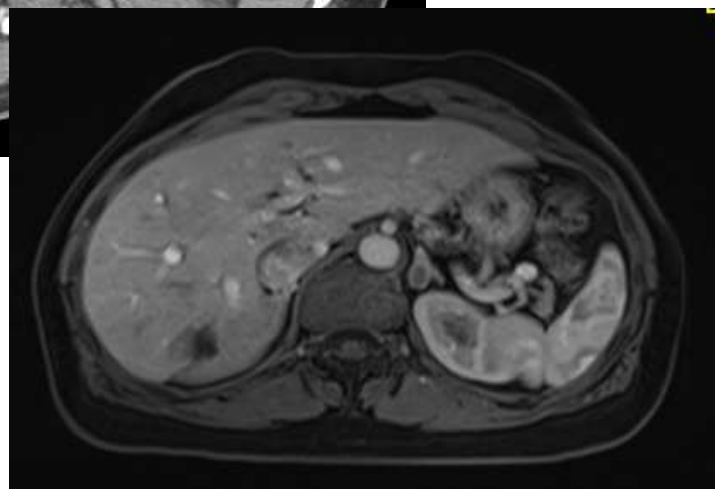


Case in point:

- 2 rounds of left and right TAE
- Switched to TACE X 2 over 12 months
- Excellent ORR with hypovascular remenant lesions
- Follow up 3 monthly for 1 year, then 6 monthly for 2nd year.
- Retreated left lesion 2 years later

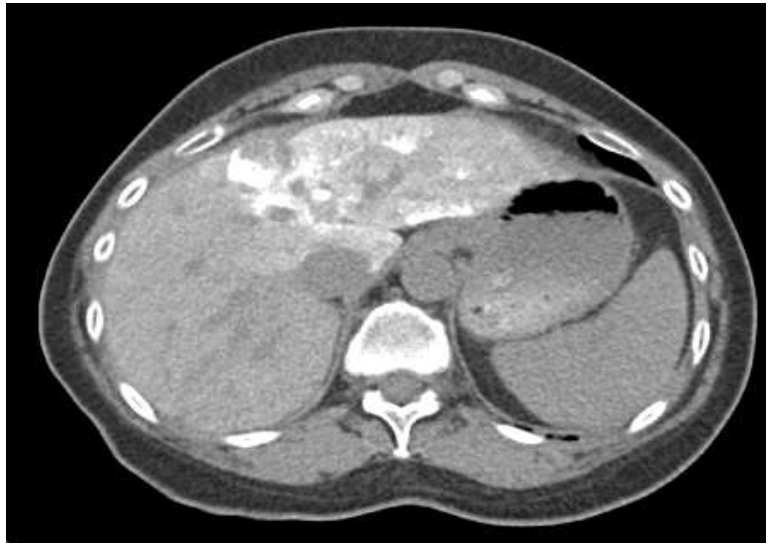


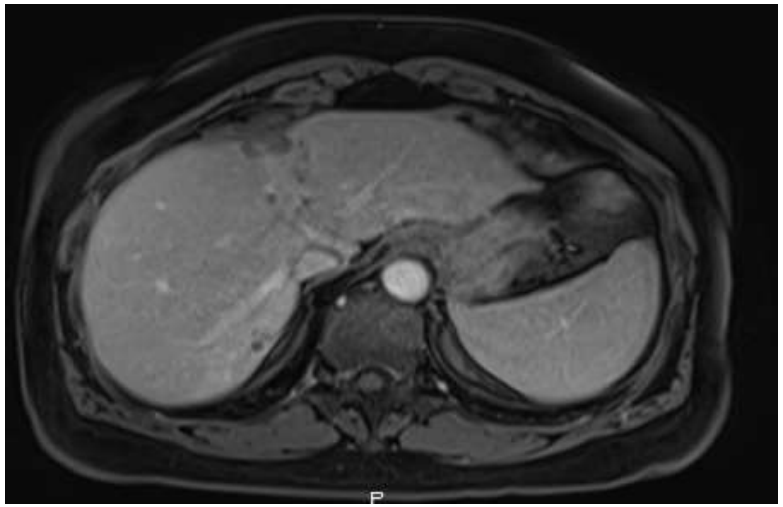




Case in point:

- 2 rounds of left and right TAE
- Switched to TACE X 2 over 12 months
- Excellent ORR with hypo vascular remnant lesions; symptom response
- Follow up 3 monthly for 1 year, then 6 monthly for 2nd year.
- Retreated TACE left lesion 2 years later, 4 smaller lesions, responded.
- 2024 still minimal tumor burden

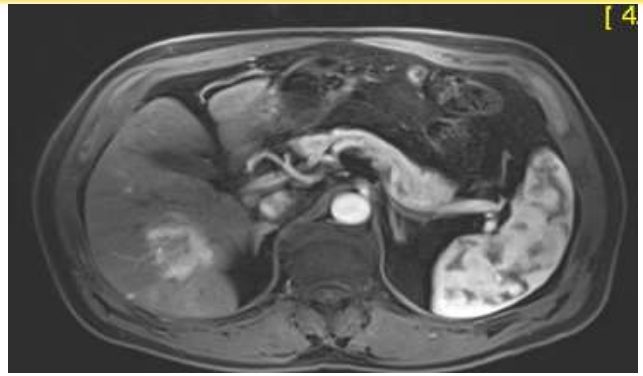


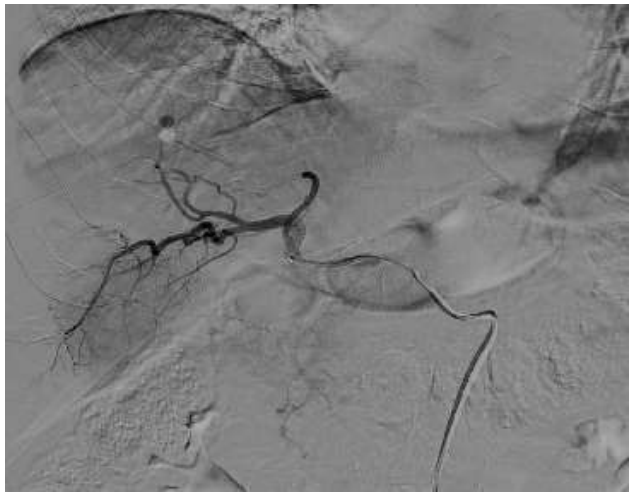


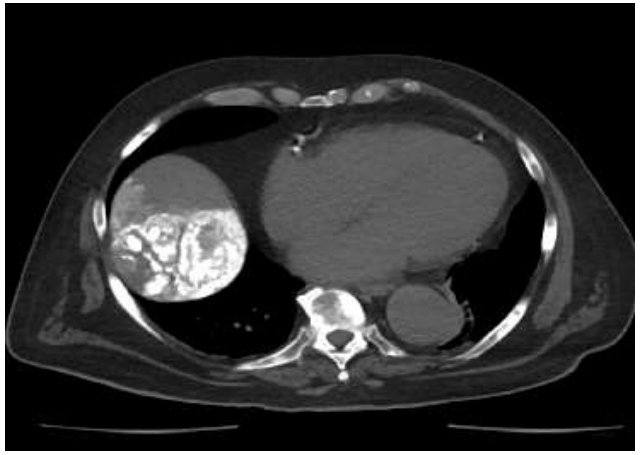
Our Working approach:

- NET Multidisciplinary Tumor Board
- Well differentiated NET liver mets, mulitofcal, unresectable/ un-ablatable tumors
- Non surgical patients: Liver Directed options retain as many options as possible, long surviving patients

1. TAE first (minimize AE's)
2. TACE second, when lesions refractory to TAE
3. TARE third (preserve background non tumor liver)
   -when refractory to TACE,
   - or when previous Biliary enteric surgery (reduce abscess risk, as high as 30-50% with TACE)
   - selected compensated poorly diff. NET







Conclusion

- Latest guidelines continues to include local liver therapies for non surgical, liver mets
- No evidence supporting TAE over TACE over TARE
- No role for DEB-TACE in NET
- May adopt sequential approach: TAE/TACE/TARE
- Await RETNET RCT trial result

THANK YOU