Interventional Oncology in NCCN Guidelines: mNET and Other Tumor Types

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Disclosures

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Neuroendocrine and Adrenal Tumors

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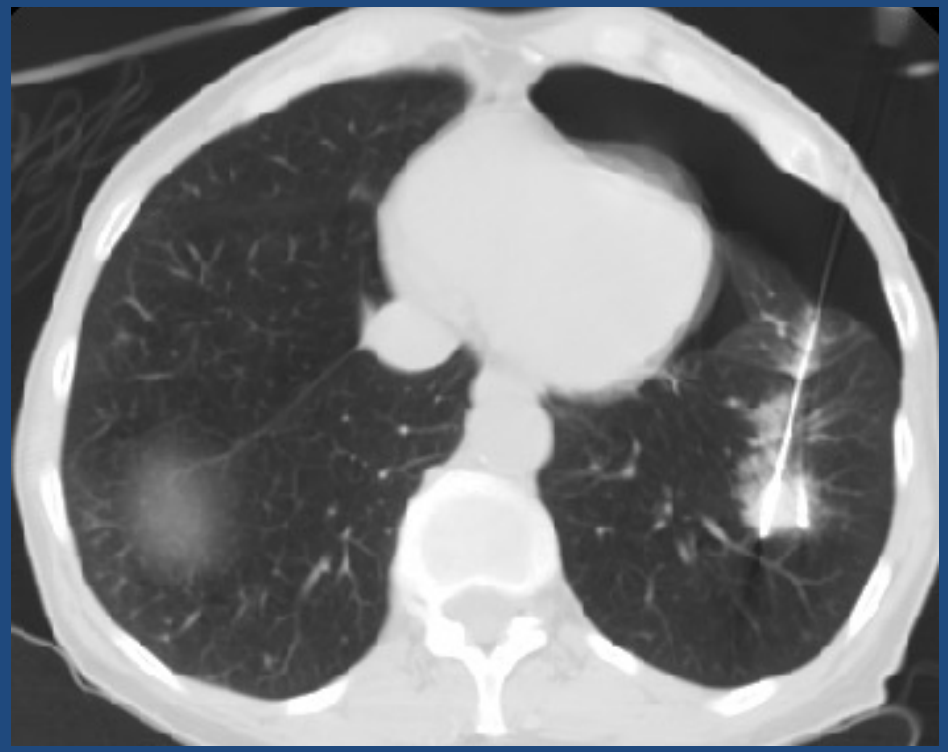
Relevant Changes: 2021
Bronchopulmonary/Thymus

NET-7: Thermal ablation for lung carcinoid primary tumor (if surgery and RT contraindicated)



2021: Recommended thermal ablation **or** RT if surgery contraindicated.

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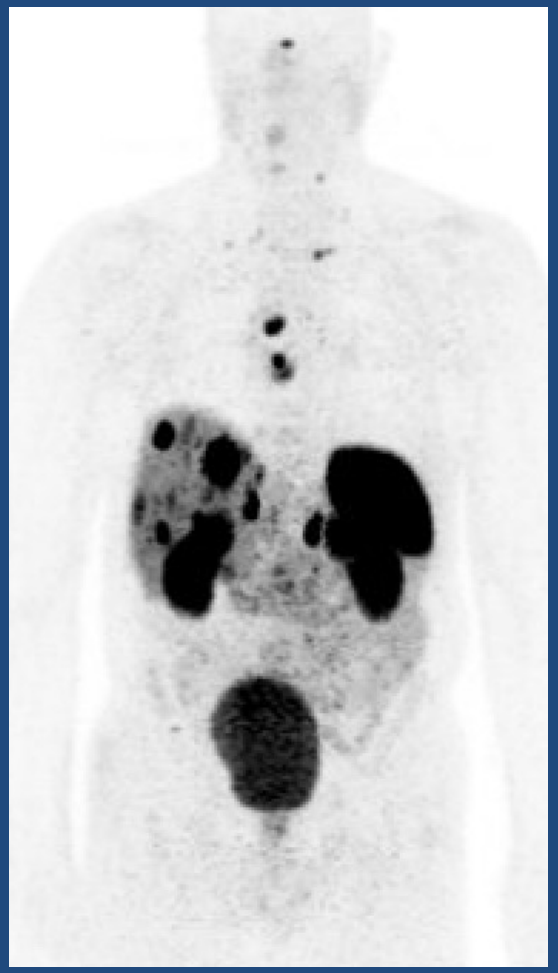
Relevant Changes: 2021
Bronchopulmonary/Thymus

NET-10:

Added LDT for liver-predominant disease and referenced Principles of Liver-Directed Therapy for mNET (NE-G)



65M bronchial NET

Principles of LDT for mNET

PRINCIPLES OF LIVER-DIRECTED THERAPY FOR NEUROENDOCRINE TUMOR METASTASES

Liver-directed therapy consists of three categories of treatment:
Surgical resection (which may include intraoperative thermal ablation of lesions); see Surgical Principles For Management of Neuroendocrine Tumors (NE-D)
Hepatic arterial embolization, including bland transarterial embolization [TAE], chemoembolization [TACE], and radioembolization [TARE]
Percutaneous thermal ablation

Indications for Hepatic Arterial Embolization

- **Embolization is recommended for well-differentiated NETs with liver-dominant, unresectable metastases that are:**
  - **Symptomatic on an SSA or following another form of systemic therapy**
  - **Progressive on an SSA or following another form of systemic therapy**
  - **Presenting with bulky liver disease; embolization may be employed as debulking therapy without waiting for progression.**
- **Objective radiologic response rates vary widely in retrospective studies, but average approximately 60%, with symptom palliation in approximately 85% of patients with hormonal syndromes.**
- **Relative contraindications include significant baseline liver dysfunction (jaundice, ascites) and a liver tumor burden >70%. Prior Whipple surgery or biliary instrumentation (sphincterotomy, stent) increases the risk of liver abscess due to biliary bacterial colonization; infectious complications occur in about 20% of cases following TAE/TACE and 8% after TARE, even with broad-spectrum antibiotic coverage.**

Embolization Modalities

- **TAE and TACE**
  - **There are no completed randomized studies comparing TAE with conventional TACE and both are acceptable.**
  - **Drug-eluting embolics are associated with increased hepatobiliary toxicity in the NET population, and are not recommended.**
  - **In patients with bilobar disease, TAE/TACE is generally performed over at least two procedures, approximately one month apart. Patients with very high liver tumor burden may require three or four embolizations to safely treat the entire liver. Short-acting octreotide should be administered pre-embolization for patients with hormonal syndromes. Overnight observation is typically appropriate to monitor and treat symptoms of post-embolization syndrome such as pain and nausea and exacerbation of hormone-related symptoms.**
- **TARE may be considered particularly in the following scenarios:**
  - **Lobar or segmental (less than lobular) disease distribution.**
  - **Patients with prior Whipple surgery or biliary tract instrumentation (lower risk of hepatobiliary infection than TAE/TACE).[1-4]**
  - **TARE is better tolerated than TAE/TACE, but late radioembolization-induced chronic hepatotoxicity (RECHT) may occur in long-term survivors, and is particularly a concern among patients undergoing bilobar radioembolization.**
  - **To date there is no evidence for or against the safety of sequencing TARE and PRRT.[5,6]**

Ablative Therapy (category 2B)

- **Percutaneous thermal ablation, often using microwave energy (radiofrequency and cryoablation are also acceptable), can be considered for oligometastatic liver disease, generally up to four lesions each smaller than 3 cm. Feasibility considerations include safe percutaneous imaging-guided approach to the target lesions, and proximity to vessels, bile ducts, or adjacent non-target structures that may require hydro- or aero-dissection for displacement.**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

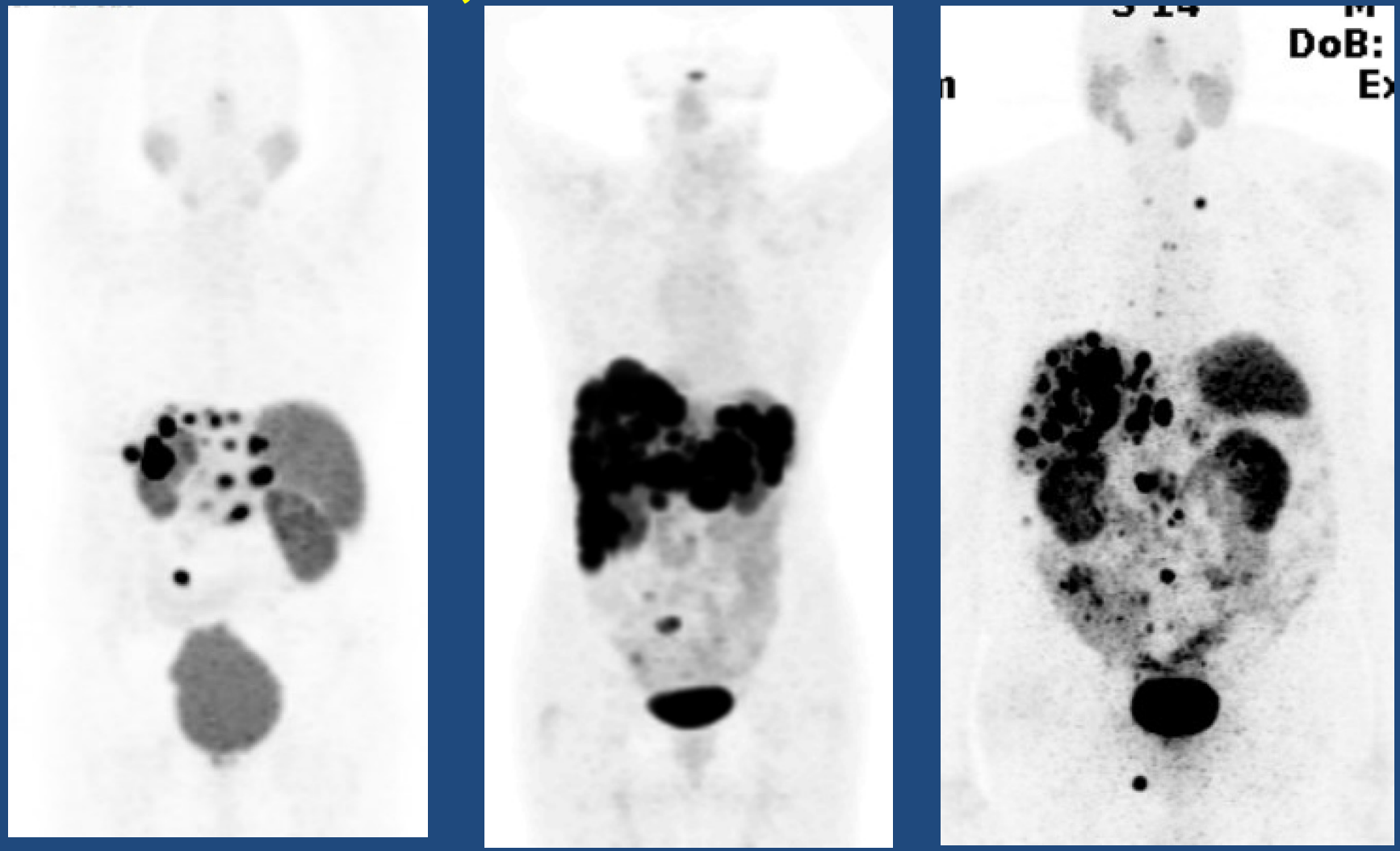
References

LDT Definitions (2021)

1. Surgical resection (may include intraop thermal ablation)
2. Hepatic arterial embolization: TAE, TACE, TARE
3. Percutaneous thermal ablation

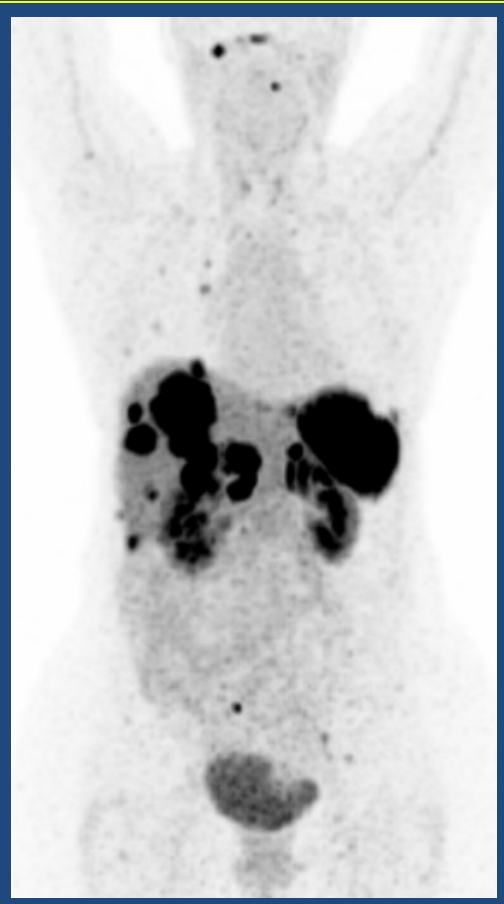
Indications for TAE (2021)

Liver-only or liver-dominant, WD, unresectable

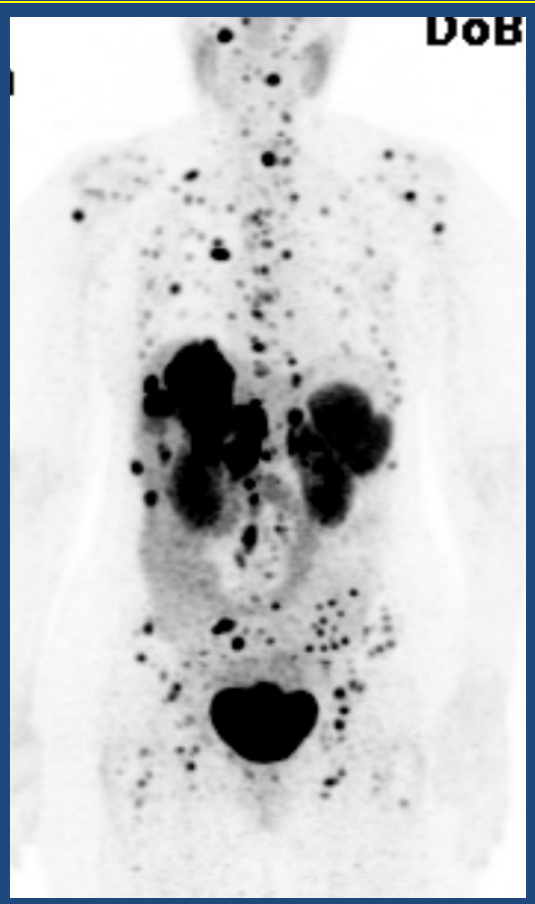


Ga-68 DOTATATE PET

Catching Window for Liver-Directed Therapy is Key



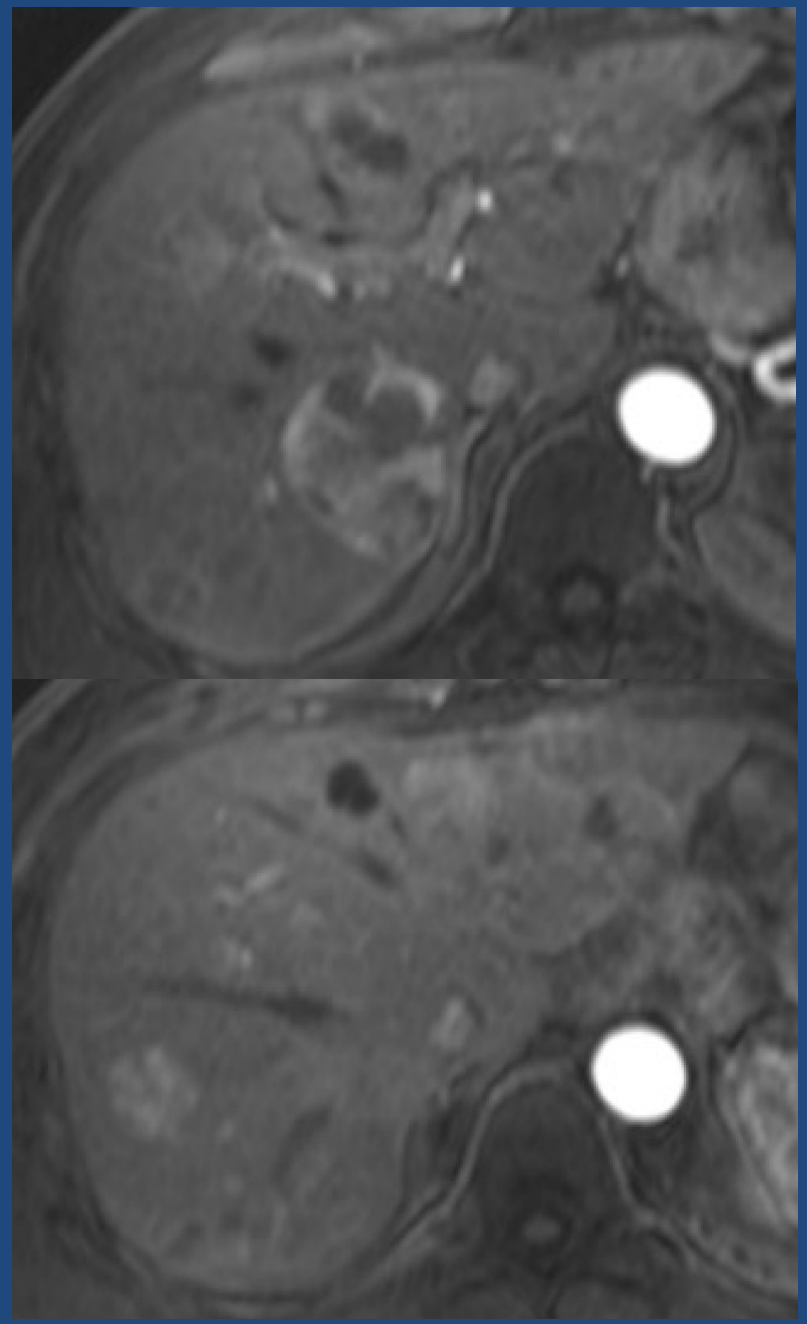
Ga-68 DOTATATE



2 years later

Indications for TAE (2021)

1. **Symptomatic** on SSA or other treatment
2. **Progressive** on SSA or other treatment
3. **Bulky** but stable

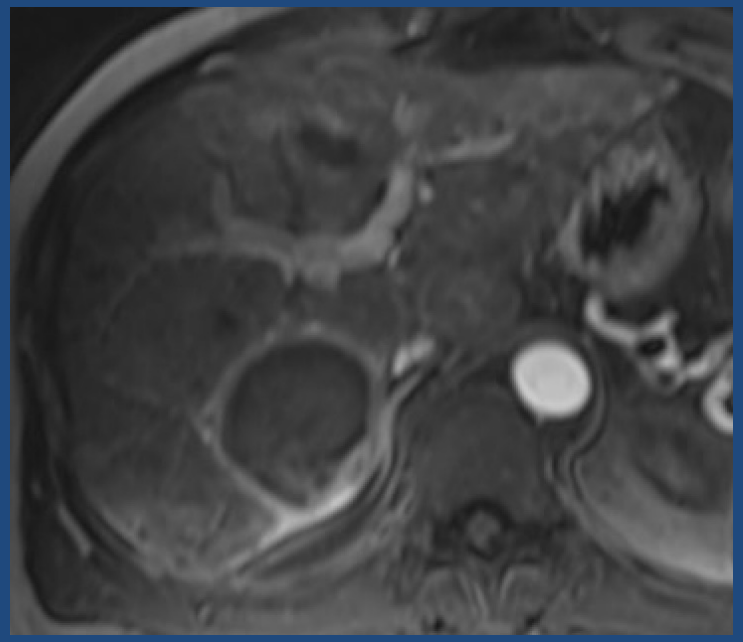


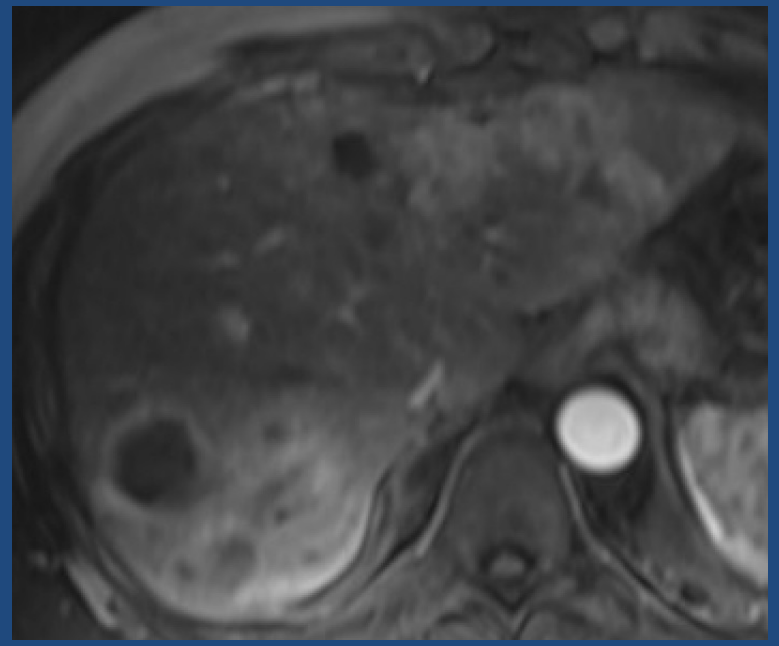
Symptomatic on SSA

63M with severe flushing and diarrhea

6-8 BM per day
Nearly constant flushing

TACE to largest lesions in segment 7





Hormone Effect Reduction

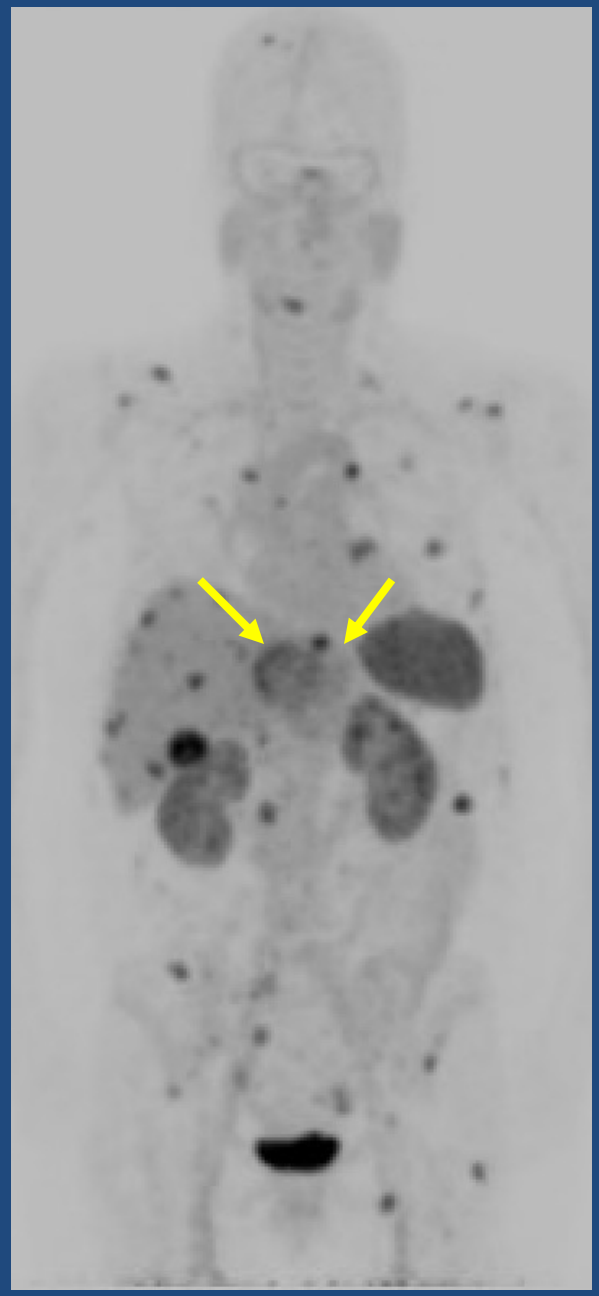
2-3 BM per day
Flushing improved

- Limited embolization may be adequate

- Number of treatments titrated to symptomatic improvement

PD on SSA

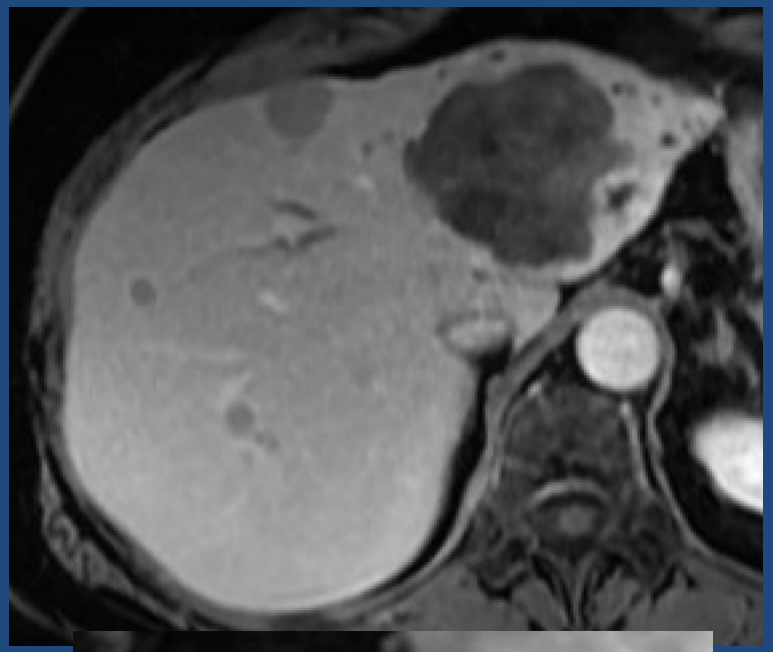
- One (few) enlarging liver lesion less DOTA-avid
- Other lesions more DOTA-avid – good PRRT targets

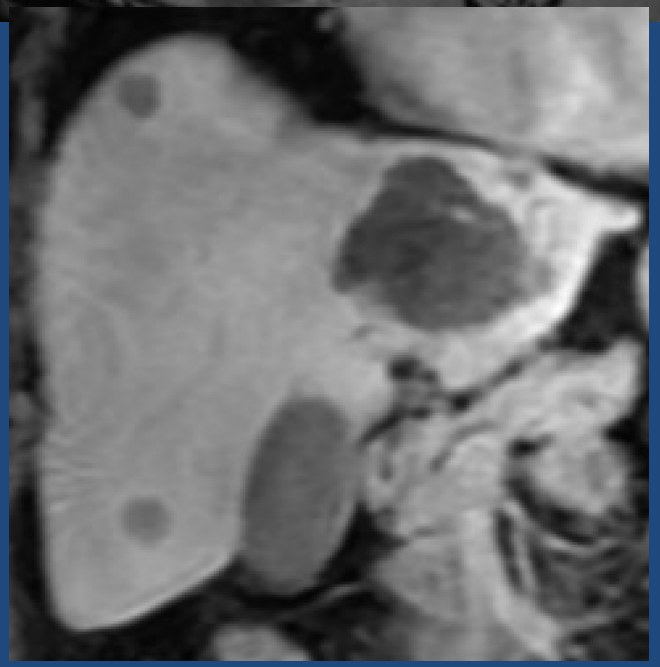


Ga-68 DOTA-TATE

63F with carcinoid

Pre-TACE

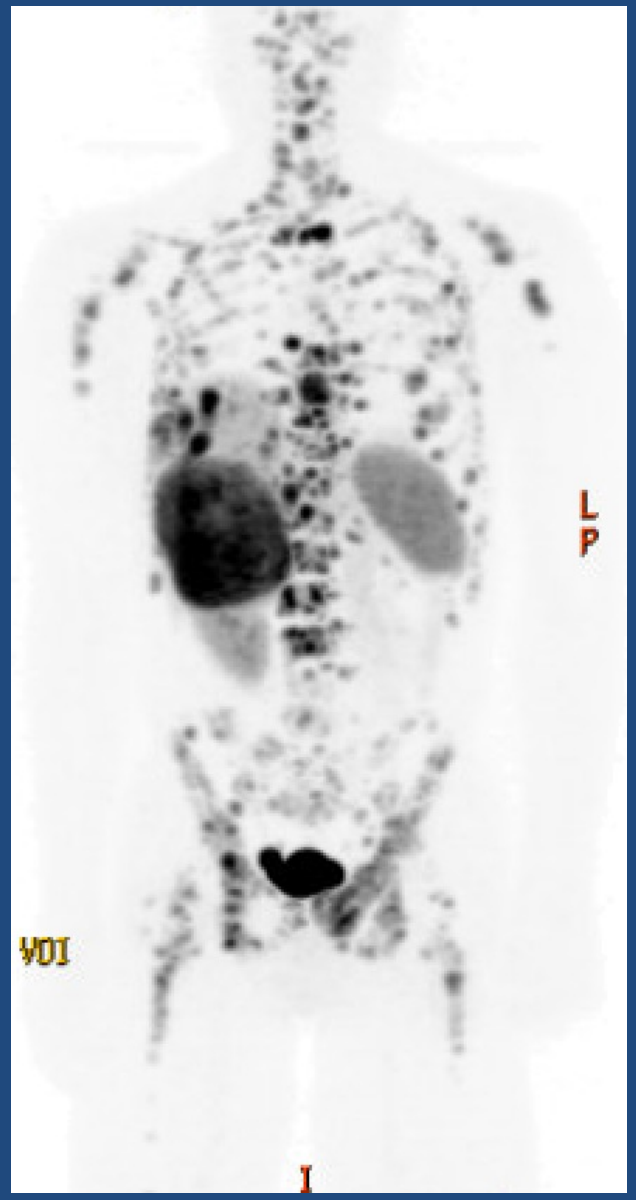




1mo s/p TACE

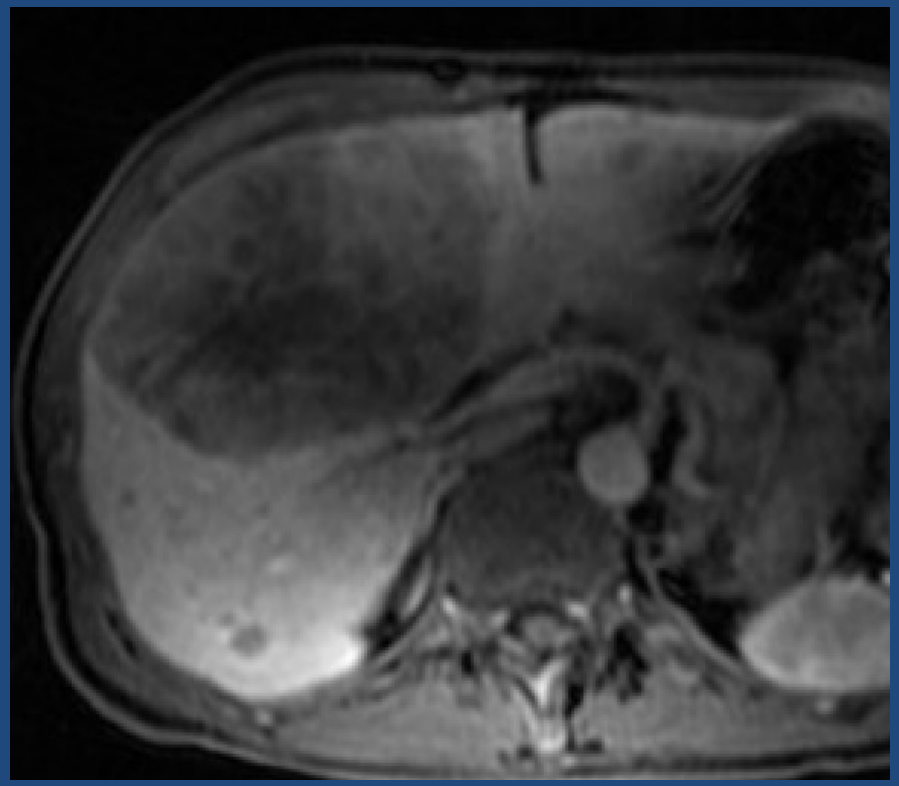
PD on SSA

- One (few) bulky liver lesions
- Other lesions smaller
- ? Improve PRRT distribution to smaller lesions

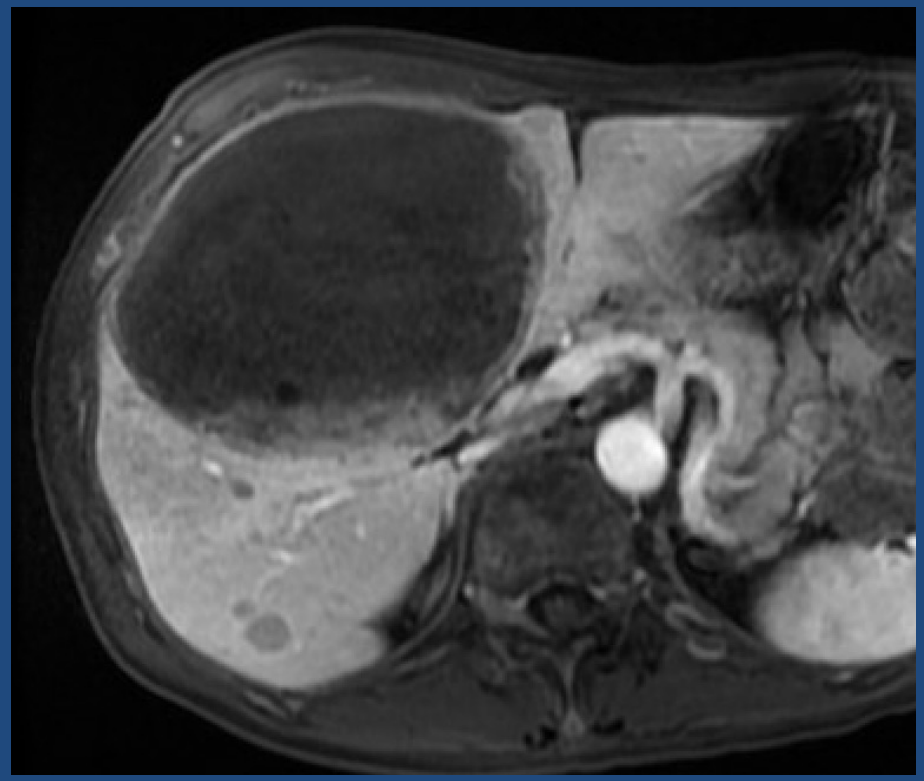


Ga-68 DOTA-TATE

50M with renal carcinoid



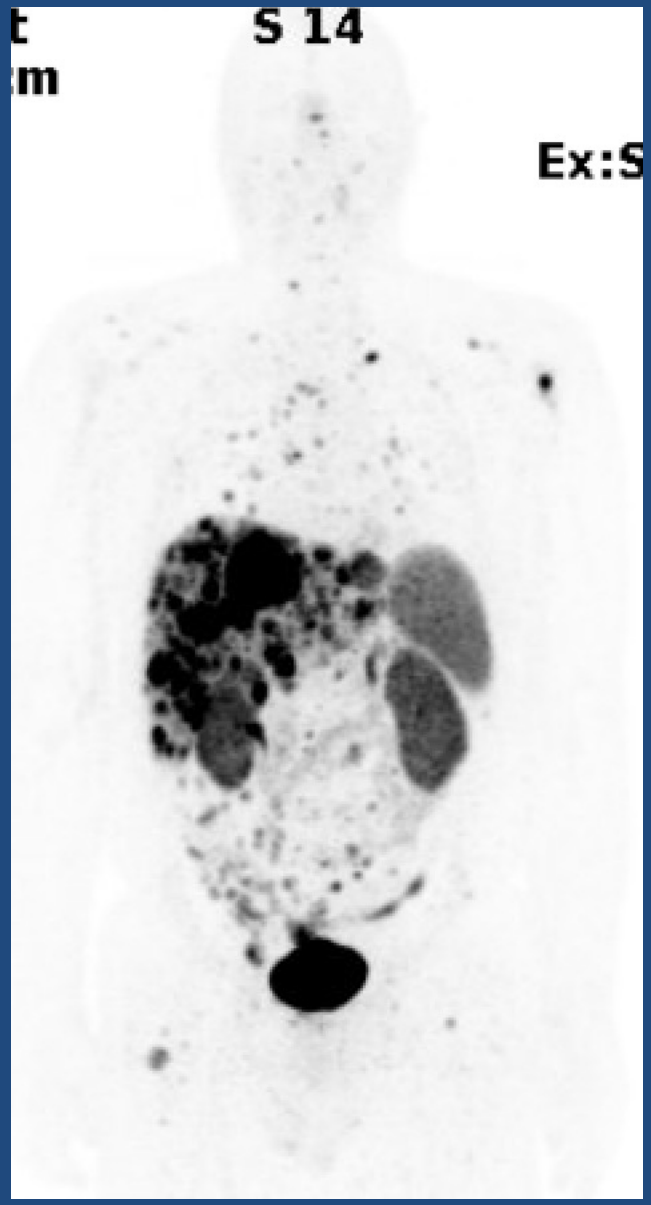
Pre-TACE



1 mo s/p TACE

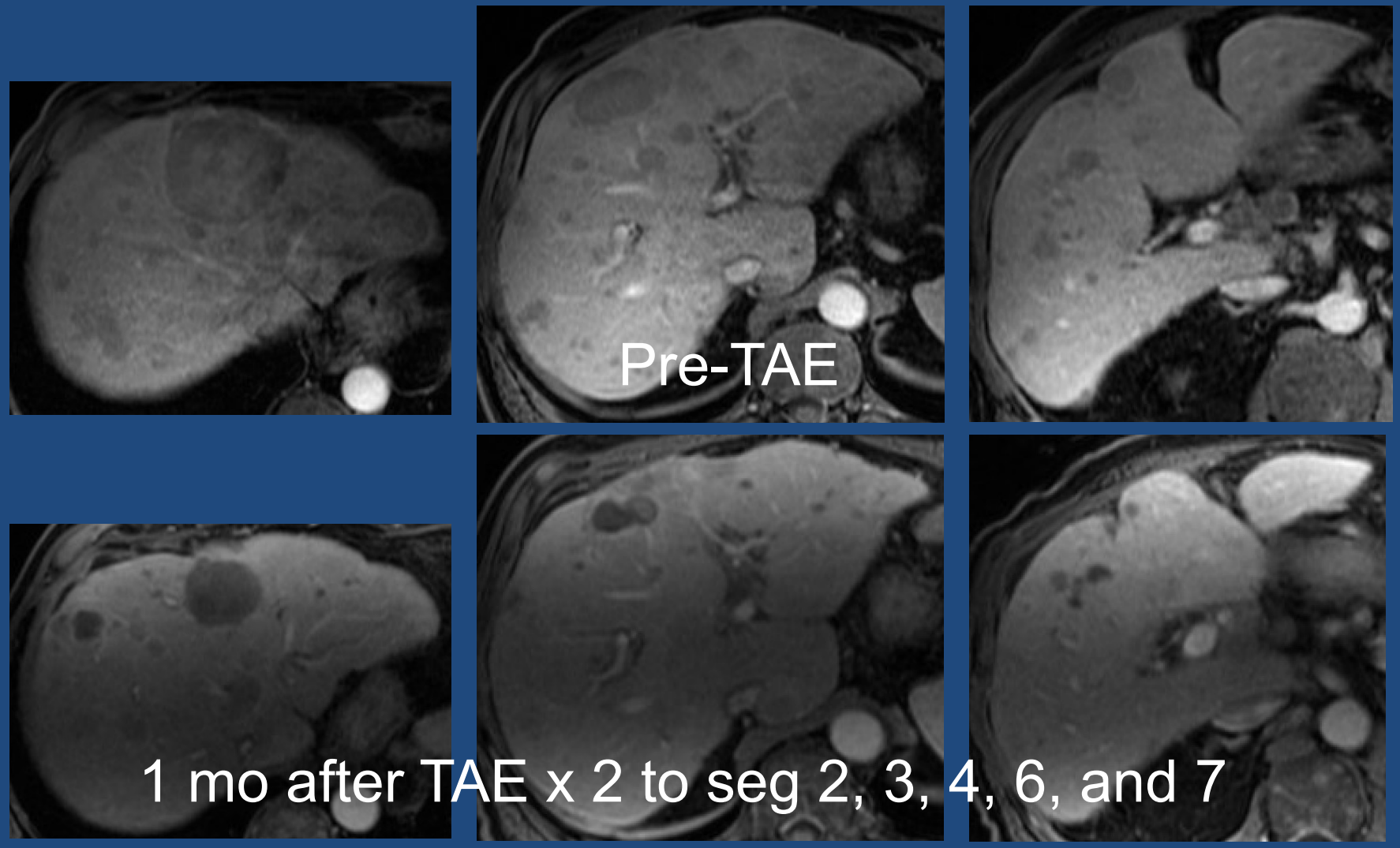
Progression after PRRT

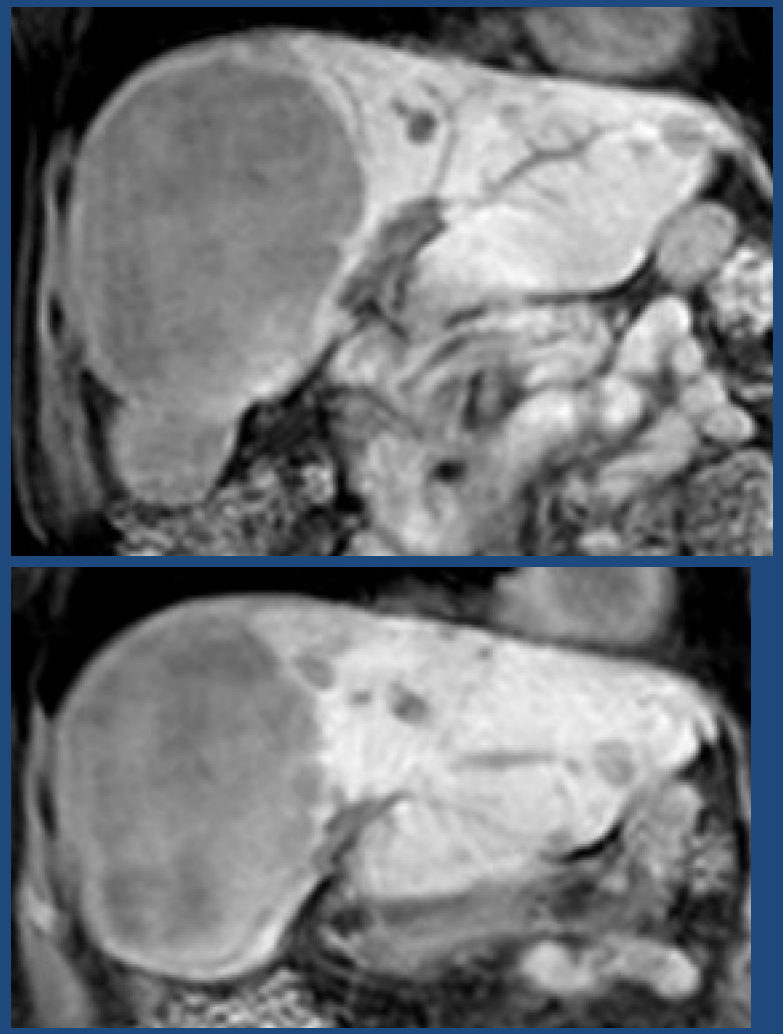
- Preserved liver function
- Liver-dominant disease distribution



Ga-68 DOTA-TATE

62M with carcinoid (Ki-67 6.7%), s/p PRRT x 4 one year earlier



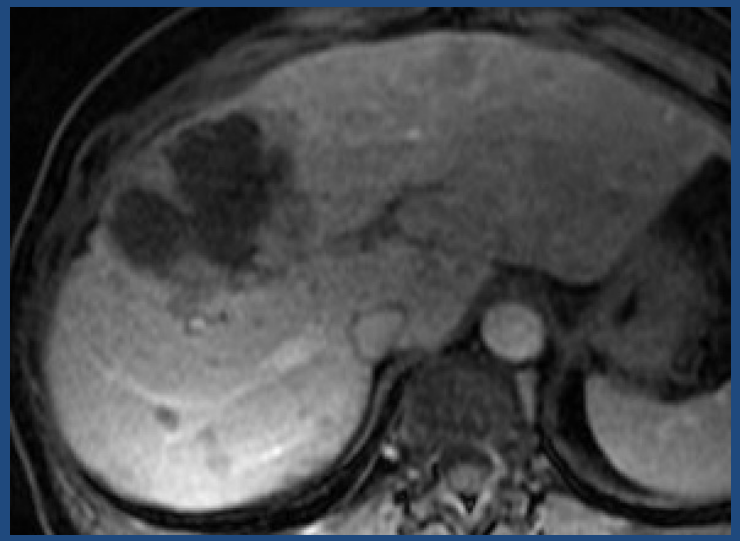


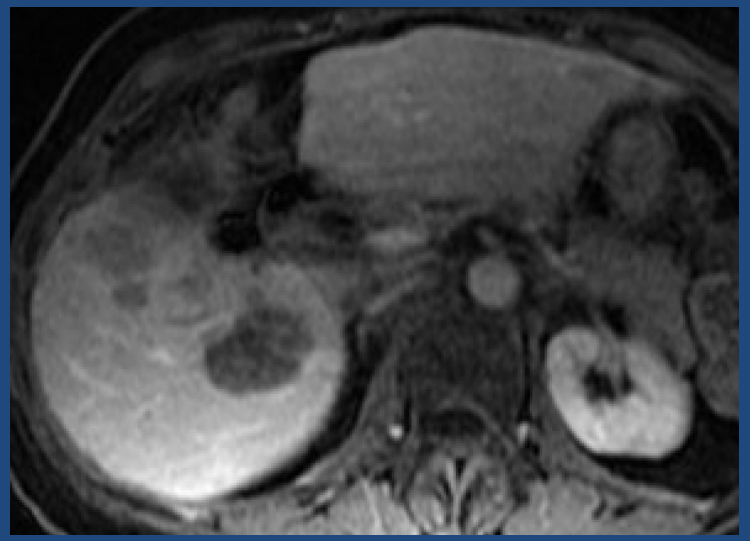
Bulky, but stable

57F with carcinoid heart disease s/p TVR

24-hr urine 5-HIAA 139 (Goal < 50 for valvular disease prevention)

TACE to right lobe lesions (3 sessions)





Carcinoid heart disease prevention

	24-hr 5-HIAA
Baseline	139
After TACE 2	57
After TACE 3	39
3 yrs after TACE 3	37

Right lobe treatment adequate

Either cTACE or TAE acceptable

- Meta-analysis of retrospective case series up to 67 pts

	TAE	TACE
Symptomatic improvement	64-93%	60-95%
Biochemical improvement	50-69%	50-90%
Imaging improvement	32-82%	33-80%
Progression-free survival	18-88 months	18-24 months

Chemo used: doxorubicin, mitomycin C, cisplatin, 5-FU, streptozotocin

Vogl TJ, Eur J Rad 2009; 72:517

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TACE vs. TAE: Prospective Trial

Penn Medicine

CLINICAL RESEARCH PROTOCOL

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

A phase 2 randomized multicenter trial to compare hepatic progression-free survival following bland embolization, lipiodol chemoembolization, and drug-eluting bead chemoembolization of neuroendocrine liver metastases.

PI Michael Soulen, MD

- 13 sites
- Nearly completely enrolled

NCT02724540

DEB-TACE: Higher risk of biliary injury

	de Baere[1]	Gaur[2]	Bhagat[3]
Best response (EASL) Objective response Disease control rate	 80% 95%	 58% 100%	 78% 100%
Median TTP	15 months	14 months	NR
Symptomatic improvement	81%	NR	NR
Major complications	5 bilomas (25%) (none required drainage)	1 stricture (stented) 1 “biliary injury”	7 bilomas (52%) (3 drained for infxn, 1 for pain)

[1]de Baere T, et al. JVIR 2008; 19:855
[2]Gaur SK, et al. CVIR 2011; 34:566
[3]Bhagat N, et al. CVIR 2013; 36:449

Radioembolization

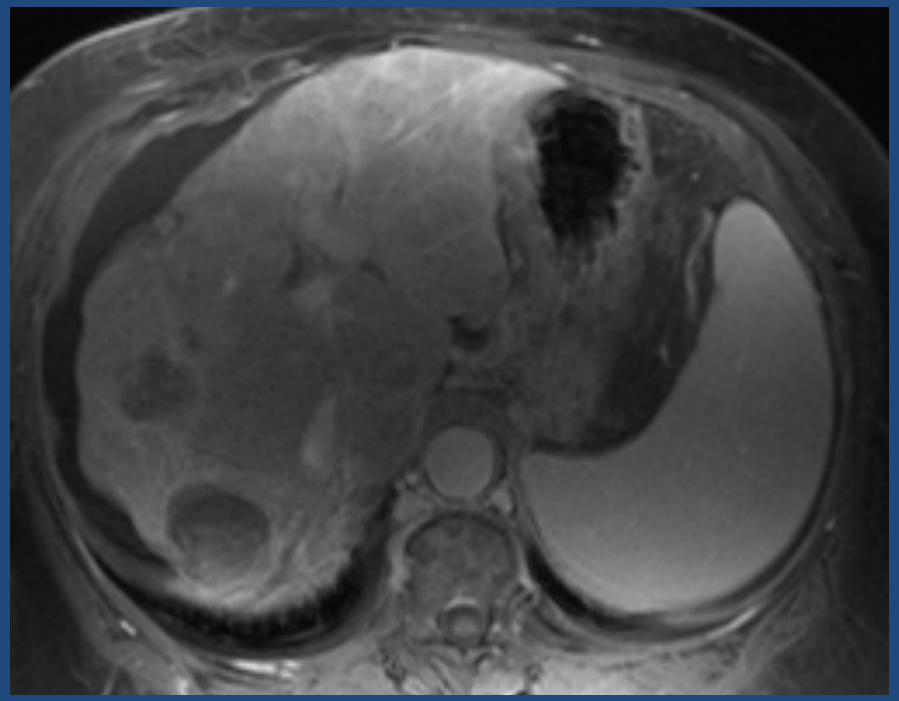
- Meta-analysis of 12 studies (3 prospective, 9 retrospective)
- 414 patients (435 procedures)
- > 70% carcinoid
- Median activity 1.7GBq (range 1.2-3.4 GBq)

	Weighted average	95% CI
RECIST response		
Objective response	50%	38-62%
Disease control rate	86%	78-92%
Overall survival (median)	28 mo	18-50 mo

Devcic Z, et al. J Nucl Med 2014; 55:1404

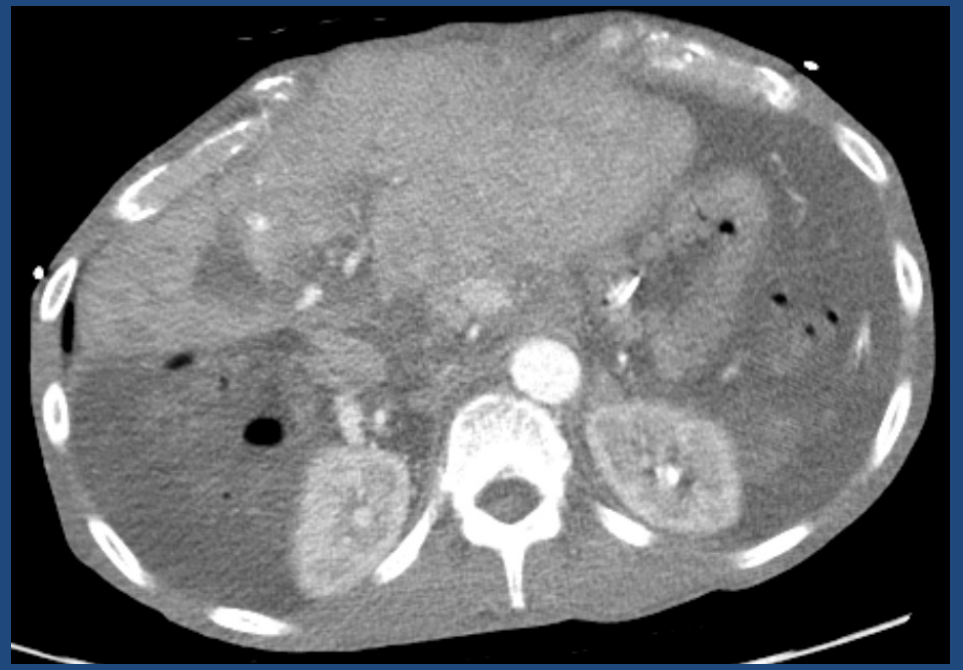
SIRT may be different

70F with rectal carcinoid



S/p SIRT x 3
- 3 years after first SIRT

69M with PNET



S/p SIRT x 3
- 4 years after first SIRT

Both patients had PRRT and chemotherapy after SIRT

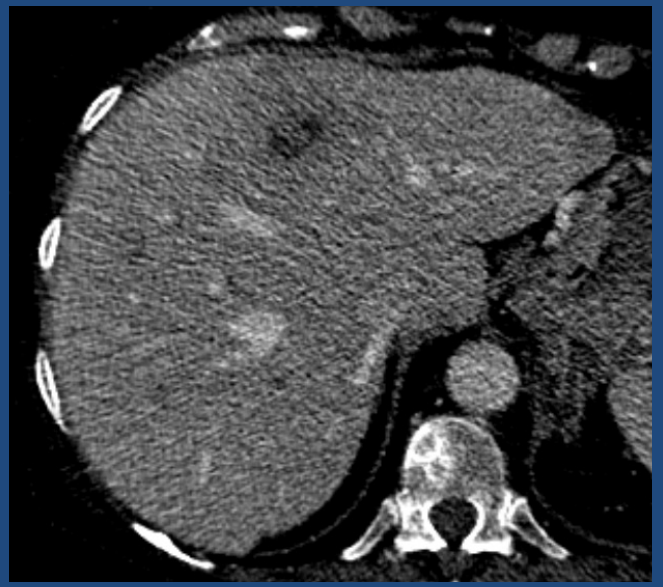
Late radiation-induced liver disease manifests for 10-20% pts

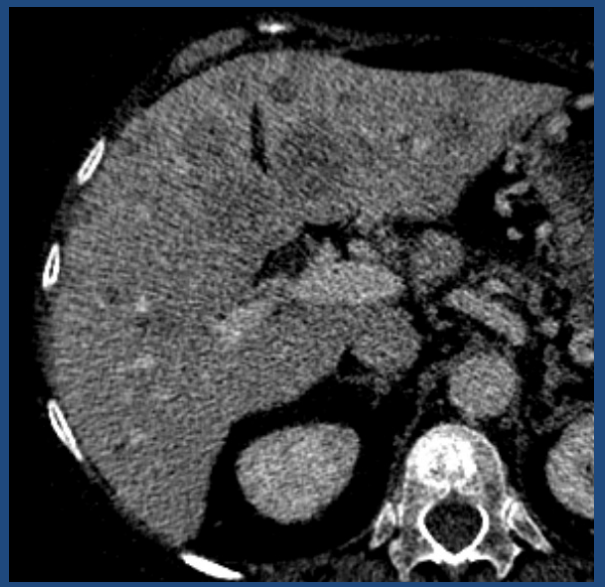
Possible Roles for SIRT

- Lack of avidity on Ga-68 DOTA scans
- Bulky unilobar disease distribution
- Liver dominant, rapid progression, grade 2, multiple prior therapies
- Enlarging liver lesion(s) in setting of prior biliary tract instrumentation (Whipple, drains, stents)
  - Reduced risk of hepatobiliary infection compared to TACE/TAE or ablation
  - 2% risk for SIRT with resin microspheres[1]
  - 11% risk for SIRT with glass microspheres[1]
- Safety of sequencing with PRRT unknown

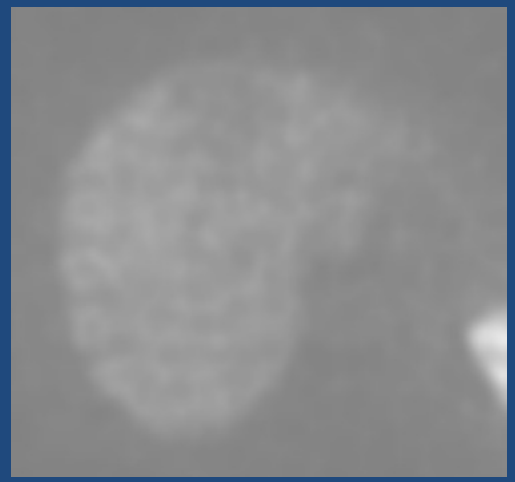
[1]Devulapalli et al. Radiology 2018

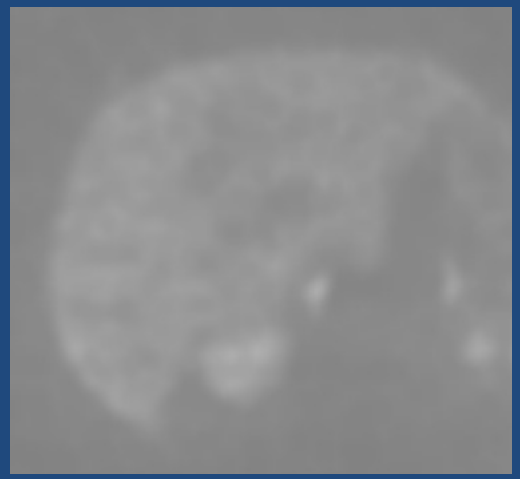
63F with bronchial carcinoid





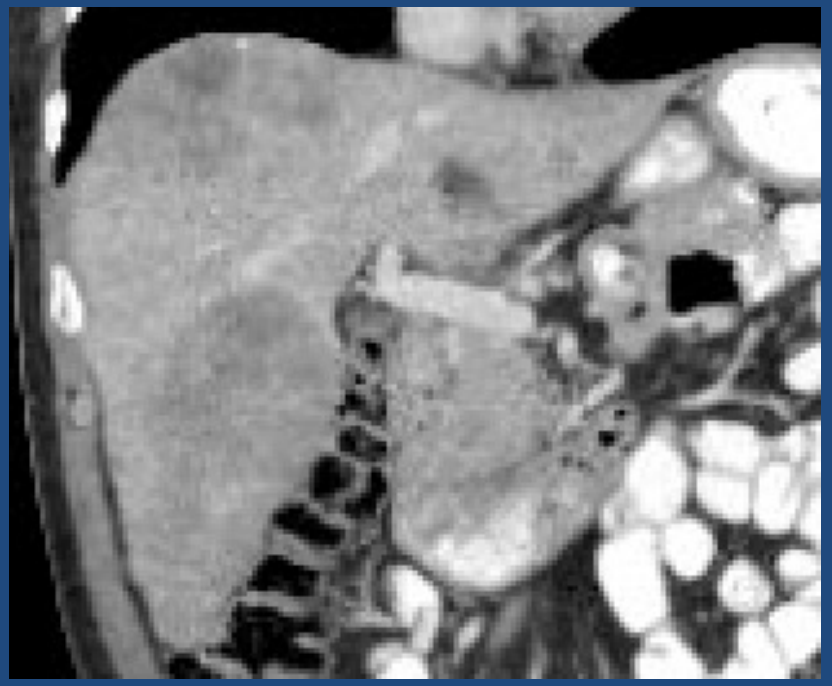
CT



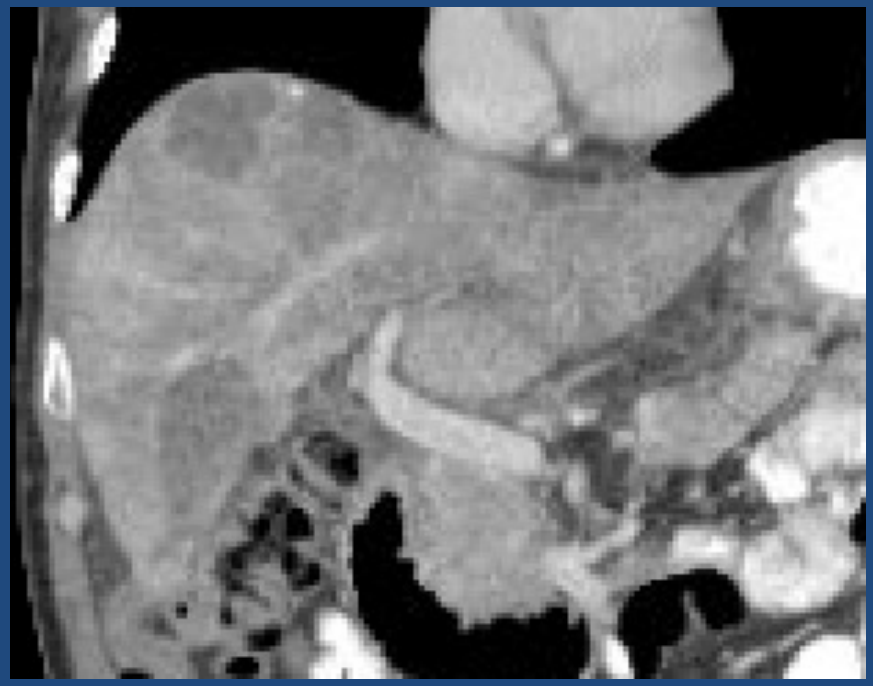


Ga-68 DOTA

Rapid bilobar progression



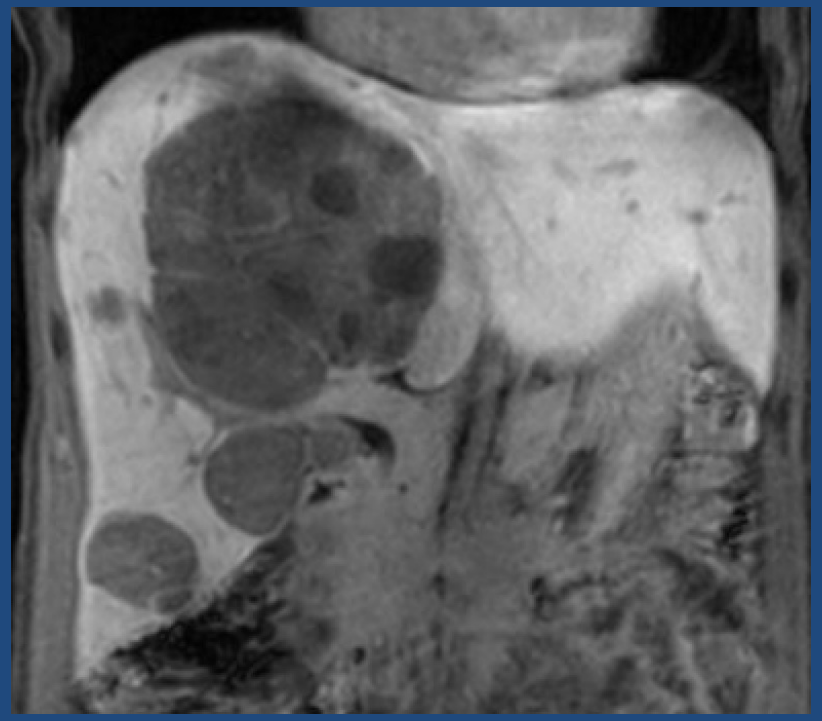
Pre-TARE



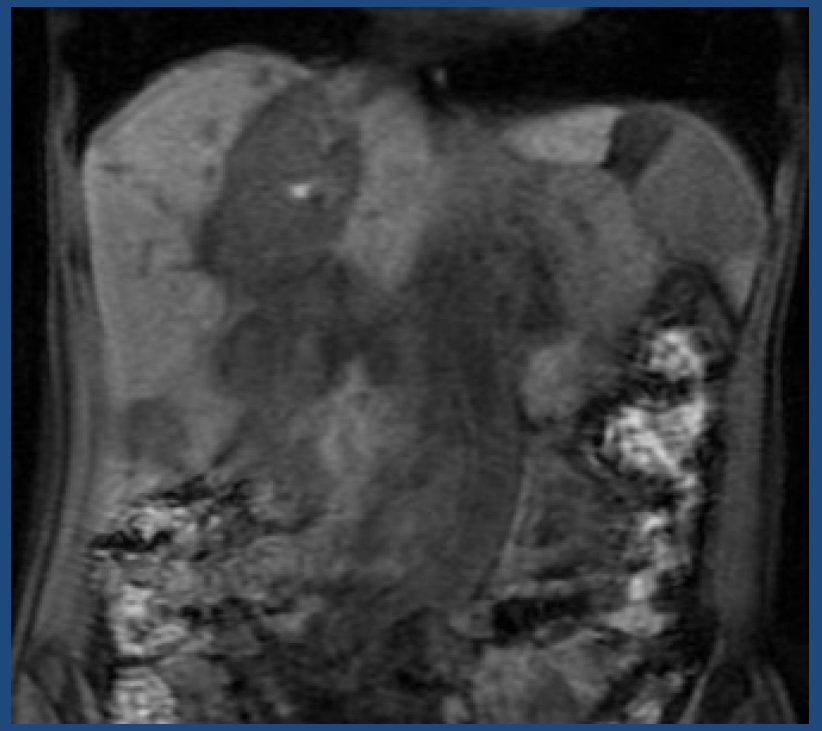
3 months post

59M, WD PNET, Ki-67 40%

Bulky one lobe-dominant



Pre-TARE

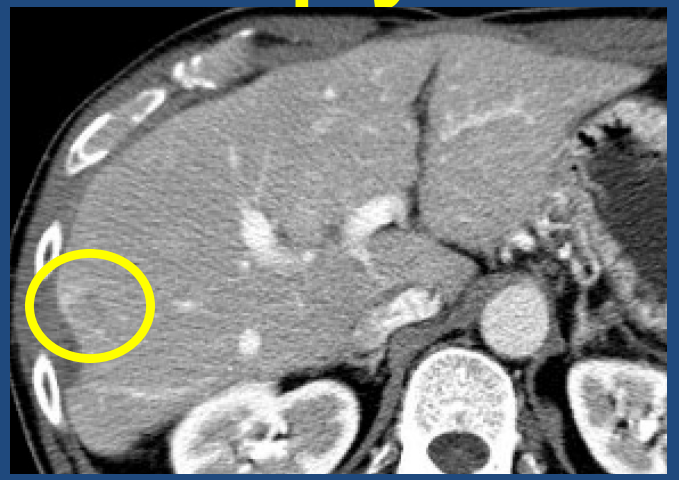


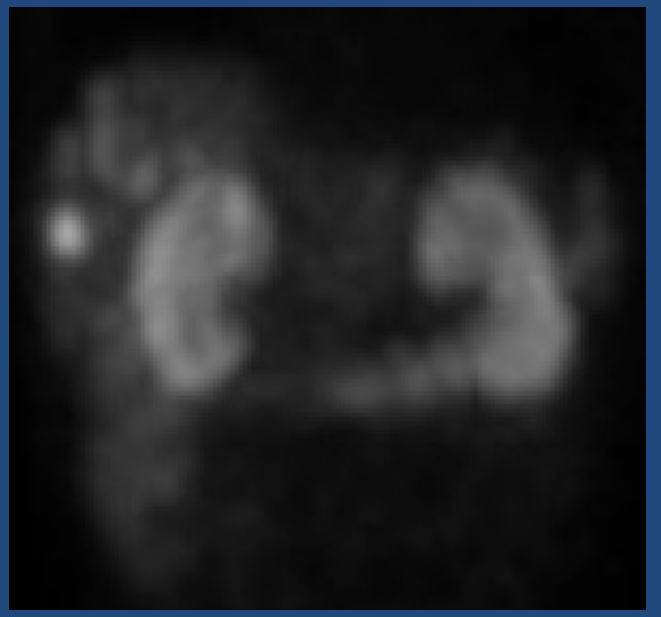
6 months post

59F, WD SB NET, Ki-67 7%

Ablative Therapy

- MWA or cryo
- Oligometastatic liver disease
- Up to 4 lesions, each < 3cm
- Typical anatomic and technical constraints for percutaneous approach apply





In-111 Octreoscan

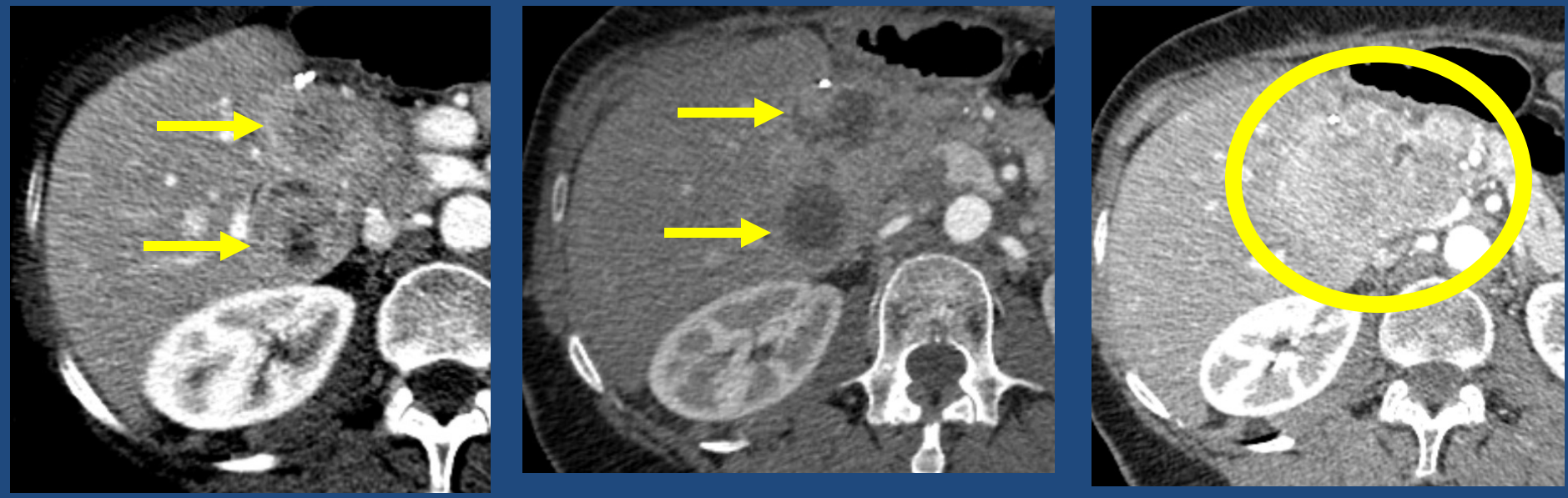
IO for Other Tumor Types

~~HCC~~
~~ICC~~
~~mCRC~~
~~mNET~~
~~Lung and lung metastases~~
~~RCC~~

GIST
Uveal melanoma
Locally advanced pancreas adenocarcinoma
Prostate
Giant cell bone tumor

GIST (2021)

- Ablation, TAE, or TACE for liver-only or liver-limited disease



Baseline

1 mo s/p TAE x 2

3 mo s/p TAE x 2

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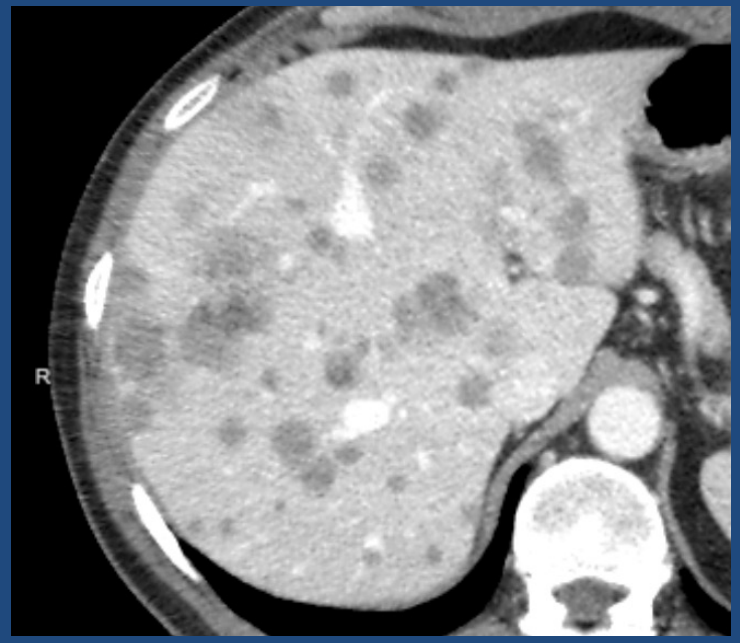
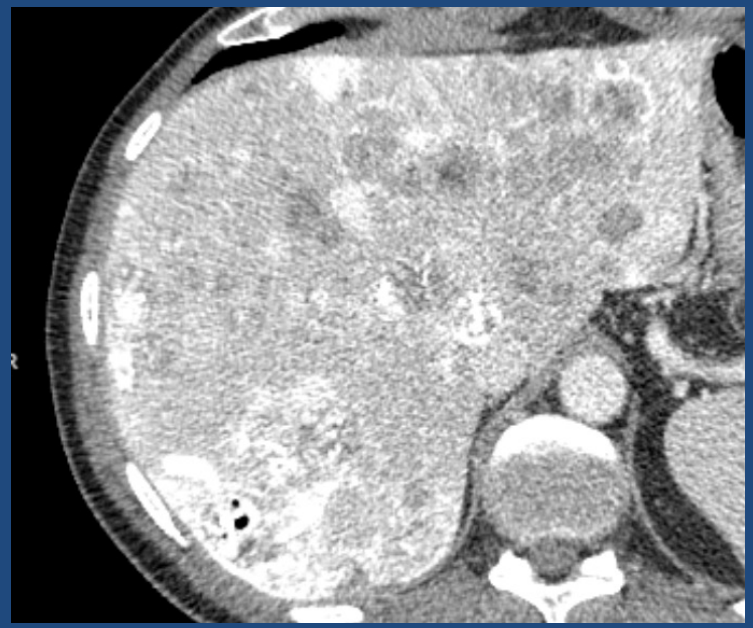
Uveal melanoma (2021)

- Regional isolation perfusion of liver (Delcath)
- TACE, TARE, immunoembolization, ablation for liver-only or liver-limited disease



Baseline



1 mo s/p BCNU TACE x 2

Cutaneous melanoma (2021)

- Ablation for palliation of symptomatic unresectable disease

Locally advanced pancreas adenocarcinoma (2021)

- Irreversible electroporation (IRE) … may be safe and feasible and may improve survival outcomes. However, due to concerns about complications and technical expertise, the panel ***does not currently recommend IRE*** for treatment of locally advanced pancreatic cancer.
- Angiography and embolization for bleeding from primary tumor

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Localized prostate cancer (2022)

Cryotherapy (cryoablation) or other local therapies are **not recommended** as routine primary therapy for localized prostate cancer due to lack of long-term data comparing these treatments to radiation or radical prostatectomy. At this time, the panel recommends only cryosurgery and high-intensity focused ultrasound (HIFU; category 2B) as local therapy options after EBRT recurrence in the absence of metastatic disease.

Bone cancer (2021)

- Giant cell bone tumor
  - Resectable with unacceptable morbidity and/or unresectable axial lesions → **serial embolization** (preferred)
  - Serial arterial embolizations have been shown to be effective in the management of patients with giant cell tumors of the extremities, especially for tumors with large cortical defects or joint involvement and for those with large giant cell tumors of the sacrum.
- SBRT or ablation for unresectable pulmonary metastases

Summary

- Liver-directed therapy indications
  - Well-differentiated NET (ablation, TAE, TACE, TARE)
  - Uveal melanoma (ablation, TACE, TARE, immunoembo)
  - GIST (ablation, TAE, TACE)
- Primary tumor treatment
  - Giant cell bone tumor (embolization)
  - Pancreas adenocarcinoma (embo for bleeding)
- Non-liver metastases
  - Cutaneous melanoma (ablation)
  - Sarcoma (ablation)

Thank You

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NCCN Guidelines: Where Does IO Stand in the NCCN Guidelines – Lung and Metastases to the Lung

Alda Tam, MD

Professor, Interventional Radiology

MD Anderson Cancer Center

Faculty Disclosures

Research Funding — Boston Scientific, Johnson & Johnson; Consulting — Cello Therapeutics, Boston Scientific, AstraZeneca, Endocare

Brand names are included in this presentation for participant clarification purposes only. No product promotion should be inferred.

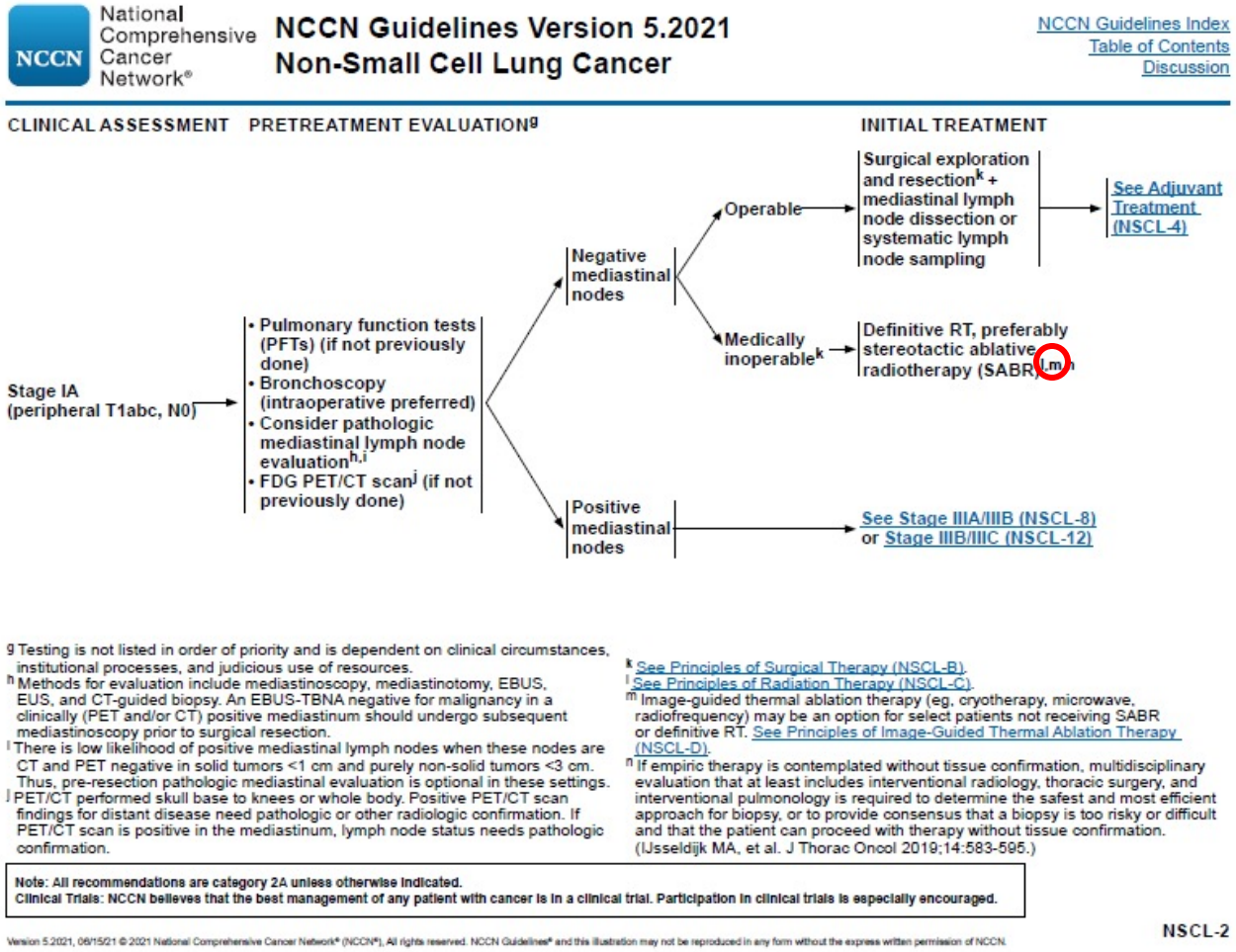
Ablation

- Ablation for many cancer types, including NSCLC and common cancers that metastasize to the lungs, is supported
- NCCN guidelines can be used to support approval and reimbursement processes
- Essential to continue to populate IR representation across panels
- Panels meet annually, but updates may occur more frequently

NSCLC

- Very active panel with multiple updates throughout the year
- Lack of prospective and/or randomized data makes it difficult to compete in this space with SBRT
- Until 2020, lack of radiology or interventional radiology representation on panel

NCCN NSCLC – New in 2020-2021



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CLINICAL ASSESSMENT | PRETREATMENT EVALUATION[g] | INITIAL TREATMENT

Stage IA (peripheral T1abc, N0)

- Pulmonary function tests (PFTs) (if not previously done)
- Bronchoscopy (intraoperative preferred)
- Consider pathologic mediastinal lymph node evaluation[h,i]
- FDG PET/CT scan[j] (if not previously done)

Negative mediastinal nodes
- Operable → Surgical exploration and resection[k] + mediastinal lymph node dissection or systematic lymph node sampling → See Adjuvant Treatment (NSCL-4)
- Medically inoperable[k] → Definitive RT, preferably stereotactic ablative radiotherapy (SABR)[l,m]

Positive mediastinal nodes → See Stage IIIA/IIIB (NSCL-8) or Stage IIIB/IIIC (NSCL-12)

[g] Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.
[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
[i] There is low likelihood of positive mediastinal lymph nodes when these nodes are CT and PET negative in solid tumors <1 cm and purely non-solid tumors <3 cm. Thus, pre-resection pathologic mediastinal evaluation is optional in these settings.
[j] PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[k] See Principles of Surgical Therapy (NSCL-B).
[l] See Principles of Radiation Therapy (NSCL-C).
[m] Image-guided thermal ablation therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[n] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NSCL-2

Added IR panel member

- For Stage IA, ablation remains a footnote
- For local recurrence (NSCL-11), ablation remains a footnote
- For multiple lung cancers, IGTA listed out as a therapy option

Move toward energy modality acceptance

- cryotherapy, MW, RFA all listed

Added new section of Principles of Image-Guided Thermal Ablation

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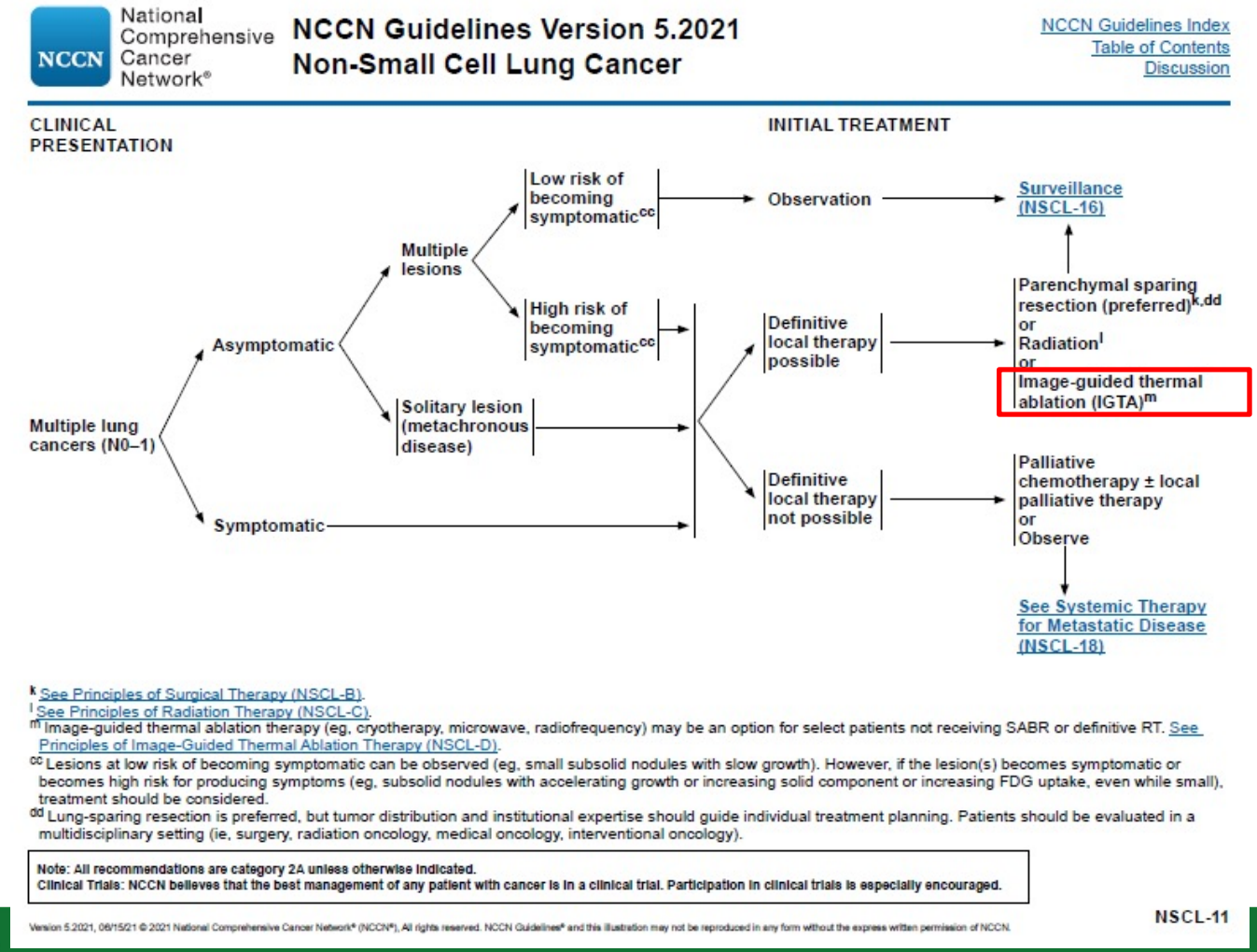

Many NCCN guidelines do not specify ablative technique, but this can be an approval criteria imposed by insurance companies depending on region.

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PRINCIPLES OF IMAGE-GUIDED THERMAL ABLATION THERAPY

General Principles

- **Interventional radiologists should actively participate in multidisciplinary discussions and meetings regarding patients with NSCLC (eg, multidisciplinary clinic and/or tumor board).**
- **Decisions about whether ablation is feasible should be performed by interventional radiologists who perform IGTA as a prominent part of their practice.**
- **IGTA includes radiofrequency ablation, microwave ablation, and cryoablation. IGTA is a form of "local therapy" or "local ablative therapy."[1]**
- **IGTA is a lung parenchymal sparing technique with at most a temporary decrement in FEV1 and DLCO, which is statistically indistinguishable from baseline after recovery.[2-6]**

Evaluation

- **IGTA may be considered for those patients who are deemed "high risk"—those with tumors that are for the most part surgically resectable but rendered medically inoperable due to comorbidities. In cases where IGTA is considered for high-risk or borderline operable patients, a multidisciplinary evaluation is recommended.**
- **IGTA has been successfully accomplished in patients considered "high risk," objectively defined with a single major and/or two or more minor criteria. Major criteria included an FEV1 or DCLO ≤50%, and minor criteria included a less depressed FEV1 or DLCO between 51%–60%, advanced age ≥75 years, pulmonary hypertension, LVEF ≤40%, resting or exercise PaO2 <55 mmHg, and pCO2 >45 mmHg.[4]**
- **If an interventional radiologist or center is uncertain about the feasibility or safety of IGTA, consider obtaining an additional interventional radiology opinion from a high-volume specialized center.**

Ablation

- **Each energy modality has advantages and disadvantages. Determination of energy modality to be used for ablation should take into consideration the size and location of the target tumor, risk of complication, as well as local expertise and/or operator familiarity.[7]**

Ablation for NSCLC

- **IGTA is an option for the management of NSCLC lesions <3 cm. Ablation for NSCLC lesions >3 cm may be associated with higher rates of local recurrence and complications.[8,9]**
- **There is evidence on the use of IGTA for selected patients with Stage 1A NSCLC, those who present with multiple lung cancers, or those who present with locoregional recurrence of symptomatic local thoracic disease.**

[1] Lam A, Yoshida EJ, Bui K, et al. Patient and facility demographics related outcomes in early-stage non-small cell lung cancer treated with radiofrequency ablation: a National Cancer Database analysis. J Vasc Interv Radiol 2018;29:1535-1541.
[2] Dupuy DE, DiPetrillo T, Gandhi S, et al. Radiofrequency ablation followed by conventional radiotherapy for medically inoperable stage I non-small cell lung cancer. Chest 2006;129:738-745.
[3] Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). Lancet Oncol 2008;9:621-628.
[4] Dupuy DE, Fernando HC, Hillman S, et al. Radiofrequency ablation of stage IA non-small cell lung cancer in medically inoperable patients: Results from the American College of Surgeons Oncology Group Z4033 (Alliance) trial. Cancer 2015;121:3491-3498.
[5] de Baere T, Tselikas L, Woodrum D, et al. Evaluating cryoablation of metastatic lung tumors in patients--safety and efficacy: The ECLIPSE Trial--interim analysis at 1 year. J Thorac Oncol 2015;10:1468-1474.
[6] Tada A, Hiraki T, Iguchi T, et al. Influence of radiofrequency ablation of lung cancer on pulmonary function. Cardiovasc Intervent Radiol 2012;35:860-867.
[7] Abtin F, De Baere T, Dupuy DE, et al. Updates on current role and practice of lung ablation. J Thorac Imaging 2019;34(4):266-277.
[8] Lee JM, Jin GY, Goldberg SN, et al. Percutaneous radiofrequency ablation for inoperable non-small cell lung cancer and metastases: preliminary report. Radiology 2004;230:125-134.
[9] Akeboshi M, Yamakado K, Nakatsuka A, et al. Percutaneous radiofrequency ablation of lung neoplasms: initial therapeutic response. J Vasc Interv Radiol 2004;15:463-470.

CIO

Lung Metastases – Not Footnotes!

- Colon/Rectal Cancer Guidelines have algorithms for the treatment of synchronous or metachronous lung metastases and list “local therapy” (ie, image-guided ablation) as an option
  - Unspecified energy modality facilitates approval for energy ablation modality of choice
- Sarcoma of the extremities/trunk/head and neck algorithms have a role for ablation of lung metastases both in primary treatment and treatment of metastatic lesions
- Osteosarcoma (OSTEO-3) lists ablation as treatment option for lung metastases
- Other guidelines, like kidney and thyroid, contain language that could be used to advocate for ablation of lung metastases

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Colon Cancer

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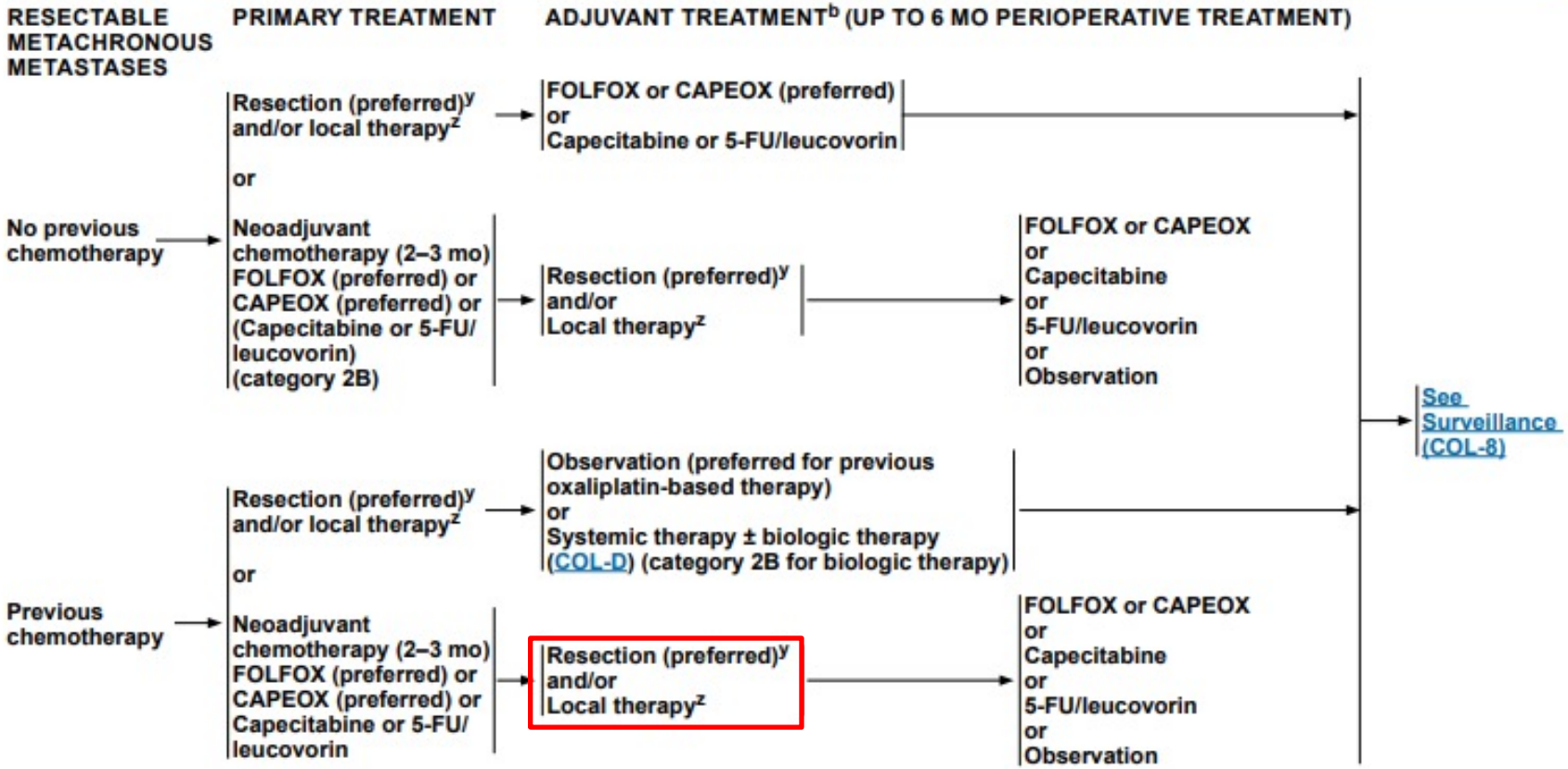

[b] See Principles of Imaging (COL-A).

[y] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

[z] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Conclusions

- Integration of interventional radiology techniques into local therapy options across applicable NCCN guidelines continues to be needed
- General theme – standardization of ablation language
  - Image-guided thermal ablation
  - Allows for flexibility for different types of energy modalities
- As more evidence accumulates, goal will be to move from footnote to listed therapy across histologies