A Novel "Diapeutic" Molecular Agent for Combined Oncologic Diagnosis and Therapy in a Broad Spectrum of Human Cancers:

Preliminary Clinical Experience with CLR1404

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PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

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Disclosure of Potential COI

The following co-authors either have or recently had a financial relationship with the following commercial organizations:

- PJ Pickhardt: Viatronix, Braintree, Mindways, VirtuoCTC, Cellectar
- M Longino, A Pinchuk, M Banach, J Grudzinski, B Titz, C Jaskowiak, JP Weichert: Cellectar

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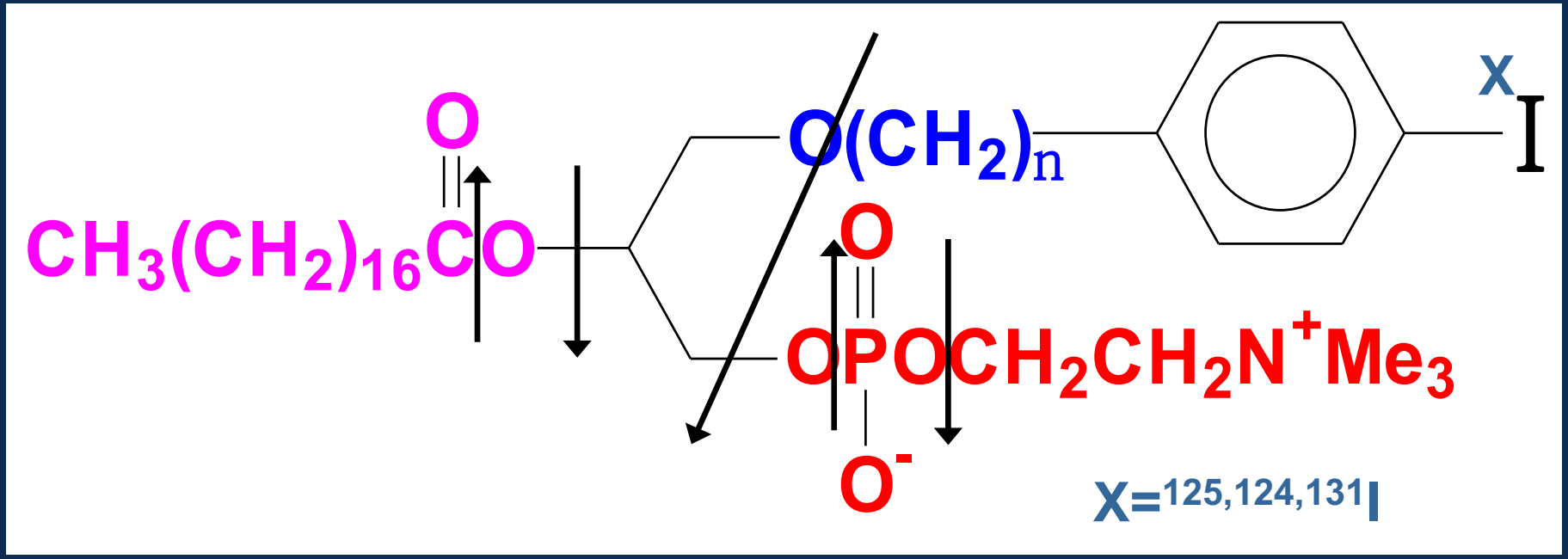
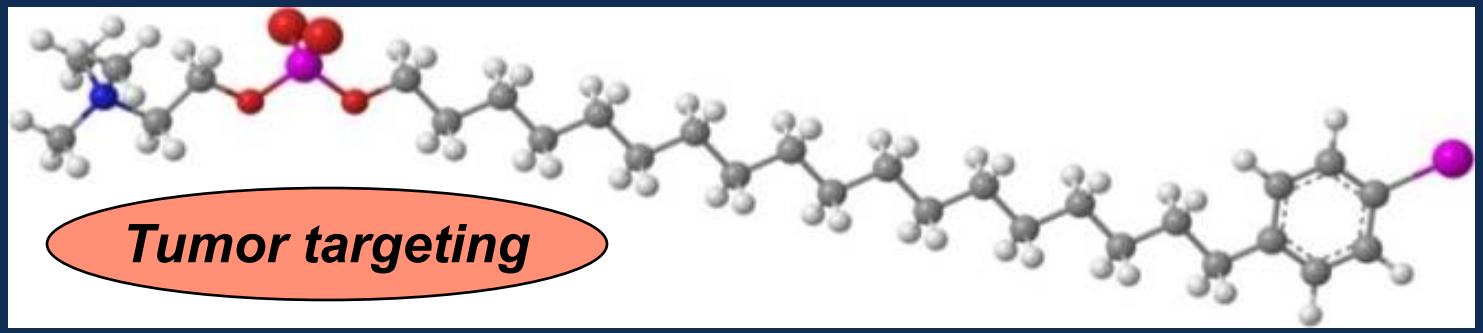
Background



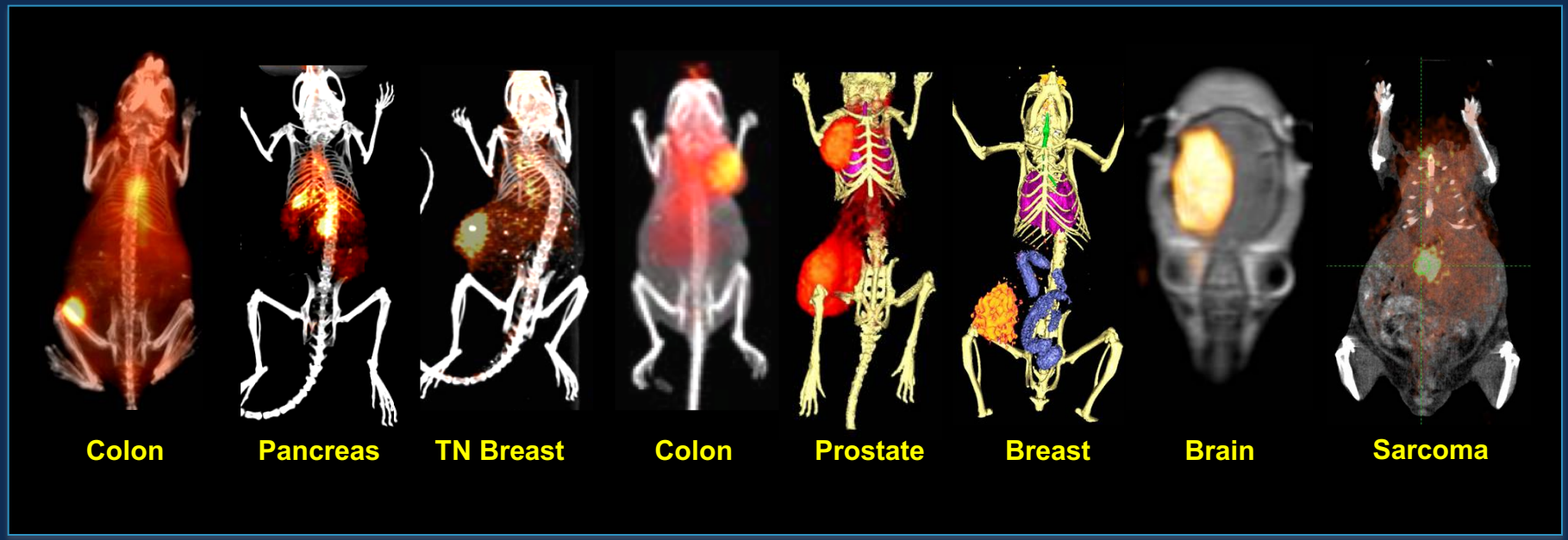
- CLR1404 – an alkylphosphocholine analog
- Capitalizes on over-abundance of phospholipid ethers present in most cancer cells

Background



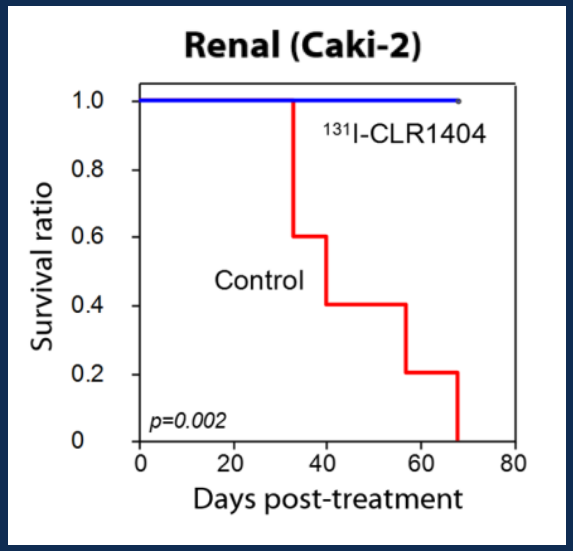
- Tumor-targeting not affected by iodine label
- PET tumor imaging with ^{124}I-CLR1404
- Molecular radiotherapy with ^{131}I-CLR1404
- Potential for both imaging diagnosis and therapeutic = "diapeutic" agent

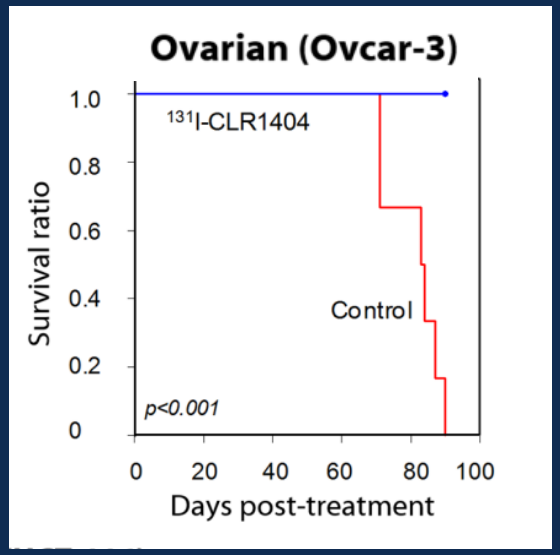
Background

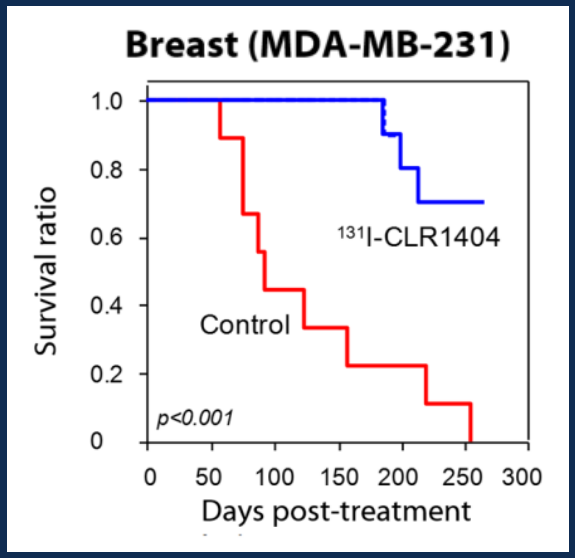


- Prolonged tumor-selective retention in >60 in vivo rodent and human cancer models & cancer stem cell models ("universal")
- No retention w/in benign or inflamed tissue

Background







- Significant tumor growth reduction and survival benefit from a single injection of ^{131}I-CLR1404 in a wide range of human tumor xenograft models
- Weichert JP et al. Sci Trans Med (in press)

Purpose

Report our initial experience with CLR1404 for localization and imaging of a broad spectrum of cancer in early human trials

- PET/CT imaging with ^{124}I-CLR1404
  - Oncologic imaging; compare with ^{18}FDG PET
- SPECT/CT imaging with ^{131}I-CLR1404
  - Therapeutic form of this “diapeutic” agent

Methods

- IRB-approved prospective imaging protocols
- All patients gave signed informed consent
- Early phase trials with ^{124}I-CLR1404 PET and subtherapeutic ^{131}I-CLR1404 SPECT
- Main inclusion criterion: biopsy-proven refractory advanced solid malignancy
  - Separate trial of primary brain tumors excluded

Methods

- ^{124}I-CLR1404 PET/CT scans:
  - 64-detector-row PET/CT scanner (Discovery VCT, GE Healthcare, Waukesha, WI)
  - Serial imaging out to 5-10 days following the injection of up to 5 mCi of ^{124}I-CLR1404
  - 2D acquisition mode
  - No correction employed for the ^{124}I cascade gammas
  - Low-dose non-contrast MDCT for attenuation correction and lesion localization using 140 kV_p and tube current modulation (70 mA average)

Methods

- ^{131}I-CLR1404 SPECT/CT scans:
  - Serial imaging (Infinia/Hawkeye, GE Healthcare) out 21 days
  - Phase I dosimetry trial not designed to show therapeutic benefit
  - Non-contrast low-dose CT was performed using 140 kV_p and 2.5 mA

Methods

- Review of imaging studies:
  - All PET/CT and SPECT/CT studies were reviewed on PACS workstation (McKesson) with fusion software (Mirada XD3)
  - Correlation with concurrent ^{18}FDG PET/CT in most cases
  - Additional relevant cross-sectional imaging studies were also reviewed

Results

Study Cohort: 22 patients with metastatic cancer

- Mean age, 60.4 years; 12M, 10F
- Complex prior treatment histories
- Tumor types: bronchogenic carcinoma (n=7), colorectal cancer (n=4), prostate cancer (n=3), triple-negative breast cancer (n=2), esophageal cancer (n=2), head & neck squamous cell carcinoma (n=2), pancreatic cancer (n=1), and melanoma (n=1)

Results

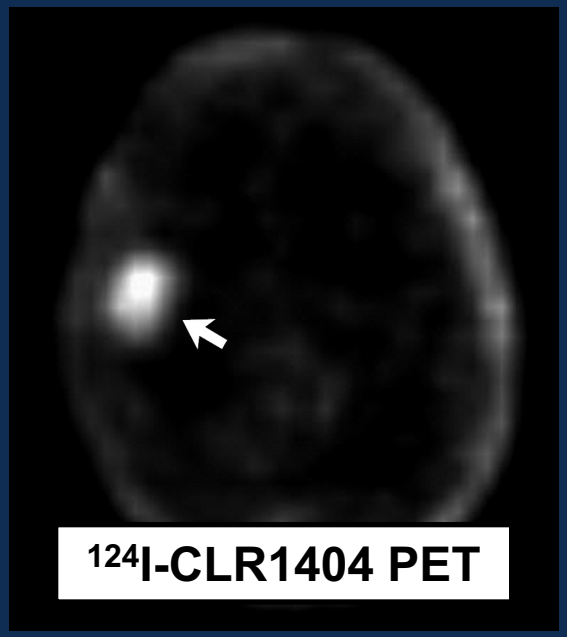
^{124}I-CLR1404 PET/CT in 14 patients and ^{131}I-CLR1404 SPECT/CT in 9 patients

- Preferential uptake of ^{124}I- and ^{131}I-CLR1404 within metastatic foci with all cancer subtypes
- Persistent retention within metastatic sites, coupled with progressive washout of background activity, favored delayed imaging (6-21 days after single injection).

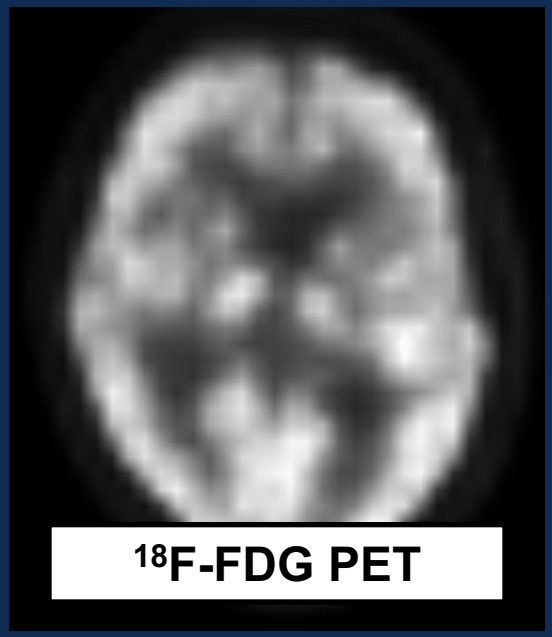
Results

^{124}I-CLR1404 PET/CT in 14 patients and ^{131}I-CLR1404 SPECT/CT in 9 patients

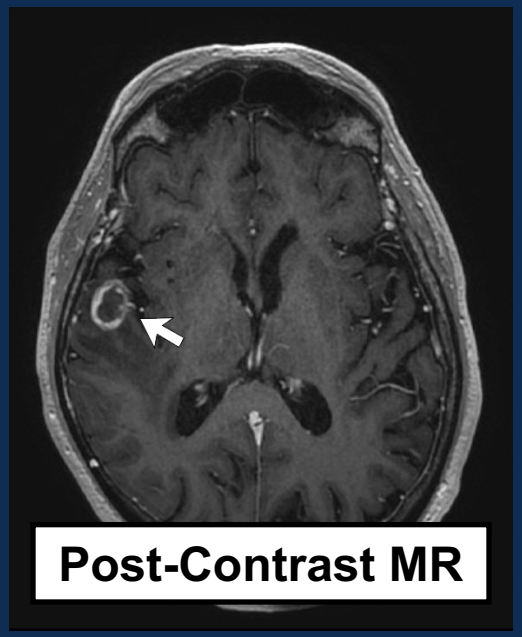
- CLR1404 uptake was evident in pulmonary, nodal, skeletal, hepatic, CNS, and other sites of active metastatic disease
- Potential advantages in oncologic imaging over FDG PET included both fewer false-negatives and fewer post-treatment false-positives



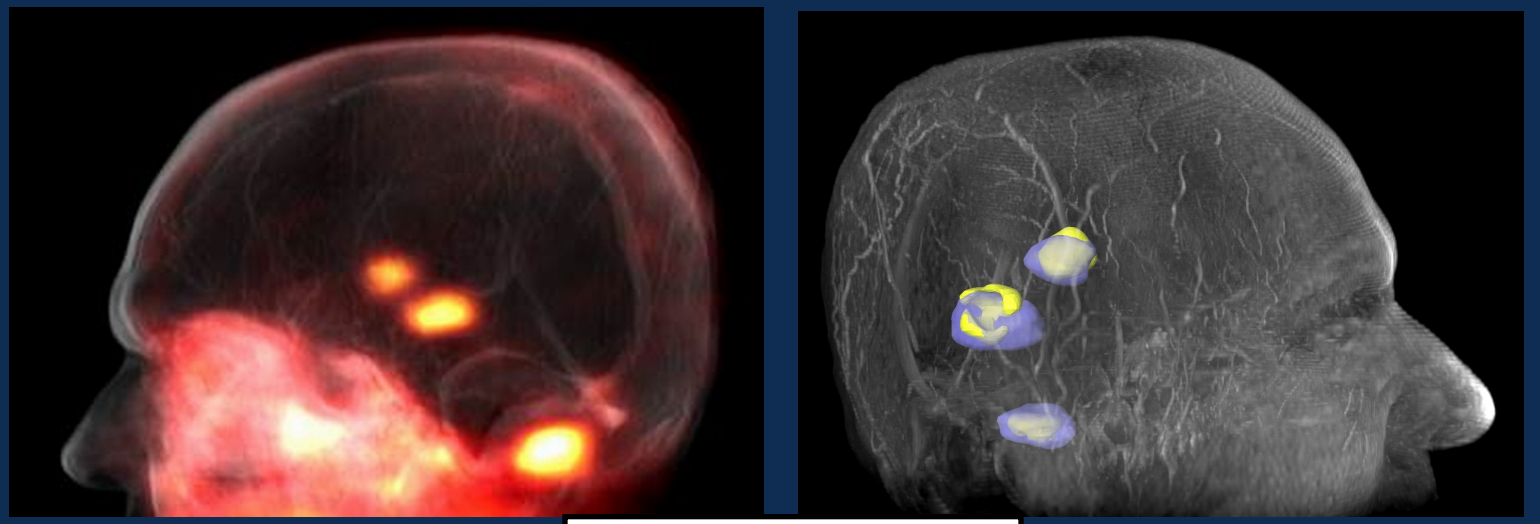
^{124}I-CLR1404 PET



^{18}F-FDG PET



Post-Contrast MR



^{124}I-CLR1404 PET

70M with bronchogenic carcinoma

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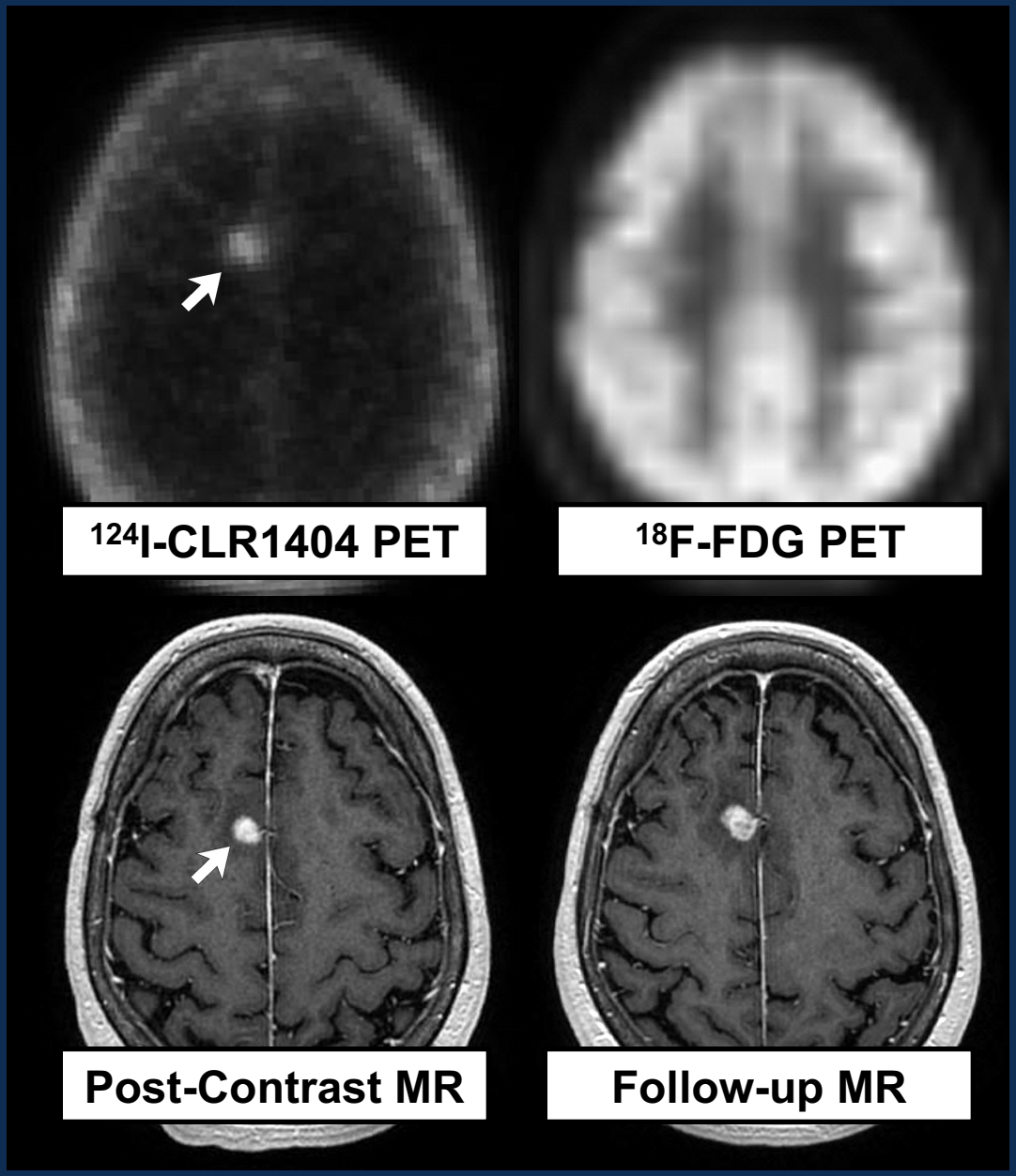

60F with recurrent malignant melanoma

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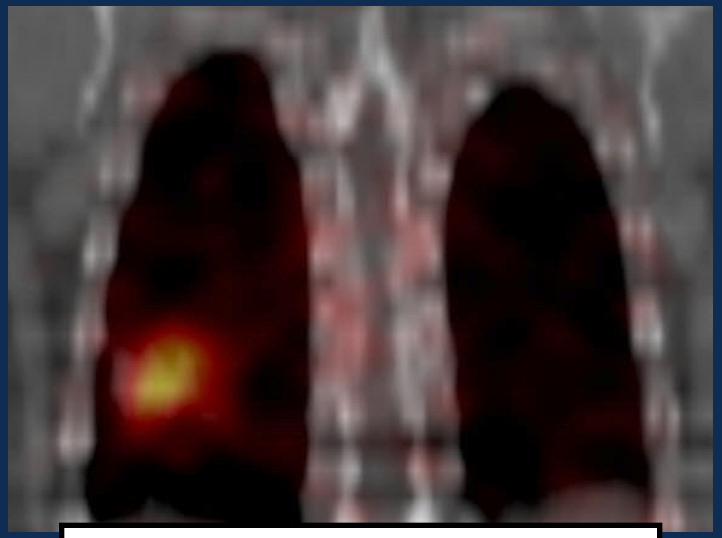
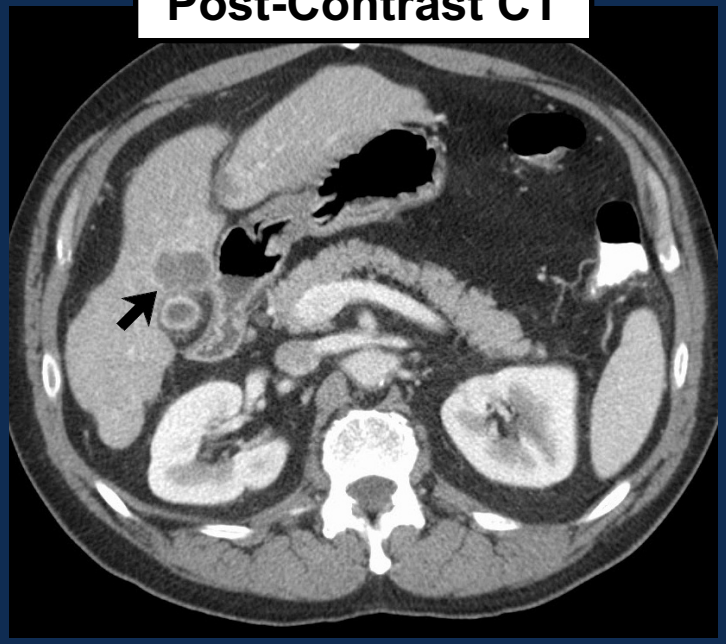
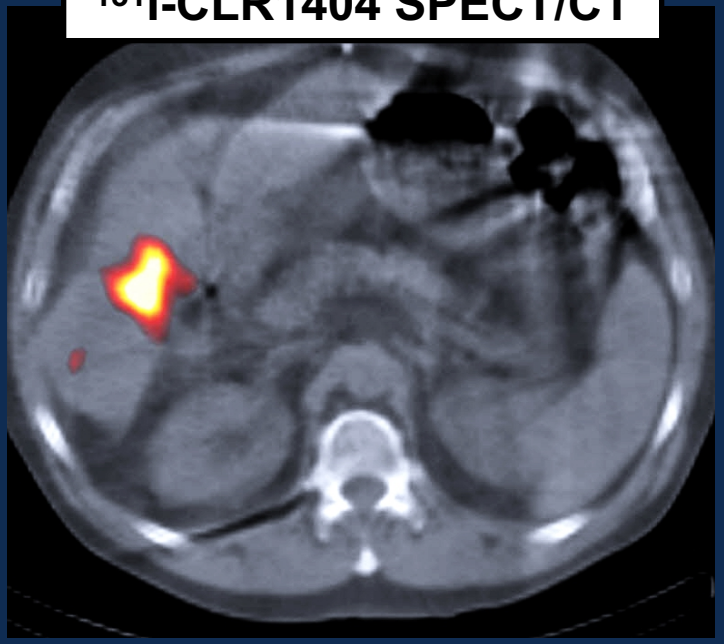


Post-Contrast CT

^{131}I-CLR1404 SPECT/CT





48M with colorectal carcinoma

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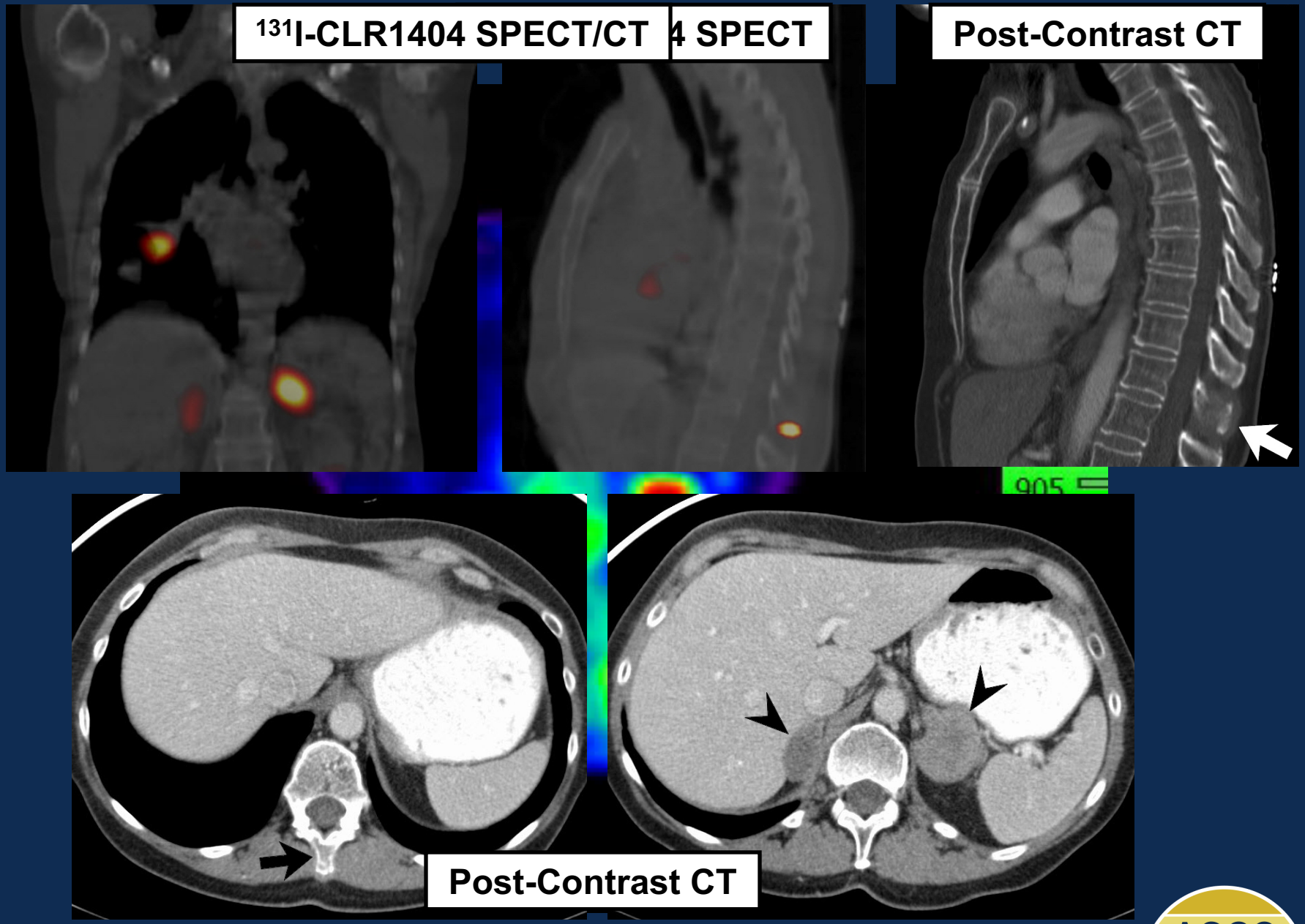

57F with colorectal carcinoma

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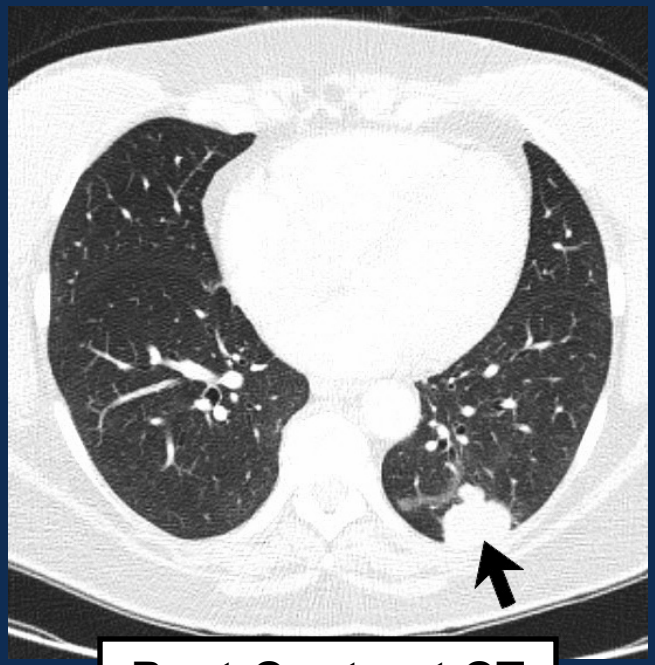
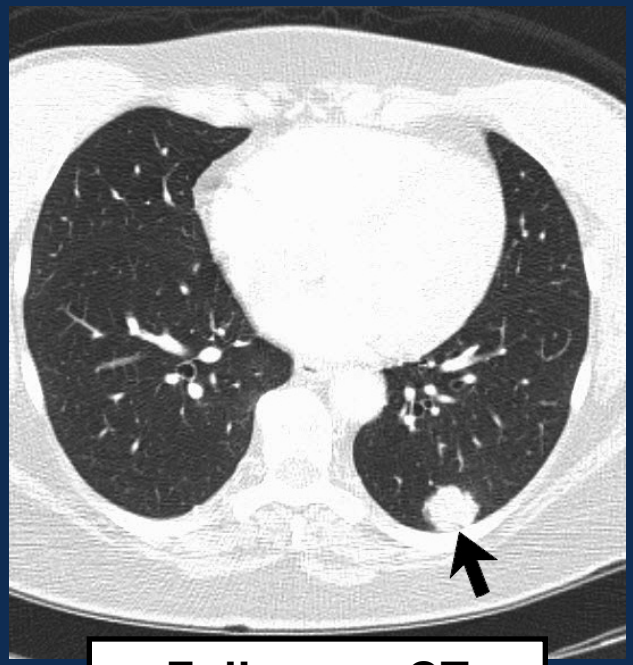
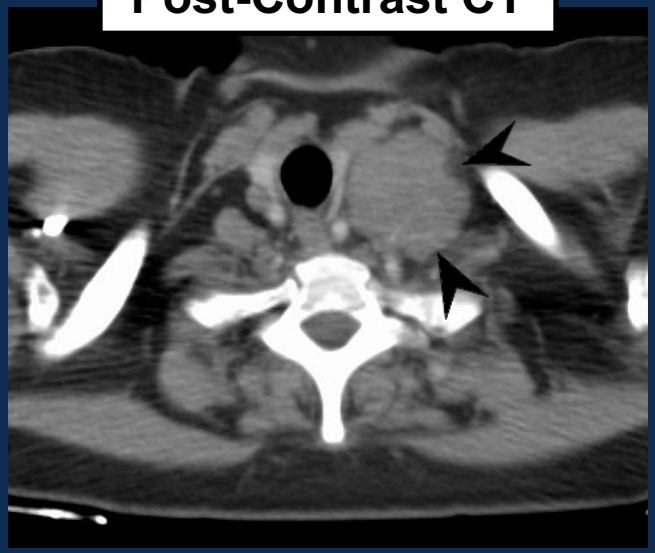
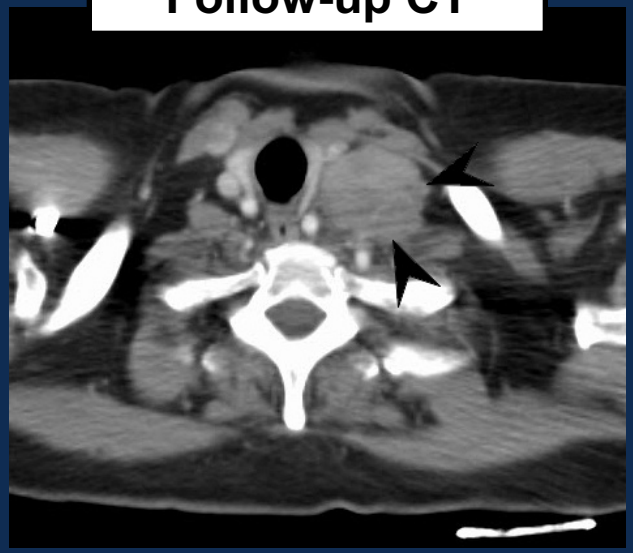


Post-Contrast CT



Follow-up CT





58F with triple-negative breast carcinoma

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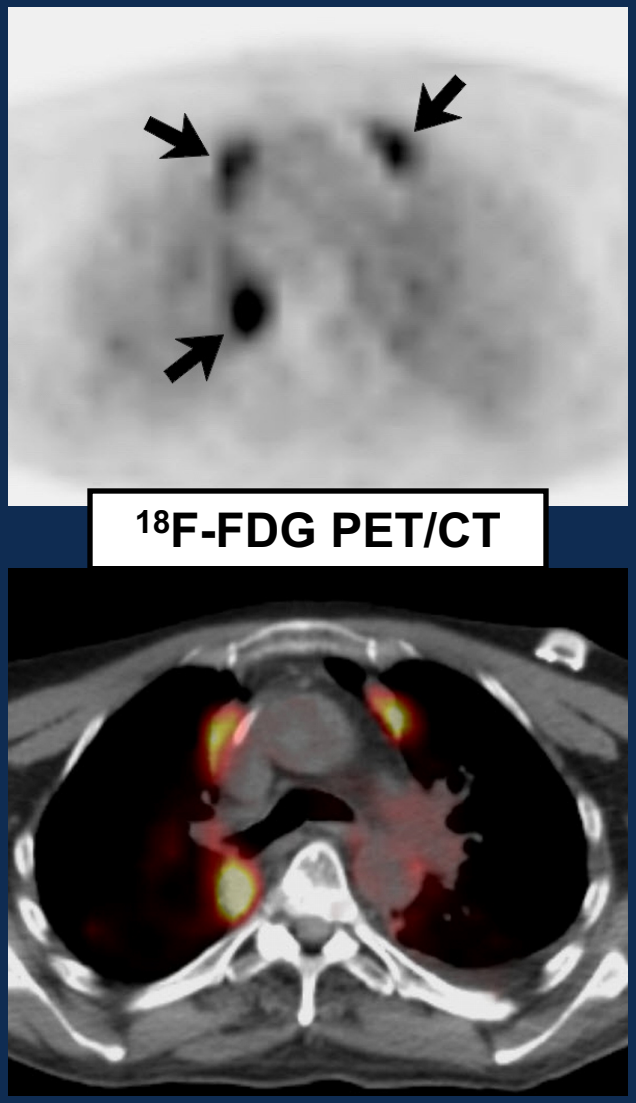
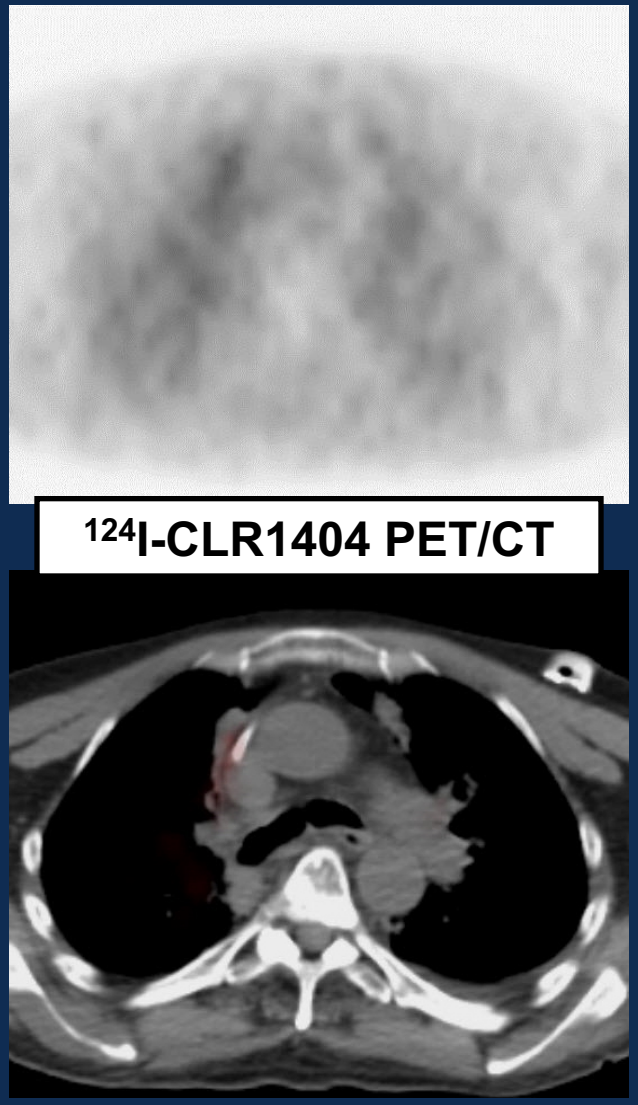


^{18}F-FDG PET/CT



^{124}I-CLR1404 PET/CT

^{124}I-CLR1404 PET/CT

65M with bronchogenic carcinoma

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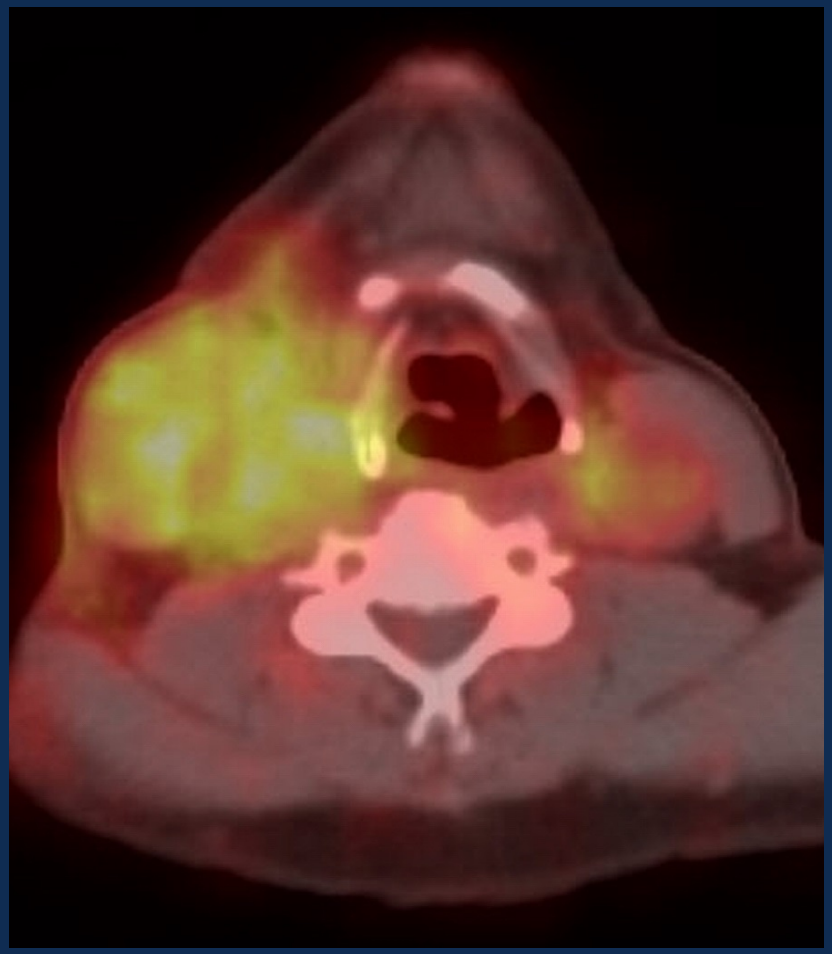

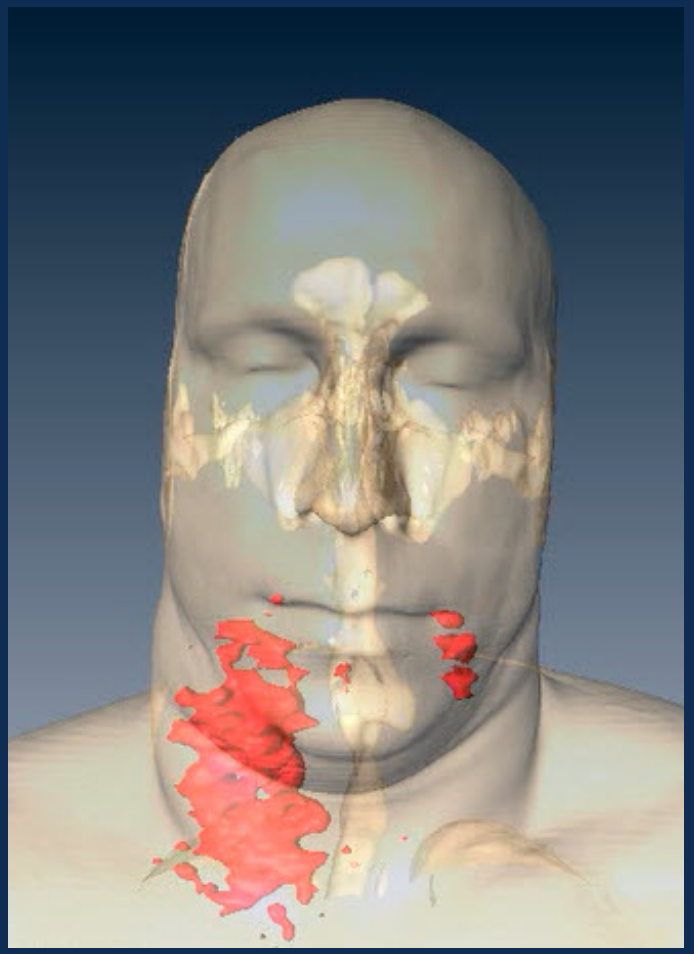

^{124}I-CLR1404 PET/CT

46M with BOT squamous cell carcinoma

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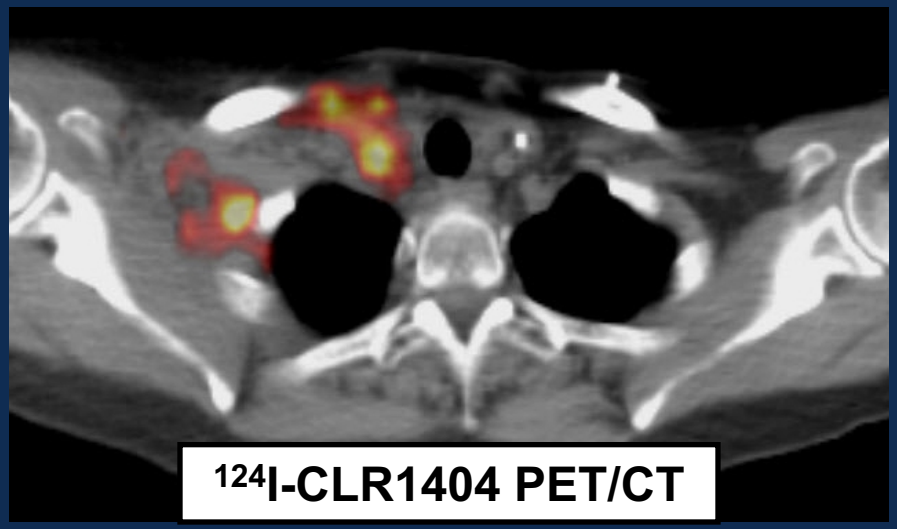

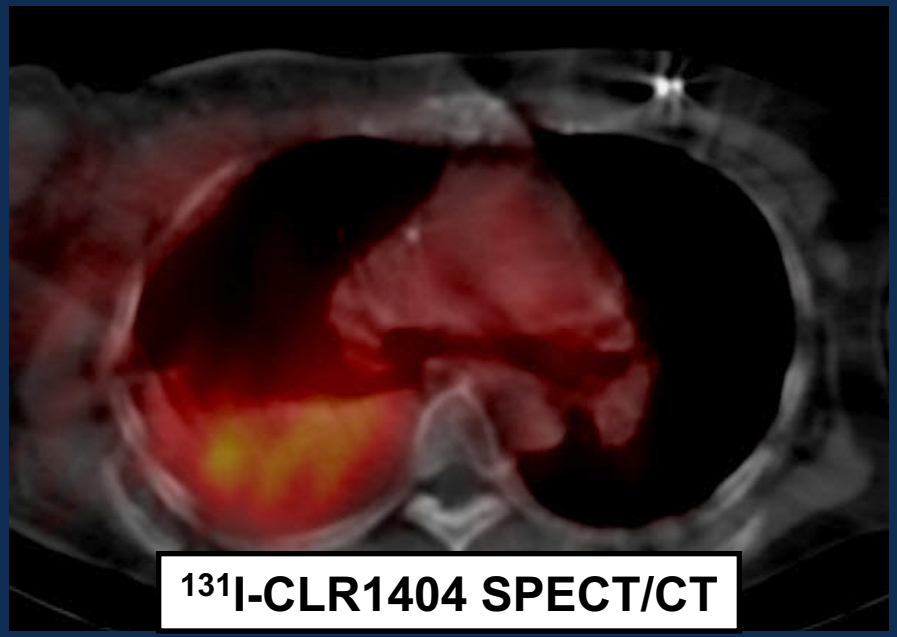

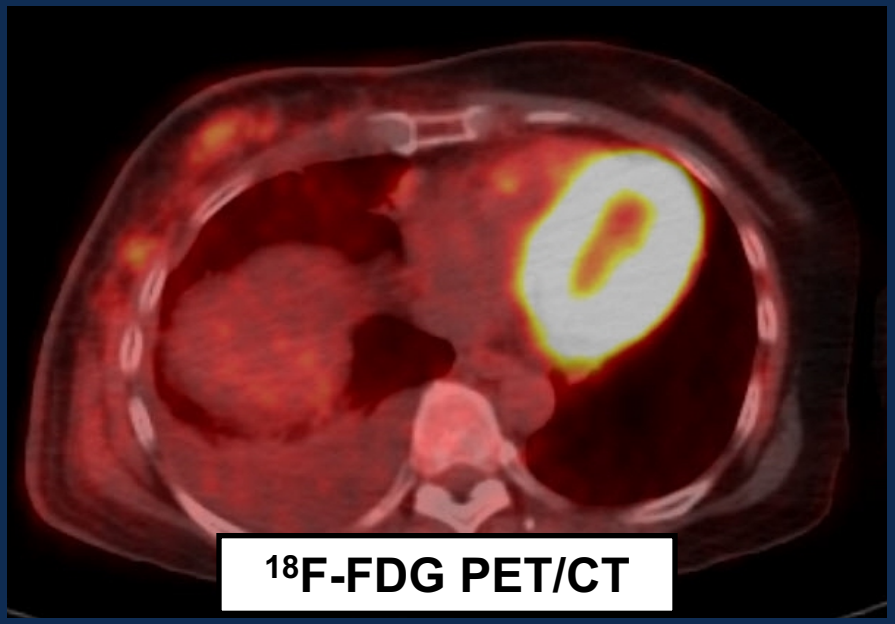

53F with triple-negative breast carcinoma

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Limitations

- Early phase investigation in humans
  - Imaging protocols not standardized or optimized, precluding quantitative analysis
  - ^{131}I-CLR1404 doses subtherapeutic
  - Wide variety of cancer types (proof of concept)
- No iodine correction
- 2D mode of acquisition for PET studies

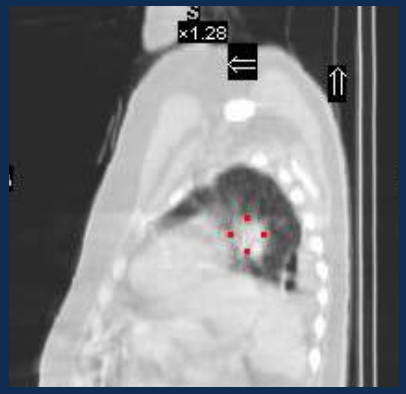
Conclusions

- Selective tumor uptake of CLR1404 with prolonged retention within a broad spectrum of historically difficult-to-treat metastatic cancers
  - Regardless of the site of metastatic disease
- Distinct advantages over FDG PET observed:
  - Detection in cases of FDG false-negatives
  - Lack of uptake in cases of FDG false-positives
  - ^{124}I-CLR1404 may improve accuracy for oncologic PET imaging

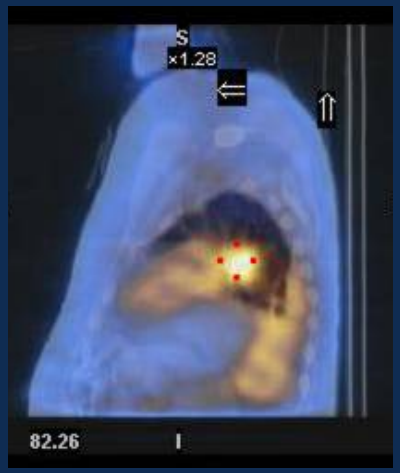
Conclusions

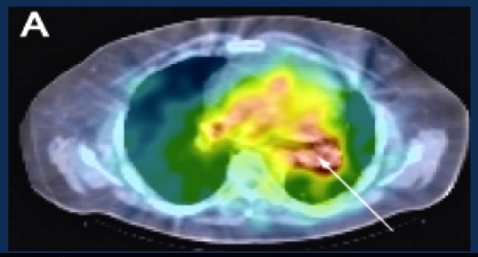
- Combined diagnosis and therapy ("diapeutic") using the same molecule (CLR1404) may allow for truly personalized cancer care:
  - Ensuring pre-treatment tumor-specific uptake
  - Providing patient-specific dose planning
  - Enabling treatment-specific imaging surveillance

Diapeutic Treatment Paradigm



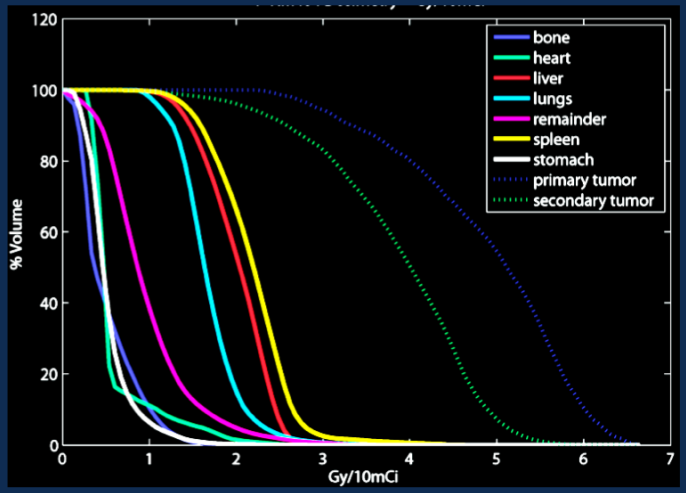
^{124}I-CLR404 PET/CT





$$D_{Tumor} = D_{BodyThresh}\left[\frac{k_{34}}{k_{43}}\left(\frac{1}{w_1 + w_2\left(\frac{k_{12}}{k_{21}}\right)}\right) + \lambda\frac{k_{34}}{k_{43}}\left((k_{43}-k_{21})(w_1k_{21}+w_2k_{12}) - w_1k_{21}\right)\right]$$

Distribution, Quantification, & Personal Dose Calculation



^{131}I-CLR1404 Therapy Dose Injection

Monitor Response w/ ^{124}I-CLR404 PET/CT

Thank You

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