# "Seeing" the Estrogen Receptor: Unmasking the Power of FES-PET Imaging and its Clinical Utility

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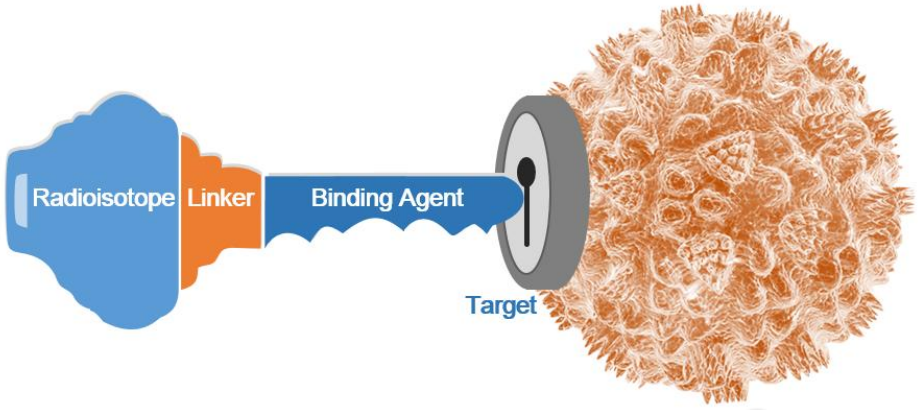
# Outline

1. Introduction: FDG vs FES
2. FES Appropriate use criteria
3. Utility of FES in “hard to diagnose” breast cancer – ILC
4. Limitation of FES
5. Clinical Cases

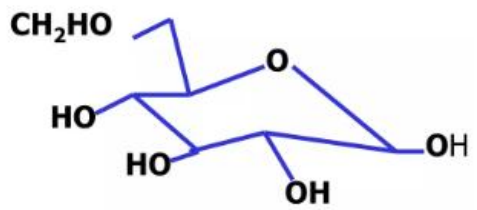
# What is PET?

- Positron Emission Tomography is an imaging technique which uses small amount of radiolabeled biologically active compounds to help in the diagnosis of disease.

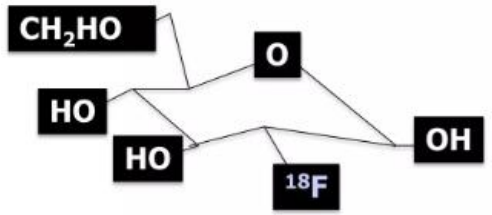


# FDG-PET

- Fluoro-deoxy-glucose is a glucose analog.
- A radioactive fluoride atom is attached to a glucose molecule.
- FDG is absorbed by all tissues just as normal glucose would be – *it is not tumor specific*
- ”Active” tissues absorbs it more than other inactive parts
- Tumor cells are usually highly metabolically active and tend to absorb it more than healthy cells



glucose



2-deoxy-2-(F-18) fluro-D-glucose

# Quantifying the Radiotracer Uptake

- SUV (Standardized Uptake Value) is a semiquantitative assessment of the radiotracer uptake
- Normal tissue such as the liver, lung and bone marrow have an SUV ranging from 1.0 to 2.5
- To detect malignant tumors, they should have an SUV above 3.0

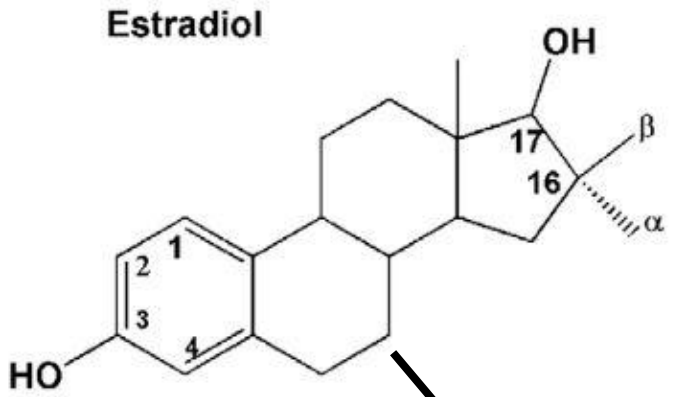
# FDG-PET in ER+ Breast Cancer

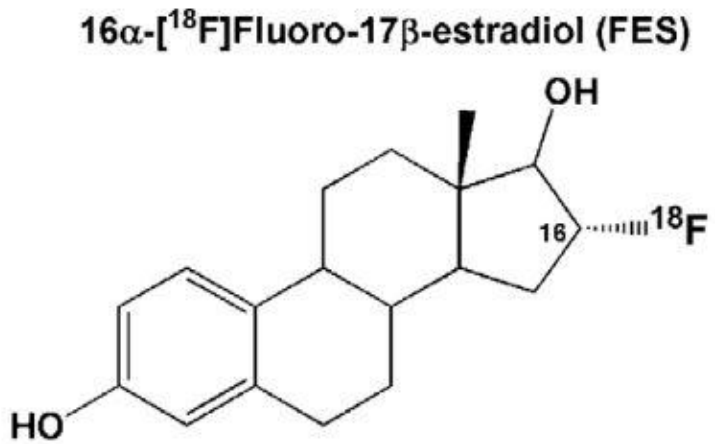
- ER+ Breast Cancers are considered indolent and exhibit low metabolic activity and proliferation
- A substantial amount of ER+ breast cancer exhibit non-measurable and/or bone only disease and given their low metabolic activity can be easily missed on FDG-PET

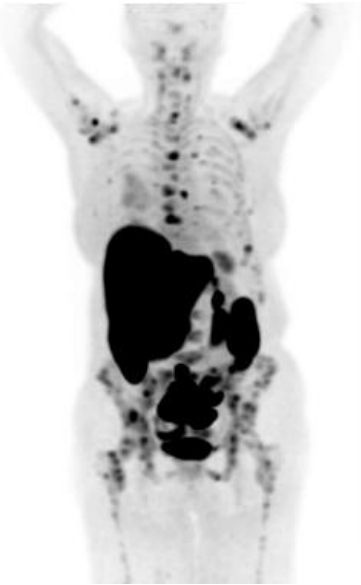
| | ER+ IDC | ER+ ILC |
|---|---|---|
| **Grade[1]** | | |
| Grade 1-2 | 70% | 90% |
| **Proliferation Activity (Ki67)[2]** | | |
| Low (<20%) | 50% | 60% |

1. Pestalozzi BC et al., *J Clin Oncol* 2006; 2. Biglia G et al, *Eur J Surg Oncol.* 2013

# FES-PET: Fluoro-estradiol (FES)



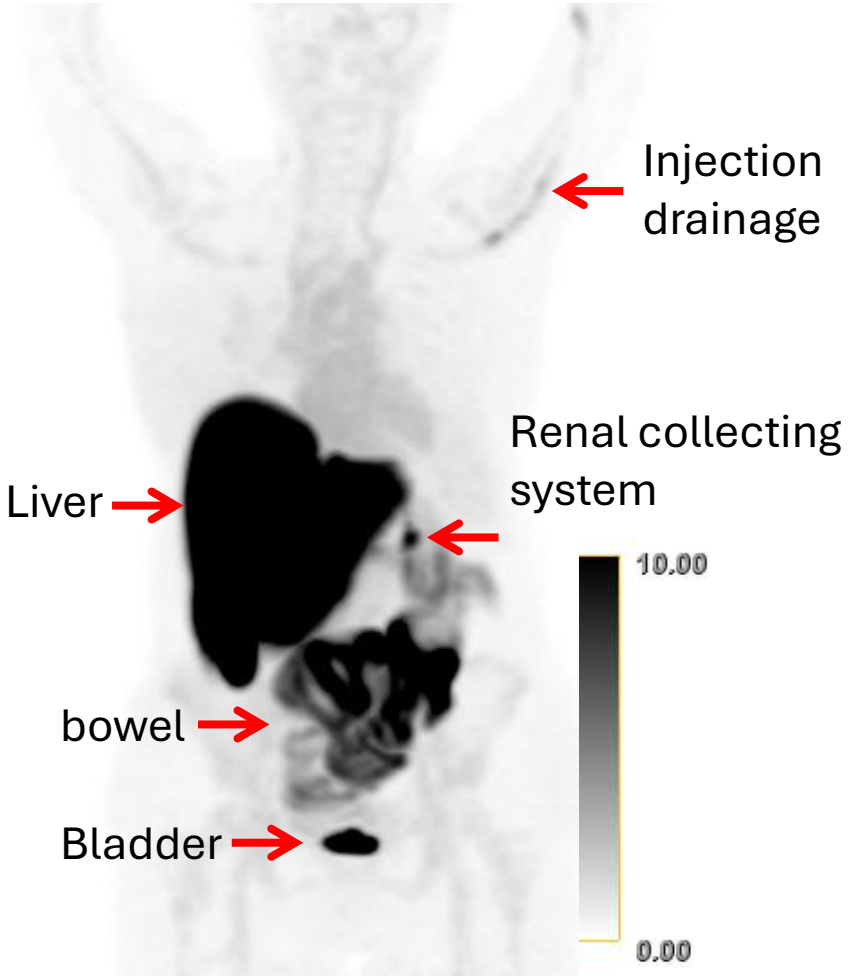



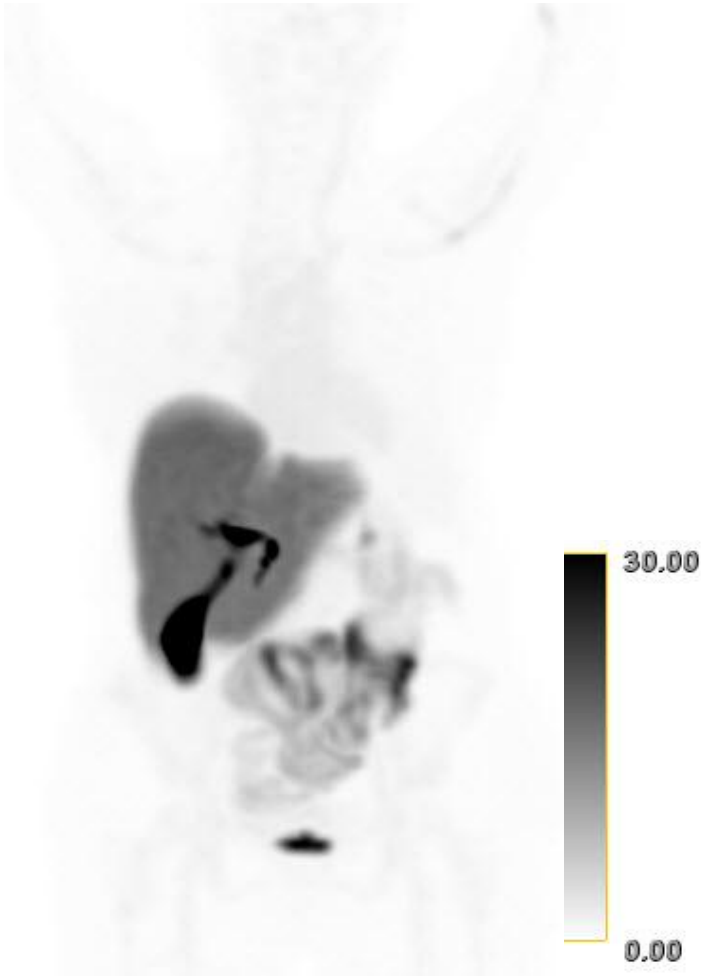



**Cerianna PET**

# FES PET/CT

## Normal Distribution



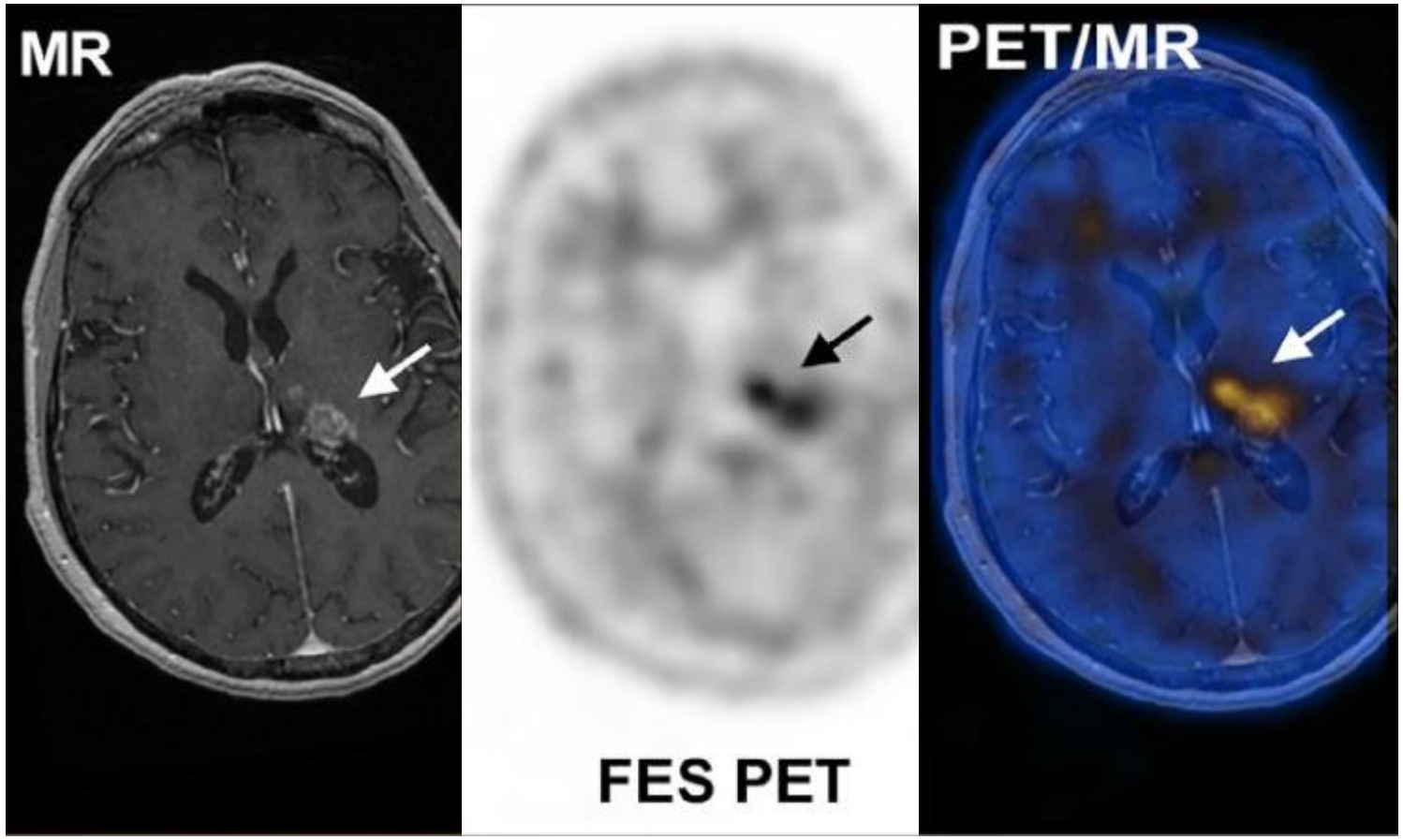



# SNMMI Appropriate Use Criteria (AUC)

| Scenario number | Description | Appropriateness | Score |
|---|---|---|---|
| **Diagnosis** | | | |
| 1 | Diagnosing primary breast cancer | Rarely appropriate | 2 |
| 2 | Diagnosing malignancy of unknown primary when a biopsy is not feasible or is nondiagnostic | May be appropriate | 5 |
| **Staging** | | | |
| 3 | Routine staging of the primary tumor (T staging) | Rarely appropriate | 1 |
| 4 | Routine staging of axillary nodes | Rarely appropriate | 3 |
| 5 | Routine staging of extra-axillary nodes and distant metastases | May be appropriate | 5 |
| 6 | Staging invasive lobular carcinoma and low-grade invasive ductal carcinoma | May be appropriate | 5 |
| **Biopsy** | | | |
| 7 | Assessing ER status, in lieu of biopsy, in lesions that are easily accessible for biopsy | May be appropriate | 5 |
| 8 | Assessing ER status in lesions that are difficult to biopsy, or when biopsy is nondiagnostic | Appropriate | 8 |
| **Selection of therapy** | | | |
| 9 | At initial diagnosis of metastatic disease, for considering endocrine therapy | Appropriate | 8 |
| 10 | After progression of metastatic disease, for considering second line of endocrine therapy | Appropriate | 8 |
| 11 | At initial diagnosis of primary breast cancer, for considering endocrine therapy | Rarely appropriate | 1 |
| **Other** | | | |
| 12 | Measuring response to therapy | Rarely appropriate | 1 |
| 13 | Detecting lesions in patients with suspected/known recurrent or metastatic breast cancer | May be appropriate | 5 |
| 14 | Detecting ER status when other imaging tests are equivocal or suspicious | Appropriate | 8 |

Ulaner G, Mouabbi J et al, JNM, 2023

# FES-PET may evaluate ER status in lesions difficult to biopsy




Kurland…Linden, *The Oncologist*, 2020

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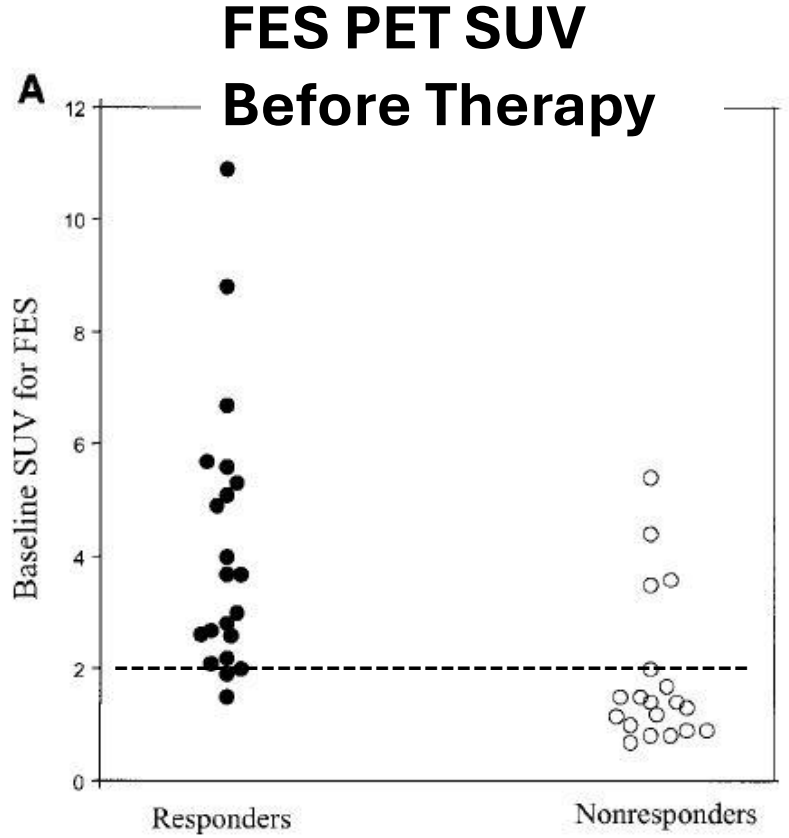
Ulaner G, Mouabbi J et al, JNM, 2023

# FES-PET Predicts response of ER+ breast cancer to endocrine therapy

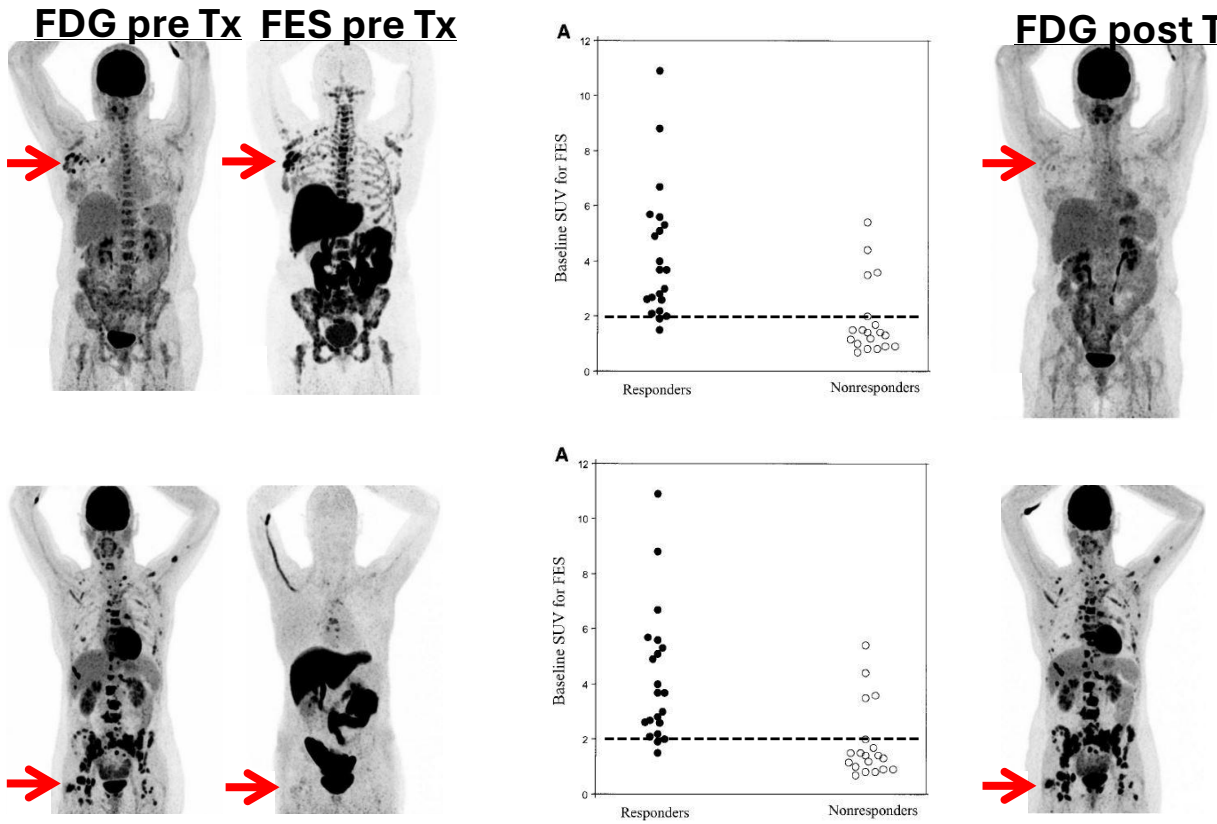
- FES-PET predict response to tamoxifen in metastatic ER+ breast cancer




Mortimer, Dehdashti, et al, J Clinical Oncology 2001

# FES-PET Predicts response of ER+ breast cancer to endocrine therapy

- FES-PET predict response to letrozole plus palbociclib in metastatic ER+ breast cancer




Boers et al, Eur J Cancer 2020

# FES-PET Predicts response of ER+ breast cancer to endocrine therapy

| Authors | Year | # subjects | Therapy |
|---|---|---|---|
| Mortimer et al. | 1996 | 43 | unspecified hormonal therapy or chemotherapy |
| Dehdashti et al. | 1999 | 11 | tamoxifen |
| Mortimer et al. | 2001 | 40 | tamoxifen |
| Linden et al. | 2006 | 47 | unspecified hormonal therapy after discontinuing tamoxifen |
| Dehdashti et al. | 2009 | 51 | fulvestrant or AI |
| Linden et al. | 2011 | 30 | tamoxifen, fulvestrant, or AI |
| Peterson et al. | 2014 | 19 | tamoxifen, fulvestrant, or AI±fulvestrant |
| Van Kruchten et al. | 2015 | 16 | fulvestrant |
| Van Kruchten et al. | 2015 | 19 | estradiol post ≥ 2 lines of endocrine therapy |
| Park et al. | 2016 | 24 | letrozole + lapatinib |
| Kurland et al. | 2017 | 90 | tamoxifen, fulvestrant, or AI±fulvestrant |
| Chae et al. | 2017 | 26 | neoadjuvant chemotherapy or letrozole |
| Boers et al. | 2020 | 30 | letrozole + palbociclib |
| He et al. | 2020 | 36 | fulvestrant |
| Liu et al. | 2020 | 12 | fulvestrant |
| Peterson et al. | 2021 | 23 | vorinostat + AI |
| Su et al. | 2021 | 30 | high-dose tamoxifen |
| Iqbal et al. | 2023 | 16 | rintodestrant |

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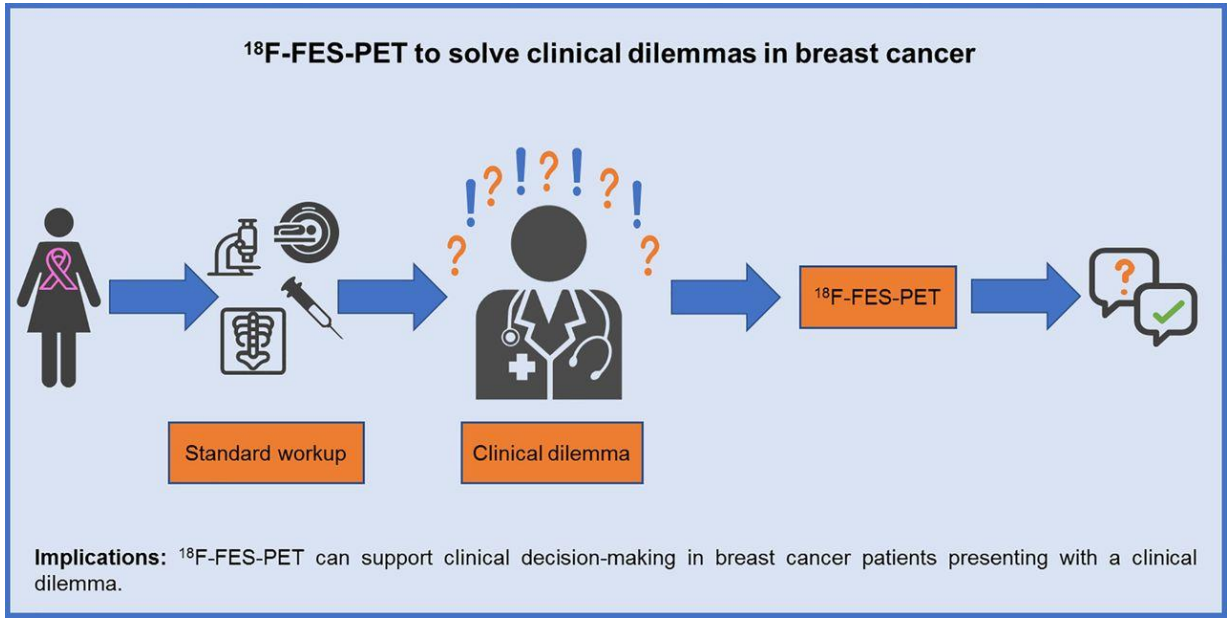
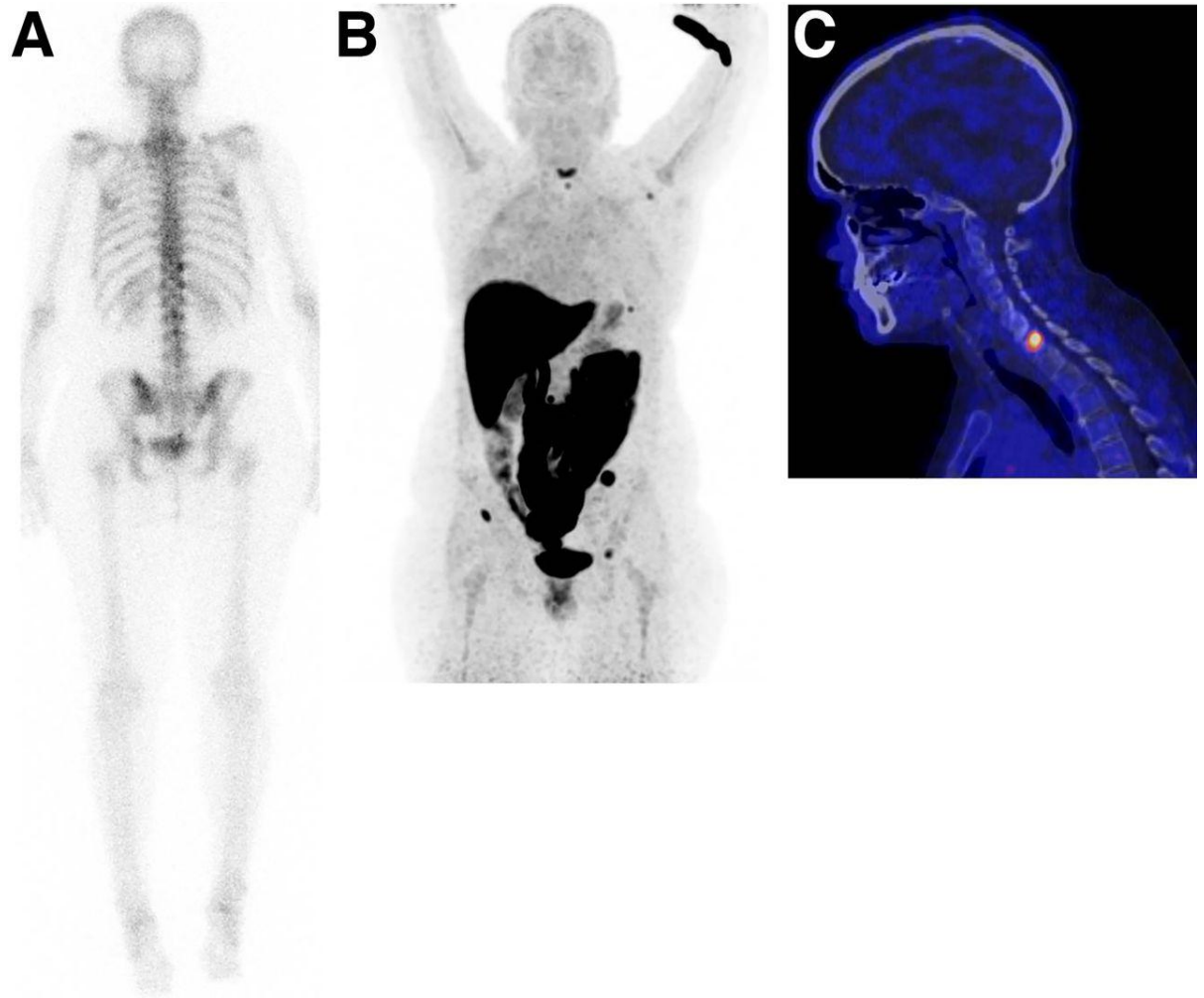
Ulaner G, Mouabbi J et al, JNM, 2023

# FES-PET can be used to solve clinical dilemmas in recurrent or metastatic breast cancer




In total FES-PET solved 87/100 imaging/diagnosis dilemmas:

- 90% of equivocal lesions
- 87% of unclear ER status of the tumor
- 80% of which tumor caused a metastasis in patients with history of multiple cancers

Boers J. et al., *J Nucl Med*. 2021

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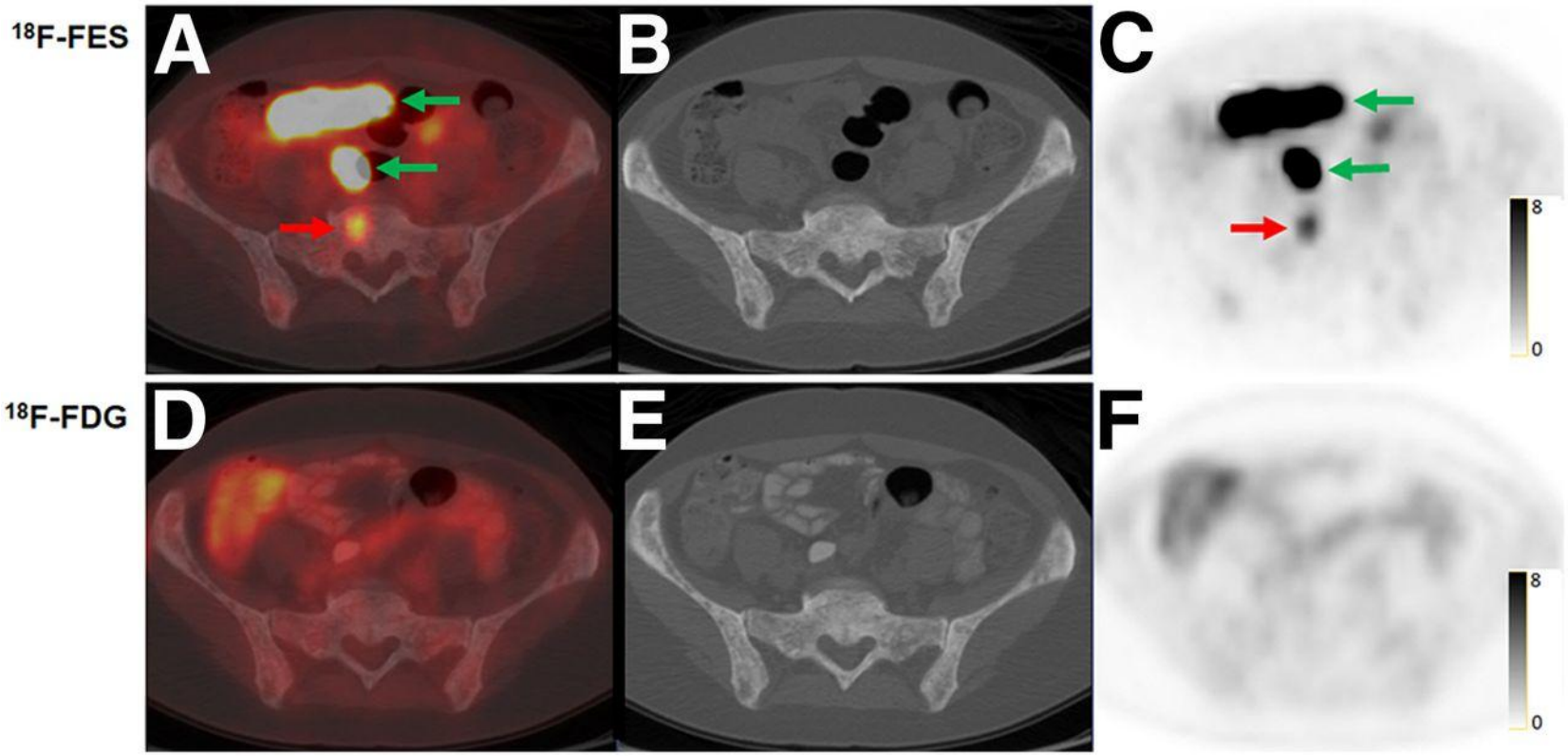
Ulaner G, Mouabbi J et al, JNM, 2023

# Challenges in the Staging of ILC – Standard of Care Imaging

- ILC has a unique growth pattern that is due to the loss of the anchoring cell surface protein **E-cadherin** (most commonly due to a mutation in the ***CDH1*** gene)[1]
- Lobular breast cancers grow in less tightly packed tumors, which are less detectable on standard of care imaging (CT scan, bone scan and FDG PET)
  - In ILC patients with peritoneal disease, the sensitivity of CT scan has been reported to be as low as 25% for implants <0.5 $cm^2$[2]
  - FDG-avidity of ILC is lower than that of IDC[3]

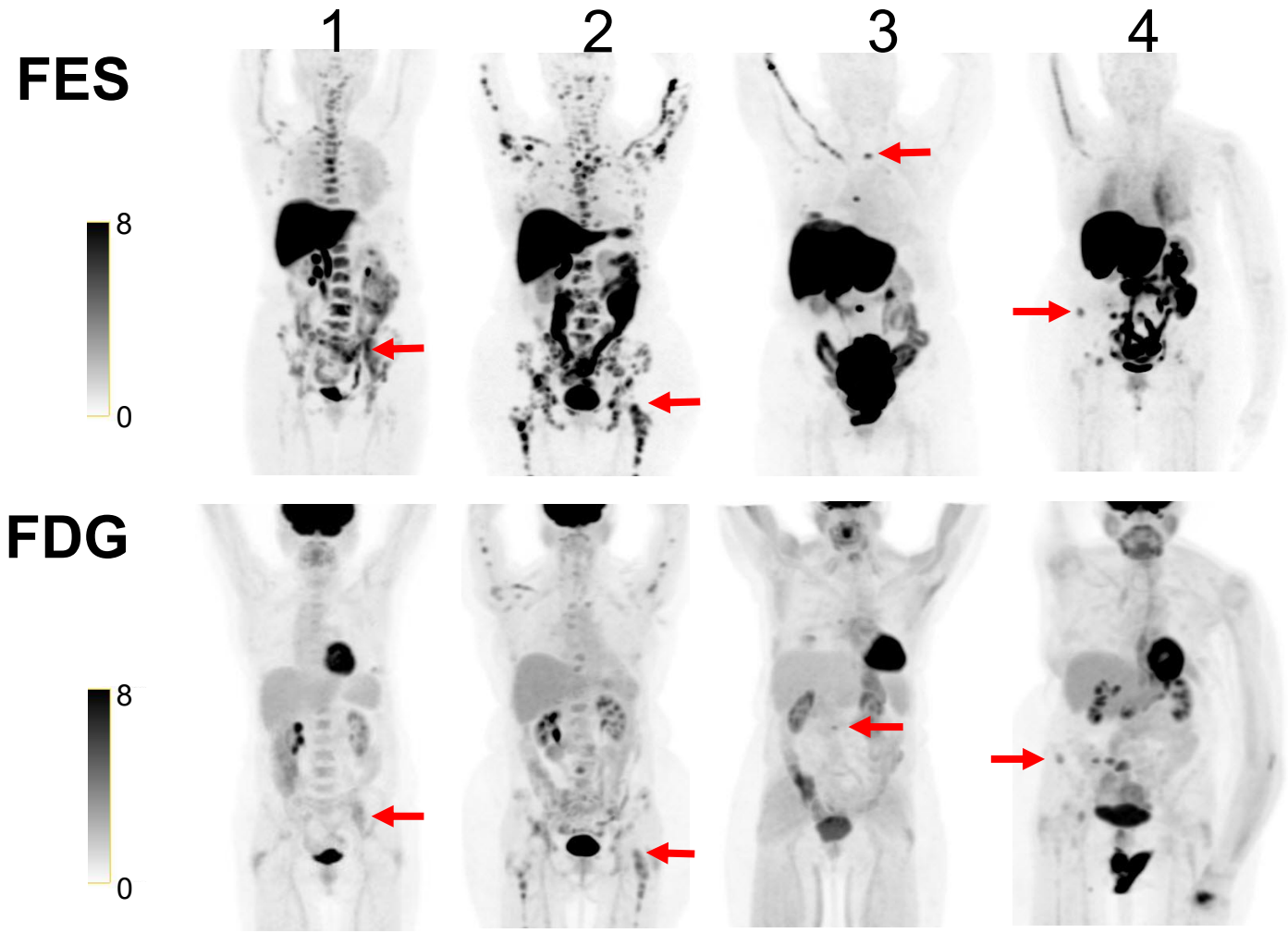
1. Mouabbi JA et al., *Breast Cancer Res* 2022; 2. Lother D. et al., *Cancer Imaging* 2023; 3. Hogan M. … Ulaner G., *J Nucl Med* 2015

# FES-PET detects mlLC better than FDG




Gary A. Ulaner et al., *J Nucl Med* 2021

# FES-PET detects mILC better than FDG




Ulaner et al, *J Nucl Med*, 2020; Covington et al, *Am J Roen* 2023; Bottoni et al, *Eur J Nucl Med Mol Imag* 2023

# The Future of staging of ILC

- FES-PET might be superior to standard of care imaging for both the initial staging of locally advanced disease and suspected recurrence:
  - 30 ILC patients (13 newly diagnosed local advanced and 17 with suspected recurrence):
    - 11/30 (~40%) had biopsy-proven metastases/recurrences
      - SOC detected 5/11 (**45%)**
      - FES-PET detected 9/11 (**82%)**

Ulaner G, NCT04883814

# Limitations

- Identifying liver lesions
  - Can be resolved by improving the exposure

# Limitations

- FES radioisotope half-life is short

| Radioisotope | Half Life |
|---|---|
| FDG | 110 min |
| Ga-68 | 68 min |
| FES | 54 min |

# Limitations

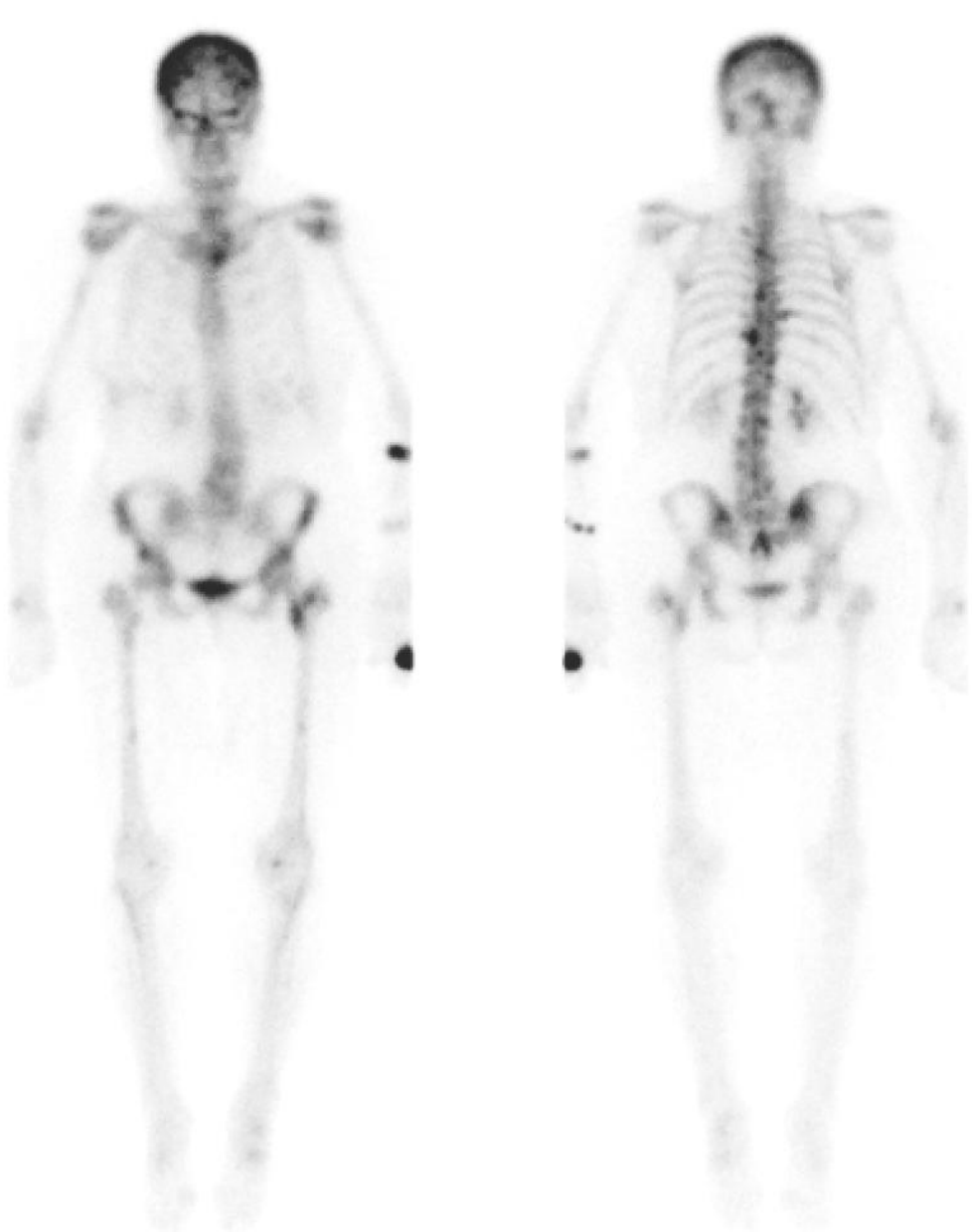
- Use of ER degrader and modulator limits its usefulness
  - Need 5x half-life to pass before it can be used

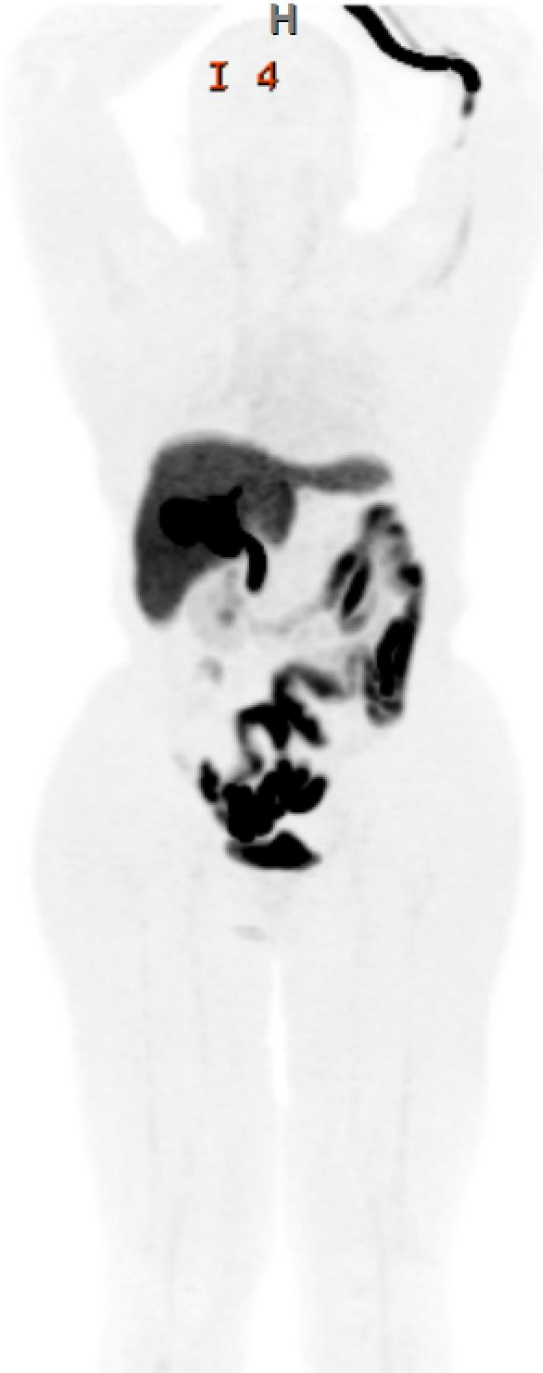
| Therapy | Class | 5x Half Life |
|---|---|---|
| Fulvestrant | SERD | 200 days (28 weeks) |
| Palazestrant | CERAN | 40 days |
| Tamoxifen | SERM | 35 days |
| Lasofoxifene | SERM | 34 days |
| Elacestrant | SERD | 10 days |
| Vepdegestrant | PROTAC | 6 day |
| Camizestrant | SERD | 3 day |

# Clinical Cases

# Case #1

- 62 yo female
- In 2012 diagnosed with right-sided T2 N2 ILC ER 95% PR 99% HER2-ve Ki67 13%
- Underwent neoadjuvant AC-T
- Underwent MRM = RD (20% cellularity); 7+/8 LN
- Underwent adjuvant XRT followed by adjuvant endocrine therapy with exemestane 5y
- 8/2023 DR in bones only = biopsy showed carcinoma (GATA3+) but biomarkers could not be performed
- Given h/o strong ER/PR positivity patient treated as ER+ mBC with 1L ET + CDK4/6is
- 8 weeks later worsening of disease
- FES/PET done

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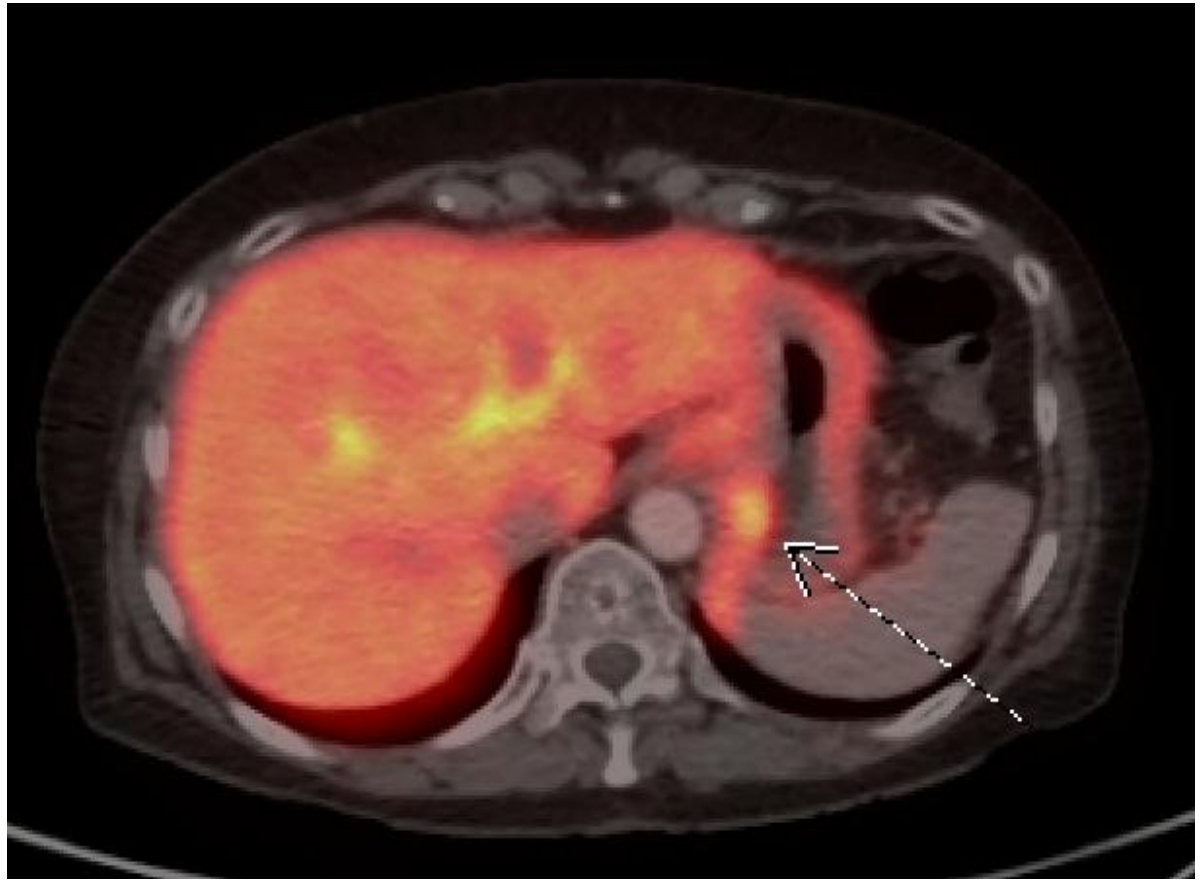
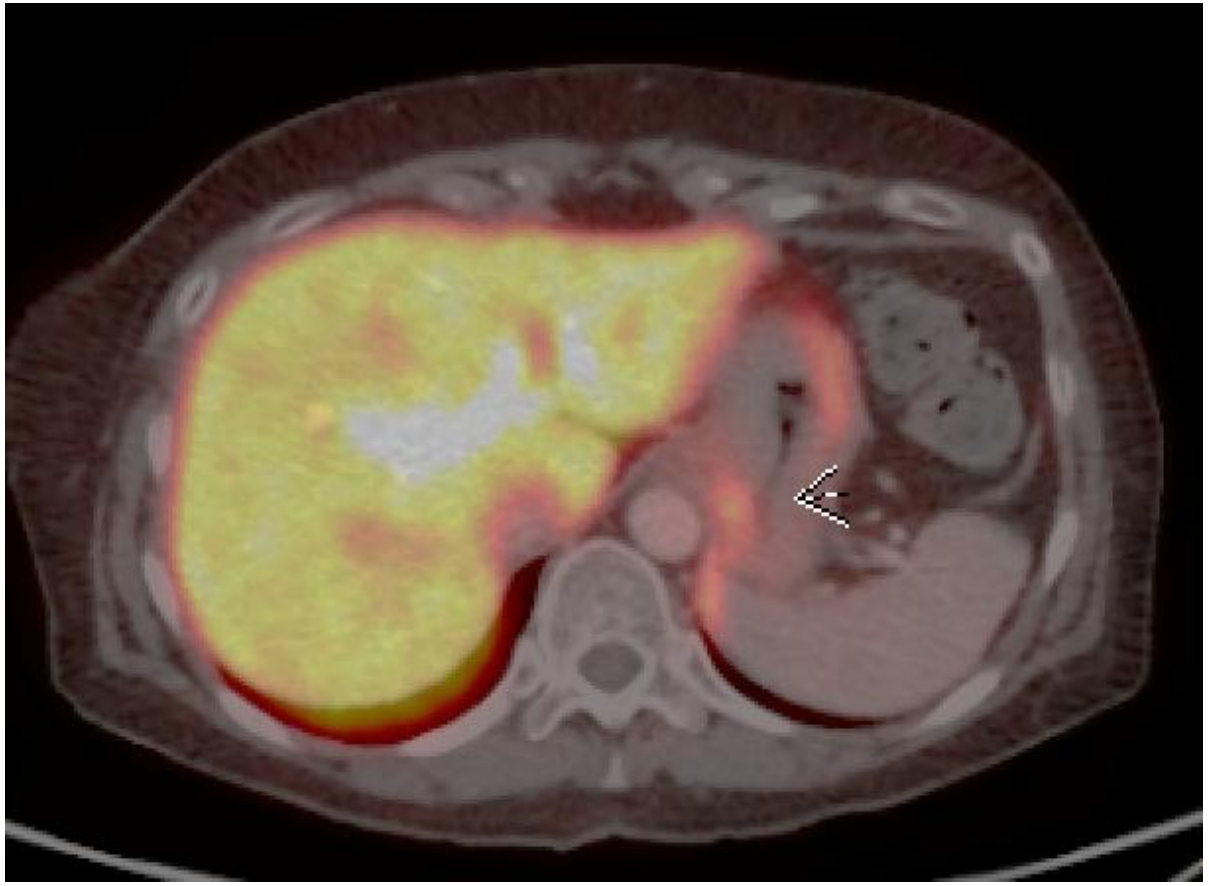
# Case #2

- 67 yo Female
- In 2003 diagnosed with left-sided T2 N1 ILC ER 95% PR 95% HER2-ve
- Underwent L/SLNB = 2.5 cm; 1+/7 LN
- Underwent adjuvant FEC x3 followed by adjuvant XRT and adjuvant endocrine therapy with anastrozole 5y
- In 2022: Gastric outlet obstruction s/p EGD showing thickening in pylorus s/p biopsy showing recurrence in stomach wall = ER+ ILC
- CT CAP/Bone scan unremarkable
- FES-PET done

Initial FES-PET

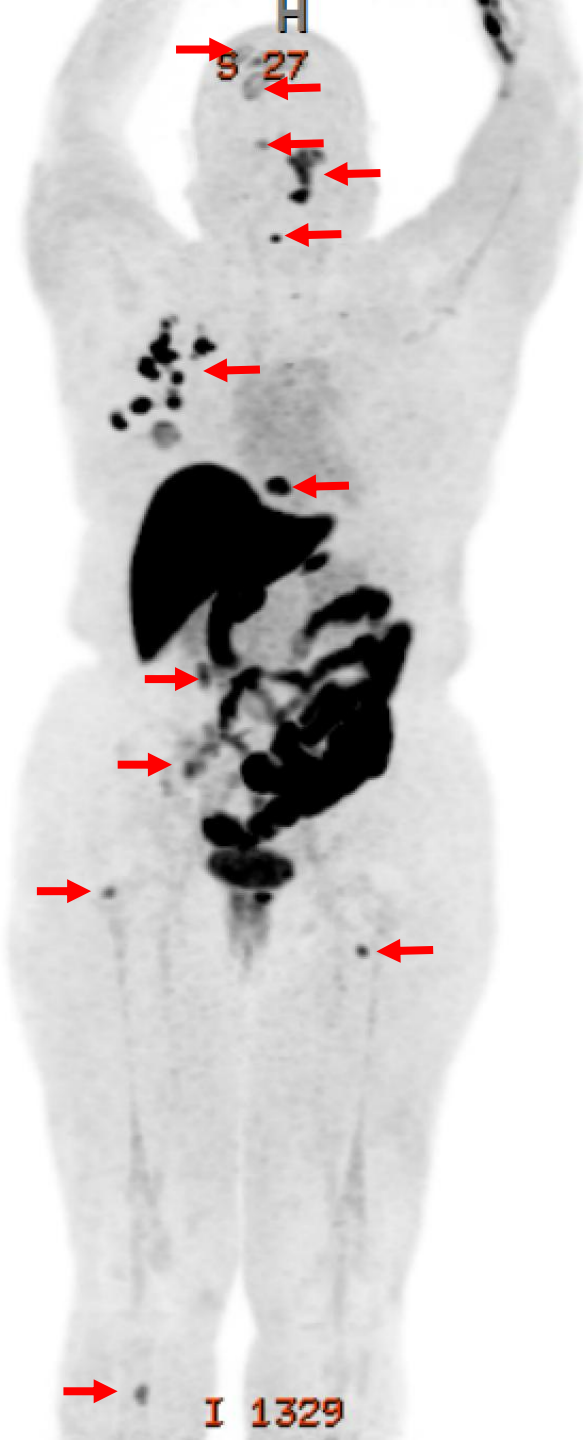


After 4 cycles of 1L letrozole + Ribociclib

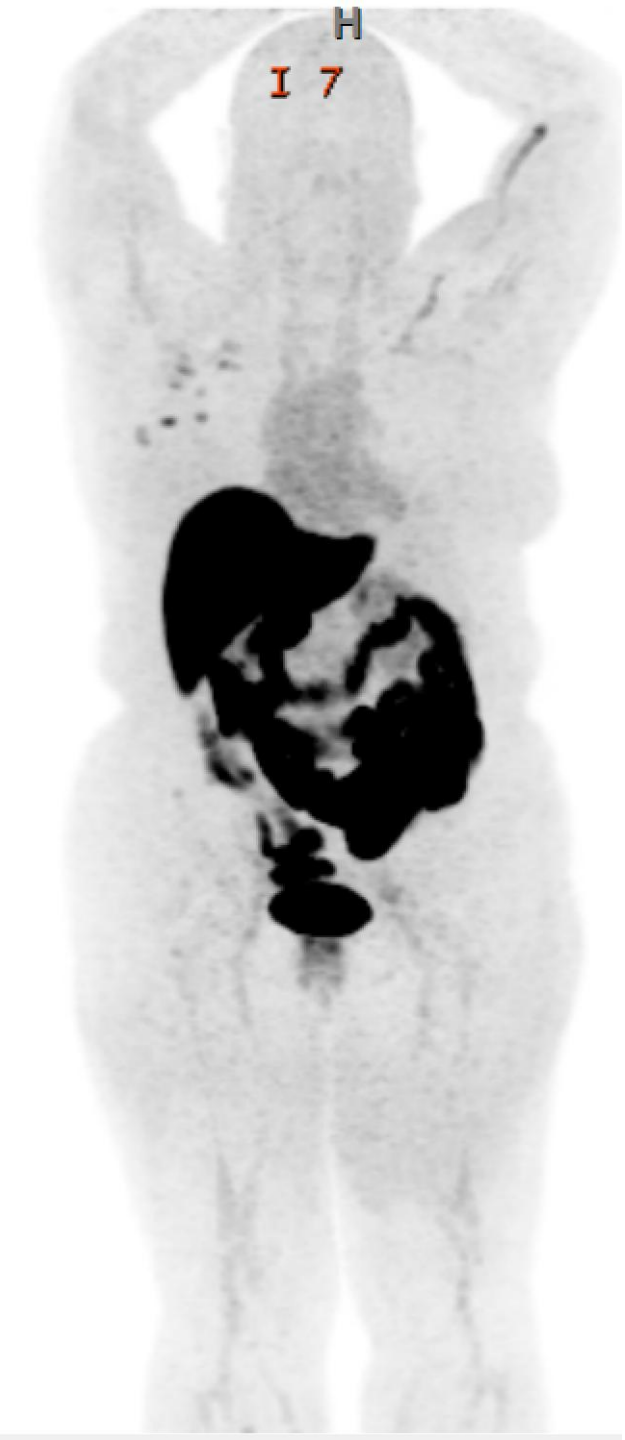


# Case #3

- 74 yo Female
- In 2022 diagnosed with right-sided T2 N0 IDC G2 ER 95% PR 50% HER2 2+ FISH-ve Ki67 20%
- Patient getting prepared for surgery but complaining of persistent mid back pain
- Staging CT CAP and Bone Scan negative
- FES-PET staging ordered



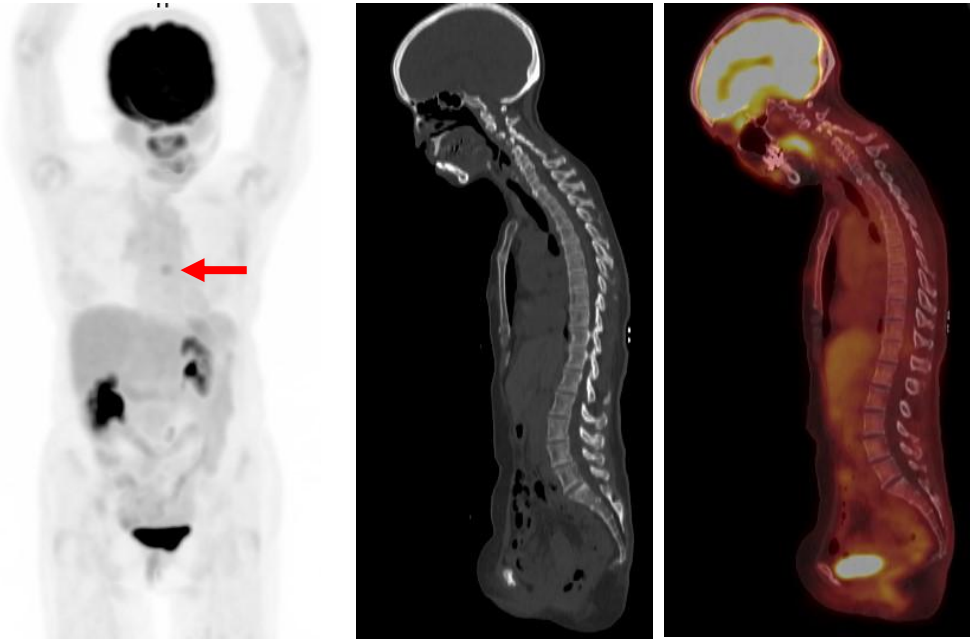

After 8 cycles of 1L letrozole + ribociclib



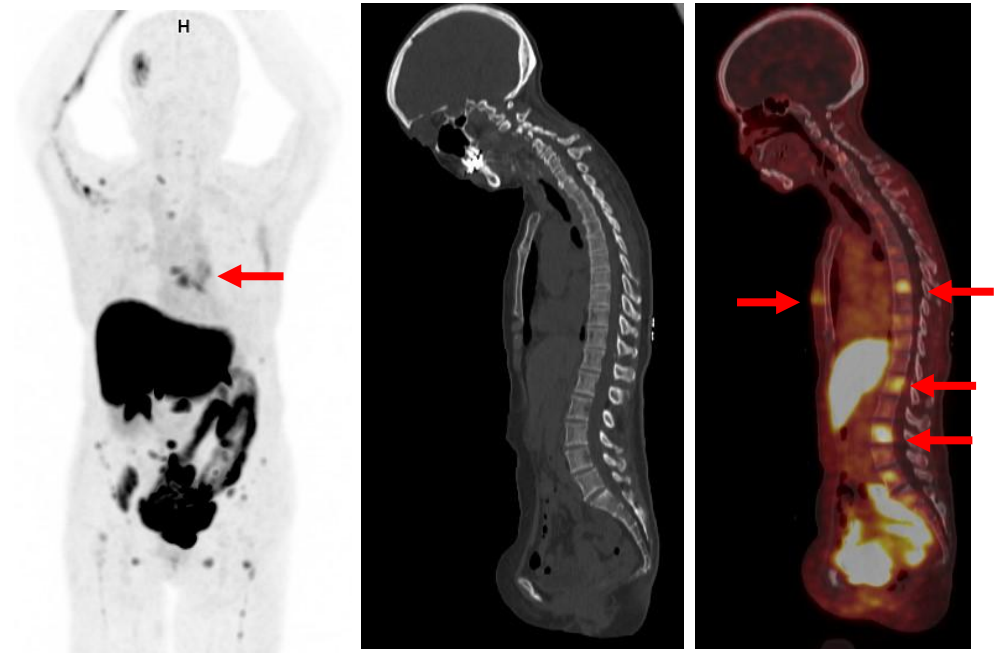
# Case #4

- 52 yo Female
- In 2015 diagnosed with left-sided T1c N0 IDC G2 ER 100% PR 90% HER2 1+ Ki67 10%
- Underwent M/SLNB = 1.6 cm; 0+/1 LN
- ODX RS 12
- Tamoxifen 5y
- 2023 left chest wall recurrence

**FDG PET/CT**



**FES PET/CT**



Importance:
More than 20 bone metastases seen on FES-PET.

Thank you