## Evidence Table

**Clinical Area:** **$^{18}$F Fluoro-Estradiol PET (FES-PET) to measure estrogen receptor expression in advanced breast cancer.**

**Reference:** **Mortimer JE, Dehdashti F, Siegel BA et al. Positron emission tomography with (*FDG and FES*) in breast cancer: correlation with estrogen receptor status and response to systemic therapy. *Clin Cancer Res* 1996; 2: 933-939.**

**Study Type:** Comparison of diagnostic tests and case series.
**Study Aim:** To evaluate the value of FES-PET and FDG-PET for predicting response to systemic therapy in women with breast cancer. Also included a comparison of estrogen-receptor (ER) status assessed by FES-PET or biopsy.

**Outcomes**

- *Primary:* Response to systemic therapy (chemotherapy and hormonal therapy)

**Design**

- *Number of subjects:* n=43.
- *Description of study population:* Median age=43 years; n=14 premenopausal, n=25 postmenopausal, n=3 perimenopausal: n=25 locally advanced disease, n=18 recurrent or metastatic disease.
- *Inclusion and exclusion criteria:* Included all women with locally advanced or metastatic breast cancer. No exclusion criteria were reported.
- *Procedure:* Obtained biopsies of the primary tumors or metastatic lesions and submitted specimens for quantitative measurement of hormone receptor concentrations, determined by the immunoassay technique. Tumor ER levels >3 fmol/mg protein were considered ER+ and 3≤ fmol/mg protein were considered ER-. FES-PET and FDG-PET were performed on 2 separate days, with a maximal interval of 9 days. On FES-PET, presumptively hormone-sensitive disease (FES+) was defined as a tumor standardized uptake ratio (SUV) ≥1 and presumptively hormone-negative disease as a tumor SUV<1.0. Systemic therapy was initiated after completing PET imaging, and there was no standardized treatment regimen.
- *Source of outcome data*: Imaging; biopsy; clinical evaluation.
- *Length of follow-up:* At least 1 year. Ranged from 12 to 58 months.

**Validity**

- *Independent blind comparison with a gold standard or follow-up of those not receiving the gold standard test?* Yes, used biopsy as the gold standard and included blinded analysis.
- *Consecutive patients?* Not specified.
- *Was population homogenous?* Variability in clinical characteristics.
- *Potential selection biases:* No clear biases, had broad eligibility criteria. May not have included consecutive patients.
- *Were intervention/ care/follow-up similar in each group?* No standardized systemic treatment regimen.
- *Did an objective observer assess outcomes?* There was both blinded and unblinded evaluation.

- *Completeness of follow-up:* Some follow-up on all patients, but variable length of follow-up.
- **Conclusions regarding validity of methods:**

The study was small and there was not a consistent hormonal regimen after FES-PET. In the diagnostic test portion of the study, included biopsy as the "gold standard". This is the best available gold standard, but has limitations because biopsy may not correctly identify ER status 100% of the time. If there is discordance between FES-PET and biopsy findings, it is not possible to determine which technique identified the "true" ER status.

**Results**

Estrogen receptor status measured by biopsy vs. FES-PET

Analysis of biopsy samples, No patients (total n=43)

ER+ 21
ER- 20

(Note: ER status could not be determined in two patients due to technical difficulties)

FES-PET

Of the 21 ER+ tumors:
FES+ 16 The apparent sensitivity of FES-PET is 16/21=76%
FES- 5

Of the 20 ER- tumors:
All 20 were also FES- The apparent specificity of FES-PET is 20/20=100%

Response to hormonal therapy by ER and FES status (n=13 patients who received hormonal treatment)

| | | CR | PR | MR | SD | NR |
|---|---|---|---|---|---|---|
| ER+ | FES+ | 2 | 5 | 3 | 0 | 0 |
| | FES- | 0 | 0 | 0 | 1 | 0 |
| ER- | FES+ | 0 | 0 | 0 | 0 | 0 |
| | FES- | 1 | 0 | 0 | 0 | 1 |

CR=complete remission, PR=partial remission, MR=minor response, SD=stable disease, NR=no response.

(Note: Response to chemotherapy was reported in the article but not included because it is beyond the scope of this evidence review)

**Authors' Conclusions**

"…When compared with the in vitro assay of ER status, FES-PET has an apparent sensitivity of 76% and specificity of 100%. Our finding of a subset of patients who have tumors that are ER+ and FES- suggests that the functional assessment of hormone sensitivity by PET imaging can identify patients with ER+ disease whose tumors are likely to be hormone refractory."

**Reviewer's Conclusions**

In this sample of breast cancer patients, 16 of the 21 patients whose biopsy results found they were ER+ were also FES+ (apparent sensitivity=76%). All 20 patients who were ER- according to biopsy were also FES- (apparent specificity=100%). Limitations of the study include the small sample size used for diagnostic accuracy analysis, and use of an imperfect gold standard. When biopsy and FES-PET results differ, there is no way to objectively confirm the true ER status.