

Supplemental Tables for:

Whole body characterization of estrogen receptor status in metastatic breast cancer with ^{18}F -FES PET: Meta-analysis and recommendations for integration into clinical applications

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Supplementary Methods: Whole body characterization of estrogen receptor status in metastatic breast cancer with ^{18}F -FES PET: Meta-analysis and recommendations for integration into clinical applications

Meta-analysis literature search strategy

Search terms intended to identify all published studies with $^{16}\alpha$ - ^{18}F -Fluoroestradiol are defined in **Table S1**. Two literature databases (PubMed and EMBASE) were queried. PubMed was searched first and was queried using the search modules in EndNote X8 (build 11010), setting the filters to return any document that has the search term mentioned anywhere in the index including, but not limited to, title, abstract, and keywords. EndNote was configured to automatically remove duplicates, based on author, year published, title, and reference type. EMBASE was searched using the on-line search tools (<https://www.embase.com/#search>) and results imported into EndNote, again removing duplicates automatically where possible. The databases were last searched in August 2019.

Table S1: Search terms used and result by term

| Search term ^a | Number of references | |
|--|----------------------|--------|
| | PubMed | EMBASE |
| [18F]16 α -fluoro-3,17 β -diol-estratriene-1,3,5(10) | 0 | 0 |
| Estra-1,3,5(10)-triene-3,17-diol, 16-[18F]-Fluoro-, (16 α ,17 β) | 0 | 0 |
| 16 α -[18F]-Fluoro-13 β -methyl-1,3,5(10)-gonatriene-3,17 β -diol | 0 | 0 |
| 16 α -[18F]-Fluoro-17 β -estradiol | 0 | 16 |
| [18F]-Fluoroestradiol | 91 | 36 |
| Fluoroestradiol F-18 | 11 | 276 |
| Fluoroestradiol F18 | 36 | 10 |
| [18F]-FES | 101 | 0 |
| 16alpha fluoroestradiol F 18 | 47 | 150 |
| FES and PET and breast | 104 | 210 |
| 94153-53-4 | 83 | 74 |
| 92817-10-2 | 83 | 0 |
| Fluoroestradiol PET | 118 | 274 |
| 18F estrogen | 279 | 251 |
| Fluoroestradiol | 173 | 385 |
| | | |
| Total Unique References | 787 | |

a. Where brackets or parentheses appear in a search term, the term was searched with and without the punctuation marks.

Study selection

One reviewer evaluated all publications identified in the search by title and abstract to identify all studies that involve the use of [¹⁸F]-FES for any indication in patients, and the full text of all articles that included patients with breast cancer was retrieved. The general subject matter of the identified studies is summarized in **Table S2**.

Table S2: Classification of publications identified in literature search

| | |
|--|------------|
| Total Available Publications | 787 |
| Not FES | 372 |
| Commentary (Review, editorial, letter) | 186 |
| Not human | 62 |

| | |
|---|------------|
| Pertaining to synthesis | 38 |
| Other imaging target (eg, uterus, ovaries) | 23 |
| Correction of prior publication | 2 |
| Not English | 1 |
| Breast Cancer | 103 |
| Pharmacokinetics | 2 |
| Cost-effectiveness | 2 |
| Study design | 10 |
| Meta-analysis | 2 |
| Related to diagnosis or treatment of breast cancer | 87 |
| Case Report | 6 |
| Published as conference abstract | 43 |
| Published as full papers | 38 |
| Excluded (did not meet selection criteria) | 26 |
| Considered for meta-analysis | 12 |

Case reports and studies reported only in abstract were excluded from consideration. For the remaining studies in patients with breast cancer, papers were selected based on the following criteria:

- 1) Study published in English
- 2) Include at least 10 patients
- 3) Provide information on sensitivity and/or specificity for the identification of ER-positive breast tumors (including both primary tumors and metastatic lesions and including those studies in which sensitivity and/or specificity can be calculated if not reported directly) and identify the reference standard[s] by which sensitivity and specificity were judged.

Study assessment

For each article, the study design, the target condition (primary or metastatic disease), the design of the blinded

reading (if done), the dose of [¹⁸F]-FES (radiation dose and bulk dose), the number of patients included, the reference test, endpoints, statistical plan, and efficacy and safety results were abstracted. The unit of assessment was assumed to be contemporaneous imaging and tissue assay of the same lesion for ER activity. However, lack of clarity on timing of assays or lesion-to-lesion matching were not used to exclude studies or individual data points.

From the studies identified as addressing diagnostic accuracy, two independent reviewers applied a limited set of questions from the QUADAS-2 assessment tool [1] to select studies for inclusion in the meta-analysis:

- 1) The spectrum of patients was representative of the patients who will receive the test in practice (including studies for which the answer to this question was unclear).
(The intended indication is for patients with metastatic breast cancer. However, because diagnostic accuracy can also be readily evaluated in patients with primary breast lesions, studies that involve primary breast lesions were eligible for inclusion. These studies were identified and, if appropriate, analyzed separately.)
- 2) The index test (FES positive/negative) and the standard of reference (ER by tissue assay) were evaluated independently.
- 3) Patients are appropriately accounted for (dropouts or missing data are explained).

The two reviewers independently provided an estimate of the overall risk of bias in each paper (Low, Unclear, or High). Major discrepancies in the estimate of the overall risk of bias (one reviewer found Low risk and the other found High risk) were resolved in consultation with a third reviewer. **Table S3** summarizes the decision tree for inclusion of a study in the meta-analysis. All 12 studies assessed met criteria for inclusion.

Table S3: Decision tree for inclusion of study in meta-analysis

| Overall risk of bias (2 reviewers) | Paper is included in meta-analysis? |
|---|--|
| Low/Low | Yes |
| Low/Unclear | Yes |
| Unclear/High | No |
| High/High | No |
| Low/High | Consult third reviewer for consensus |

Data extraction

For all studies, two reviewers extracted the threshold for a positive test result, the definition of the dichotomous reference standard (ER-positive or not), and the corresponding 2x2 table showing the numbers of participants in the cross-classification of test results and reference standard. Discrepancies were resolved by consensus. One study [2] did not provide a direct test result (FES-avid or not); we used a standard uptake value ($SUV_{max} > 1.5$) to define an FES-avid lesion.

Table 1 (manuscript) identifies the studies included in this meta-analysis, and **Table S4** gives inclusion details compared to other published meta-analyses.

Table S4: Studies included in meta-analyses for this manuscript (rows and right-hand columns; see also Table 1) and inclusion of studies compared to other published meta-analyses (left-hand columns)

| Study | Van Kruchten 2013 [3] | Evangelista 2016 [4] | Chae 2019 [5] | Current meta-analysis inclusion | | | |
|---------------------------------|-----------------------|----------------------|------------------|---------------------------------|------------------|-------------------|------------------|
| | | | | 1 | 2 | 3 | 4 |
| Chae 2019 [5] | | | | X | | X | X |
| Gupta 2017 [6] | | | | a | a | X | X |
| Peterson 2008 [7] | X | | X | X | X | X | X |
| Peterson 2014 [8] | | X ^b | c | X | a | X | X |
| Venema 2017 [9] | | | c | X | | X | X |
| Chae 2017 [10] | | | c | | a | a | a |
| Gemignani 2013 [11] | | X | X | | X | X | X |
| Yang 2013 [2] | | X ^d | | | X | X | X |
| Dehdashti 1995 [12] | X ^{d,e} | X ^d | X ^d | | | | X |
| Mintun 1988 [13] | X ^d | d,f | c,d | | | | X |
| Mortimer 1996 [14] | X | X | X | | | | X |
| van Kruchten 2012 [15] | | X ^d | | | | | X |
| Yang 2017 [16] | | | X | | | g | g |
| Results of meta-analyses | | | | | | | |
| Sensitivity (95% CI/CR) | 0.84 (0.73-0.91) | 0.82 (0.74-0.88) | 0.83 (0.72-0.91) | 0.78 (0.65-0.88) | 0.86 (0.73-0.94) | 0.83 (0.72, 0.90) | 0.81 (0.73-0.87) |
| Specificity (95% CI/CR) | 0.98 (0.90-1.00) | 0.95 (0.86-0.99) | 0.93 (0.74-0.99) | 0.98 (0.65-1) | 0.76 (0.52-0.90) | 0.83 (0.64-0.93) | 0.86 (0.68-0.94) |

CI Confidence interval; CR Confidence region

- a. Excluded from HSROC analysis (meta-analysis summary sensitivity and specificity) – no ER-negative lesions in study
- b. Evangelista 2016 [4] includes 4 additional data points (where biopsied lesions were not paired to FES PET results for the same lesion): three ER+ liver biopsies and one ER- lung lesion resected prior to FES PET.
- c. Study listed in the Chae 2019 [5] supplement table, but was not included in the meta-analysis for having <5 lesions (either ER+ or ER-)
- d. Study tissue assay results are interpreted differently in different meta-analyses

- e. Van Kruchten 2013 [3] also includes 10 benign lesions.
- f. Study listed in the Evangelista 2016 [4] Table 3, but was excluded from pooled sensitivity/specificity estimates (with 2 other studies that were also not selected for other meta-analyses) for “risk of bias due to underreported methods”
- g. Correlation-based analysis in the published manuscript did not provide data on the number of ER-positive or ER-negative lesions

References

1. Whiting PF, Rutjes AW, Westwood ME et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011;155:529-536.
2. Yang Z, Sun Y, Xue J et al. Can positron emission tomography/computed tomography with the dual tracers fluorine-18 fluoroestradiol and fluorodeoxyglucose predict neoadjuvant chemotherapy response of breast cancer?--A pilot study. *PLoS One.* 2013;8:e78192.
3. van Kruchten M, de Vries EGE, Brown M et al. PET imaging of oestrogen receptors in patients with breast cancer. *Lancet Oncol.* 2013;14:e465-e475.
4. Evangelista L, Guarneri V, Conte PF. 18F-Fluoroestradiol Positron Emission Tomography in Breast Cancer Patients: Systematic Review of the Literature & Meta-Analysis. *Curr Radiopharm.* 2016;9:244-257.
5. Chae SY, Ahn SH, Kim SB et al. Diagnostic accuracy and safety of 16alpha-[(18)F]fluoro-17beta-estradiol PET-CT for the assessment of oestrogen receptor status in recurrent or metastatic lesions in patients with breast cancer: a prospective cohort study. *Lancet Oncol.* 2019;20:546-555.
6. Gupta M, Datta A, Choudhury PS et al. Can (18)F-Fluoroestradiol Positron Emission Tomography Become a New Imaging Standard in the Estrogen Receptor-positive Breast Cancer Patient: A Prospective Comparative Study with (18)F-Fluorodeoxyglucose Positron Emission Tomography? *World J Nucl Med.* 2017;16:133-139.
7. Peterson LM, Mankoff DA, Lawton T et al. Quantitative imaging of estrogen receptor expression in breast cancer with PET and 18F-fluoroestradiol. *J Nucl Med.* 2008;49:367-374.
8. Peterson LM, Kurland BF, Schubert EK et al. A phase 2 study of 16alpha-[18F]-fluoro-17beta-estradiol positron emission tomography (FES-PET) as a marker of hormone sensitivity in metastatic breast cancer (MBC). *Mol Imaging Biol.* 2014;16:431-440.
9. Venema CM, Mammatas LH, Schroder CP et al. Androgen and estrogen receptor imaging in metastatic breast cancer patients as a surrogate for tissue biopsies. *J Nucl Med.* 2017.
10. Chae SY, Kim SB, Ahn SH et al. A Randomized Feasibility Study of (18)F-Fluoroestradiol PET to Predict Pathologic Response to Neoadjuvant Therapy in Estrogen Receptor-Rich Postmenopausal Breast Cancer. *J Nucl Med.* 2017;58:563-568.
11. Gemignani ML, Patil S, Seshan VE et al. Feasibility and predictability of perioperative PET and estrogen receptor ligand in patients with invasive breast cancer. *J Nucl Med.* 2013;54:1697-1702.

- 12.** Dehdashti F, Mortimer JE, Siegel BA et al. Positron tomographic assessment of estrogen receptors in breast cancer: comparison with FDG-PET and in vitro receptor assays. *J Nucl Med.* 1995;36:1766-1774.
- 13.** Mintun MA, Welch MJ, Siegel BA et al. Breast cancer: PET imaging of estrogen receptors. *Radiology.* 1988;169:45-48.
- 14.** Mortimer JE, Dehdashti F, Siegel BA et al. Positron emission tomography with 2-[¹⁸F]Fluoro-2-deoxy-D-glucose and 16alpha-[¹⁸F]fluoro-17beta-estradiol in breast cancer: correlation with estrogen receptor status and response to systemic therapy. *Clin Cancer Res.* 1996;2:933-939.
- 15.** van Kruchten M, Glaudemans AW, de Vries EF et al. PET imaging of estrogen receptors as a diagnostic tool for breast cancer patients presenting with a clinical dilemma. *J Nucl Med.* 2012;53:182-190.
- 16.** Yang Z, Sun Y, Xu X et al. The Assessment of Estrogen Receptor Status and Its Intratumoral Heterogeneity in Patients With Breast Cancer by Using ¹⁸F-Fluoroestradiol PET/CT. *Clin Nucl Med.* 2017;42:421-427.