^{18}F-FES PET/MRI for tailoring treatment of luminal A and lobular breast cancer: a phase II prospective cohort study evaluating the performance of FES PET/MRI in axillary staging compared with axillary surgery (FESTA trial)

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Background

Breast cancer (BC) staging is essential to planning the most appropriate treatment pathway. Currently, BC management has become more tailored to the tumor and patient's characteristics.
However, BC imaging shows varying performance according to tumor subtypes.
In particular, routine imaging may pose some challenges when evaluating luminal A BC (LumA) and lobular BC (Lob). LumA, due to low grade and proliferation index (< 20%) shows lower sensitivity on axillary US, reduced MRI enhancement, and low FDG-avidity on PET. Similarly, Lob, due to its peculiar single-cell growth pattern, exhibits inferior sensitivity on axillary MRI and FDG-avidity. LumA and Lob account for >50% of all BCs. Despite their favorable prognosis, metastases and recurrences still occur; this translates into a higher absolute number of events than in other subtypes.
As a result, a concrete risk of disease underestimation and under-treatment exists. Two ongoing studies on FDG-PET/MRI imaging in our institution have already demonstrated that its sensitivity also decreases in LumA and Lob.
Based on these premises, our hypothesis states that by combining the advantages of hybrid PET/MRI with the high accuracy of 16α-18F-fluoro-17-beta-estradiol(FES), a radiolabeled form of estrogen binding to functionally active ER, we could obtain a reliable, non-invasive, operator-independent, one-stage imaging method for staging LumA and ER-positive Lob.

Trial design

FESTA trial is a prospective cohort study (Fig.1) where patients with LumA and ER-positive Lob will be enrolled in four **cohorts** undergoing: A) primary surgery; B) induction endocrine therapy; C) neoadjuvant chemotherapy, and D) systemic therapy for metastatic disease. FES PET/MRI examinations will be performed at baseline for local and systemic staging in all cohorts and a second exam after systemic therapy in cohorts C-D. Correlations between the FES PET/MRI parameters and pathology, gene expression, and FDG PET parameters, when available, will be investigated.

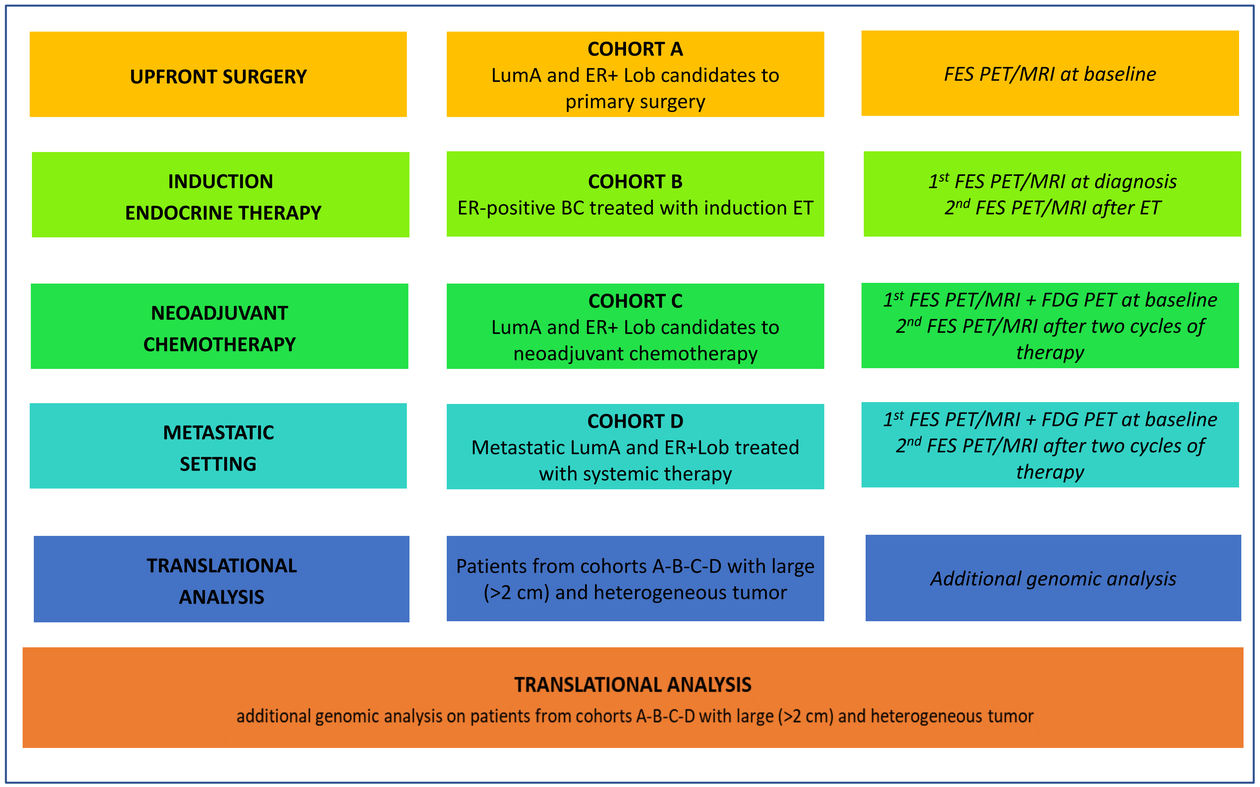

Fig.1 Study design

Study aims:

- The performance of the *FES PET/MRI in axillary staging compared with axillary surgery*;
- The *potential correlations between changes in FES uptake and changes in proliferation index* after three weeks of endocrine therapy (ET);
- The performance of the *FES PET/MRI in systemic staging* of patients undergoing systemic therapy in *comparison with standard imaging* ;
- The biological determinants of *tumor heterogeneity* on pathological, imaging, and genomic levels.

Statistics

The primary analysis in **cohort A** will test the sensitivity of the FES PET/MRI in detecting macrometastatic axillary nodes (Fig 1). Assuming that the probability that a patient has positive nodes is 33%, 106 patients will provide 80% power to reject the null hypothesis about sensitivity at a 5% significance level if the true sensitivity is at least 50%. Results from the FES PET/MRI will be also compared with standard imaging in terms of sensitivity and number of lesions detected using the Mc-Nemar test for paired proportions and the Wilcoxon signed-rank test for paired data.

The primary analysis in **cohort B** will test the association between the FES-SUV change from pre-ET to post-ET and the Ki-67 change from core biopsy to post-ET in ER positive BC patients with a Ki-67>10% (Fig 2). The association between these changes will be measured by the Pearson correlation index ρ. A total of 46 patients from Cohort B will provide 80% power to reject the null hypothesis about ρ at a 5% significance level if the true ρ is at least 0.4

No formal sample size was calculated for **cohort C and D**: results will be considered descriptive in nature, informing sample size considerations for future trials. We intent to recruit 20 and 30 patients, respectively. Accrual has not started yet.

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