Early MRI and dedicated breast PET biomarkers for hormone receptor-positive/HER2-negative early-stage breast cancer in the setting of neoadjuvant endocrine therapy in the I-SPY 2 TRIAL

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Purpose

To examine changes in functional tumor volume (FTV) on MRI and 18F-fluoroestradiol (an estrogen receptor-targeted tracer, FES) uptake on dedicated breast PET (dbPET) in patients with hormone receptor positive (HR+) /HER2-negative (HER2–) breast cancer receiving neoadjuvant endocrine therapy (NET).

To compare MRI change in NET with change in a similar cohort of patients receiving neoadjuvant chemotherapy (NAC).

Background

- **Neoadjuvant endocrine therapy (NET)** is increasingly utilized for HR+ /HER2– breast cancer. In I-SPY 2, a sub cohort of HR+ /HER2– patients receive NET in Endocrine optimization protocol (EOP)
- **Biomarkers for NET are lacking.** There is limited evidence that pathological response (such as pCR) or change in a biomarker (such as Ki67) after NET is predictive of survival outcome[1]. Also, there is limited imaging research to assess response during NET.

1. Korde LA, et al. J Clin Oncol. 2021 May 01; 39(13) 1485-1505

- **Dedicated breast PET (dbPET)** is an emerging PET technology specially designed for breast imaging. Using dbPET combined with an estrogen receptor targeting tracer (18F-fluoroestradiol, FES), functional interaction between estrogen and its receptor within breast cancer and parenchyma can be visualized.

Methods

Study cohort

NET cohort (N = 65)
- HR+/HER2– patients in EOP
- 3 arms: amcenestrant (an oral selective estrogen receptor degrader [SERD]), with or without addition of abemaciclib (a CDK4/6 inhibitor) or letrozole (an aromatase inhibitor)

NAC cohort (N = 68)
- HR+/HER2– patients in I-SPY 2
- Control arm : standard of care (paclitaxel + AC)

	NET cohort	NAC cohort
Period	2021 – 2022	2010 – 2016
Subtype	HR+/HER2- negative	HR+/HER2- negative
Stage	Stage 2–3	Stage 2–3
Mamma Print	• Low-risk (0 to 1) • High-risk 1 (-0.57 to 0)	• High-risk 1 (-0.57 to 0)
Imaging	MRI FES-dbPET	MRI

Methods

Dynamic contrast-enhanced breast MRI (DCE-MRI)

- **Functional tumor volume (FTV)** is derived as a quantitative measure of tumor burden from each MRI[2]

2. Hylton NM, Magn Reson Imaging Clin N Am. 1999 May; 7(2) 411-20

Dedicated breast PET with 18F-fluoroestradiol (FES-dbPET)

- Available for patients in NET cohort at a single institution (UCSF)
- **Maximum standardized uptake value (SUVmax)** over the tumor volume (or location*) was measured to quantify FES uptake

* For exams, where tumor uptake is indistinguishable from background

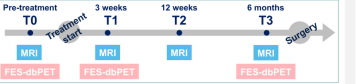
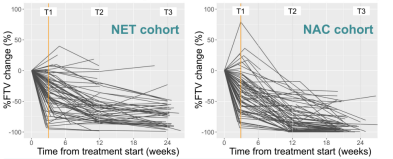


Figure 1: Imaging time points before and during neoadjuvant treatment

Results

Longitudinal change in FTV on MRI (as of 09/2022)



FTV change	NET cohort		NAC cohort	
	No. of patients	Median [1st, 3rd quartiles]	No. of patients	Median [1st, 3rd quartiles]
3 weeks (T1)	65	-32.5% [-64.1, -12.1]	68	-33.9% [-59.6, -11.2]
12 weeks (T2)	60	-68.1% [-80.7, -50.0]	63	-83.8% [-95.0, -60.8]
6 months (T3)	46	-71.9% [-89.1, -59.8]	64	-93.5% [-98.1, -82.4]

Longitudinal change in SUV_{max} on FES-dbPET

SUV_{max} change	NET cohort	
	No. of patients	Median [1st, 3rd quartiles]
3 weeks (T1)	7	-45.9% [-53.7, -43.0]
12 weeks (T2)	NA	NA
6 months (T3)	7	-74.7% [-77.8, -64.2]

At T1 and T3, tumor uptake decreased in all patients, and SUV_{max} showed apparent decrease

Image comparison between FES uptake and MRI

- 7 patients in NET cohort underwent FES-dbPET
- At T0, tumor FES uptake exceeded background uptake in all 7 patients with a median SUVmax of 8.2.
- At T1 and T3, tumor uptake was indistinguishable from background for 3 patients (43%) at T1 and 5 patients (71%) at T3, despite evidence of residual tumor on MRI.

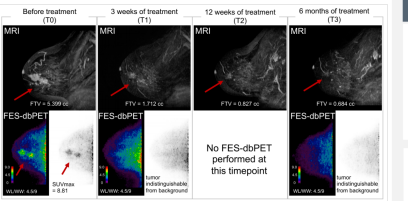


Figure 2: Representative case in NET cohort

MRI (upper row) and FES-dbPET (lower row) maximum intensity projection (MIP) images. At T1 and T3, residual tumor is identified on MRI, but FES uptake on dbPET decreased and was indistinguishable from background. This illustrates that the ability of estrogen receptor of cancer cells to combine with estrogen decreased to background tissue level, although there is residual tumor.

Key findings

DCE-MRI
- At T1, median FTV change was similar in the NET and NAC cohorts. At T2 and T3, a more gradual response was observed for the NET cohort compared to the NAC cohort.
- After 3 weeks of NET, we observed a large dynamic range of FTV change similar to that seen in NAC.

FES-dbPET
- Tumor SUVmax decreased in all patients at T1 with greater decrease at T3
- After 3 weeks of NET, a decrease in FES uptake was observed, with diminishment to background levels in 43% of subjects.

Conclusions

These results suggest the potential for MRI and FES-dbPET to be used in combination as biomarkers of early response to neoadjuvant endocrine treatment.

Advocate perspective

Endocrine therapy continues to play an increasingly critical role in the treatment against both high and low risk ER+/HER2- early and late recurrence breast cancer. More neoadjuvant endocrine studies are needed to find reliable biomarkers that will allow early assessment of treatment to enable treatment switching. This study is a positive first step to find a combination imaging biomarker approach that will allow for increased treatment efficacy and avoid unnecessary toxicity. Susie Brain, Diane Heditsian, Research Advocates

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