Fibroblast Activation Protein (FAP)-targeted dedicated breast PET for primary invasive lobular carcinoma: A Pictorial Review

Natsuko Onishi[1], Rita Mukhtar[1], Thomas Hope[1], Pouya Metanat[1], Yingbing Wang[1], Bonnie Joe[1], Ray Kimberly[1], Sarah Choi[1], Leena Awni[1], Diane Heditsian[2], Deborah Romer[2], Susie Brain[2], I-SPY 2 Imaging Working Group, I-SPY 2 Investigator Network, Alexander D. Borowsky[1], Hope Rugo[1], Jo Chien[1], Laura Esserman[1], Nola Hylton[1]

[1]*University of California, San Francisco, CA;* [2]*I-SPY 2 Advocacy Group, San Francisco, CA*

INTRODUCTION

Dedicated breast positron emission tomography (dbPET)

- An innovative PET imaging designed to scan only the breasts
- High spatial resolution and detailed characterization of tumor uptake levels, distribution, and textures

Fibroblast activation protein (FAP) targeted radiotracer

- Fibroblast activation protein (FAP): Predominantly expressed in cancer-associated fibroblasts within tumor stroma. In breast cancer, FAP is also expressed within tumor cells.
- Whole-body PET/CT with FAP-targeted tracer (FAP-whole-body PET/CT) showed higher sensitivity in the detection of primary and metastatic invasive breast cancer compared to the standard ^{18}F-fluorodeoxyglucose (FDG) radiotracer
- **dbPET with FAP-targeted tracer (FAP-dbPET)** may offer advantages in depicting ***invasive lobular carcinoma (ILC)***, which has unique imaging challenges due to its diffuse growth pattern and low cellularity.

We present preliminary examinations of **FAP-dbPET** performed on the same day following FAP-whole-body PET/CT in patients with **primary ILC lesions**, as a pictorial-review style case presentation.

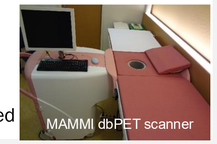
METHODS

Patient enrollment

- Patients with primary ILC co-enrolled from the the I-SPY 2 TRIAL's Endocrine Optimization Program (EOP) testing endocrine agents.

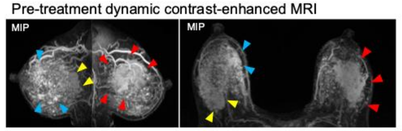
FAP-dbPET scans

- Using FAP-2286 provided by Novartis, ^{68}Ga-FAP-2286 was synthesized at the UCSF Cyclotron facility.
- After undergoing FAP-whole-body PET/CT with 3–8 mCi of ^{68}Ga-FAP-2286 on a separate research protocol, dbPET was scanned without additional radiotracer injection.
- Average interval between tracer injection and start of FAP-dbPET scanning was approximately 2.5 hours.
- Scan protocol
  Scanner: MAMMI (OncoVision, Spain)
  Position: prone
  Duration: 15 minutes per breast, starting with the ipsilateral breast followed by the contralateral breast

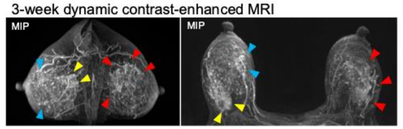


Case 1. 51-year-old premenopausal woman

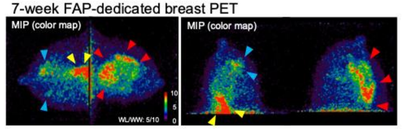
Pre-treatment dynamic contrast-enhanced MRI



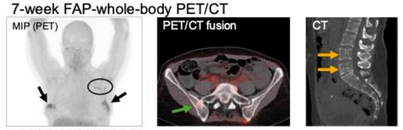
3-week dynamic contrast-enhanced MRI



7-week FAP-dedicated breast PET



7-week FAP-whole-body PET/CT



MIP = maximum intensity projection

Pre-treatment dynamic contrast-enhanced (DCE) MRI

- Multifocal and multicentric areas of suspicious contrast enhancement
- **Red▼** & **Yellow▼**: Biopsy pathology of *bilateral ILCs (both ER+ 81-90%, PR+ 81-90%, HER2-negative)*
- **Blue▼**: challenging to differentiate as malignant or benign due to marked background parenchymal enhancement (BPE).

DCE-MRI after 3 weeks of endocrine therapy

- Both tumor enhancement and BPE reduced in size and intensity.

FAP-dbPET after 7 weeks of endocrine therapy

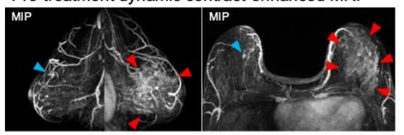
- **Red▼** & **Yellow▼**: High radiotracer uptake, correspond to MRI
- **Blue▼**: High/moderately increased uptake, potential malignancy, although pathological confirmation is not available to date.

FAP-whole-body PET/CT after 7 weeks of endocrine therapy

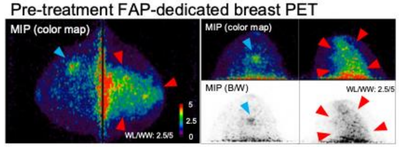
- High radiotracer uptake in the breast lesions (**Black⟶**) and left axillary lymph nodes (**Black◯**).
- Weak/equivocal radiotracer uptake matching suspicious sclerotic lesions on CT in multiple bones, including the right iliac bone (**Green⟶**) and vertebra (**Orange⟶**), biopsy confirmed *bone metastasis*.

Case 2. 59-year-old postmenopausal woman

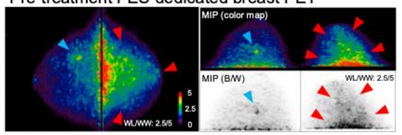
Pre-treatment dynamic contrast-enhanced MRI



Pre-treatment FAP-dedicated breast PET



Pre-treatment FES-dedicated breast PET



MIP = maximum intensity projection, FES = ^{18}F-fluoroestradiol

Pre-treatment DCE MRI

- **Red▼**: Diffuse non-mass enhancement involving all four quadrants of left breast
  Pre-treatment biopsy of *ILC (ER+ 60-70%, PR-negative, HER2-negative)*
  Surgical pathology after neoadjuvant endocrine therapy (mastectomy) identified residual ILC in nearly every slice.
- **Blue▼**: Non-mass enhancement in the right upper central breast.
  Diagnosed as *atypical ductal hyperplasia (ADH)* both in pre-treatment MRI-guided biopsy and surgical pathology.

Pre-treatment FAP-dbPET & ^{18}F-fluoroestradiol (FES)* dbPET

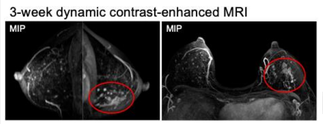
- **Red▼** : Diffusely increased FAP- and FES-tracer uptake, correspond to MRI findings.
- **Blue▼**: Moderately increased FAP- and FES-tracer uptake distributing in larger area compared to MRI
- Diffusely scattered tracer uptake in background tissue.
  Surgical pathology (right mastectomy) showed diffuse *benign fibrocystic changes*.

*^{18}F-fluoroestradiol (FES) is a radiotracer targeting estrogen receptor

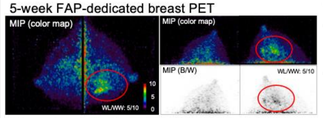
Case 3. 39-year-old premenopausal woman

ILC (ER+ 91-100%, PR+21-30%, HER2-negatve, Ki-67 5-10%)

3-week dynamic contrast-enhanced MRI



5-week FAP-dedicated breast PET



MIP = maximum intensity projection

DCE MRI (3 weeks after endocrine therapy)

- Irregular masses + non-mass enhancement, lower inner and lower out quadrants of left breast.

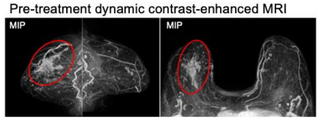
FAP-dbPET (5 weeks after endocrine therapy)

- High radiotracer uptake, correspond to MRI.
- Diffusely scattered tracer uptake in background tissue of both breasts.

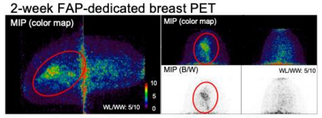
Case 4. 78-year-old postmenopausal woman

ILC (ER+ 91-100%, PR+ 71-80%, HER2 neg, Ki-67 <1%)

Pre-treatment dynamic contrast-enhanced MRI



2-week FAP-dedicated breast PET



MIP = maximum intensity projection

Pre-treatment DCE MRI

- Non-mass enhancement across the upper outer and upper inner quadrants of the right breast.

FAP-dbPET (2 weeks after endocrine therapy)

- High radiotracer uptake correspond to MRI.
- Diffuse scattered tracer uptake in background tissue of both breasts.

KEY FINDINGS & DISCUSSION

- Primary ILC lesions showed high uptake of fibroblast activation protein (FAP)-targeted radiotracer on dedicated breast PET, corresponding to tumor distribution on MRI.
- ADH and background normal/benign tissue showed moderately increased uptake.
- FAP-targeted dedicated breast PET may assist in distinguishing primary ILC lesions from background parenchymal enhancement on breast MRI.
- Future studies will validate these through radiological-pathological correlation.

ADVOCATE PERSPECTIVE

Deborah Romer, Patient Research Advocate diagnosed with mixed lobular and ductal cancer

These preliminary results are promising, showing the potential to address significant and unique imaging challenges in lobular breast cancer that can impact treatment and to better understand metastasis. This encouraging research brings hope to patients by addressing imaging gaps that lead to missed lobular detections and their associated fear and worry.

ACKNOWLEDGEMENTS: This research was supported by **UCSF PICT award 7504947 and National Institutes of Health (NIH) grants R01 CA132870, R01 CA 2277763, P01 CA210961**. The authors wish to acknowledge the generous support of the 501(c)3 study sponsors, Quantum Leap Healthcare Collaborative and express appreciation for the ongoing support for the I-SPY program from the Safeway Foundation, the William K. Bowes, Jr. Foundation, Give Breast Cancer the Boot, and the Breast Cancer Research Foundation. Sincere thanks to all the patients and our patient advocates who volunteered to participate in the I-SPY trials.