

Intratumoral heterogeneity of primary breast cancer on ^{18}F -FES PET/CT and dbPET anticipated a heterogeneous response to chemotherapy

Yurika Kitano, MD¹⁾, Kanae K. Miyake, MD, PhD²⁾, Yoichi Shimizu, PhD¹⁾, Masahiro Kawashima, MD, PhD³⁾, Yuji Nakamoto, MD, PhD¹⁾

Affiliations:

- 1) Department of Diagnostic Imaging and Nuclear Medicine, Graduate School of Medicine Kyoto University, Kyoto, Japan
- 2) Department of Advanced Imaging in Medical Magnetic Resonance, Graduate School of Medicine Kyoto University, Kyoto, Japan
- 3) Department of Breast Surgery, Graduate School of Medicine Kyoto University, Kyoto, Japan

Corresponding author: Kanae K. Miyake, MD, PhD

Department of Advanced Imaging in Medical Magnetic Resonance, Graduate School of Medicine Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto-city, Kyoto, 606-8507, Japan

E-mail address: kanaek@kuhp.kyoto-u.ac.jp

Phone. +81-75-751-3760 Fax. +81-75-771-9709

Short title: ^{18}F -FES PET/CT and dbPET findings of intratumor heterogeneity.

Disclosure: Supported by Japanese Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research (19K17196)

CNM Interesting Image

Intratumoral heterogeneity of primary breast cancer on ^{18}F -FES PET/CT and dbPET anticipated a heterogeneous response to chemotherapy

Abstract:

A 59-year-old woman with cT3N3M1 invasive breast cancer (ER low positive, PgR positive, HER2 negative) underwent PET/CT and dedicated breast PET (dbPET) scans using ^{18}F -fluorodeoxyglucose (^{18}F -FDG) and ^{18}F -fluoroestradiol (^{18}F -FES). While most primary tumor regions displayed low FES uptake, regions of high FES uptake were also identified. Following chemotherapy with the paclitaxel and bevacizumab, ^{18}F -FDG PET/CT demonstrated a favorable response, but residual disease was noted in areas with high FES uptake on the pre-treatment images. This case illustrated that ^{18}F -FES PET can depict intratumoral heterogeneity within the primary tumor, which was strongly associated with a heterogeneous response to subsequent chemotherapy. (99/100 words)

Key Words: breast cancer, ^{18}F -FDG, ^{18}F -FES, PET/CT, dbPET, intratumoral heterogeneity.

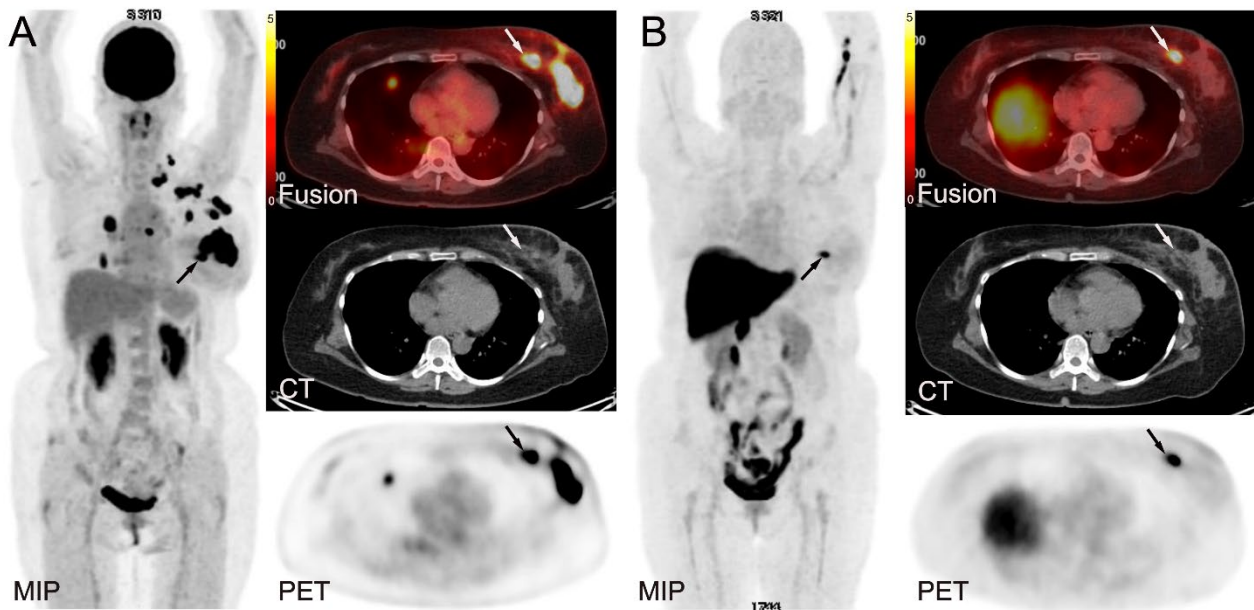


Figure 1.

A 59-year-old woman with invasive breast cancer (no special type, grade 3, estrogen receptor [ER] 10%, progesterone receptor [PgR] focal 20%, HER2 negative, Ki-67 44%, cT4N3M1, Stage IV). Pre-treatment ^{18}F -FDG PET/CT (**A**) depicted intense uptake in the large primary tumor of the left upper breast. Metastases in the left cervical, supraclavicular, levels 1-3 axillary, parasternal lymph nodes, and bilateral lung regions also exhibited uniform FDG avidity. In contrast, pre-treatment ^{18}F -fluoroestradiol (^{18}F -FES) PET/CT (**B**) revealed intense uptake only in small portions of the primary tumor (**arrows**), with most of the tumors appearing FES-negative.

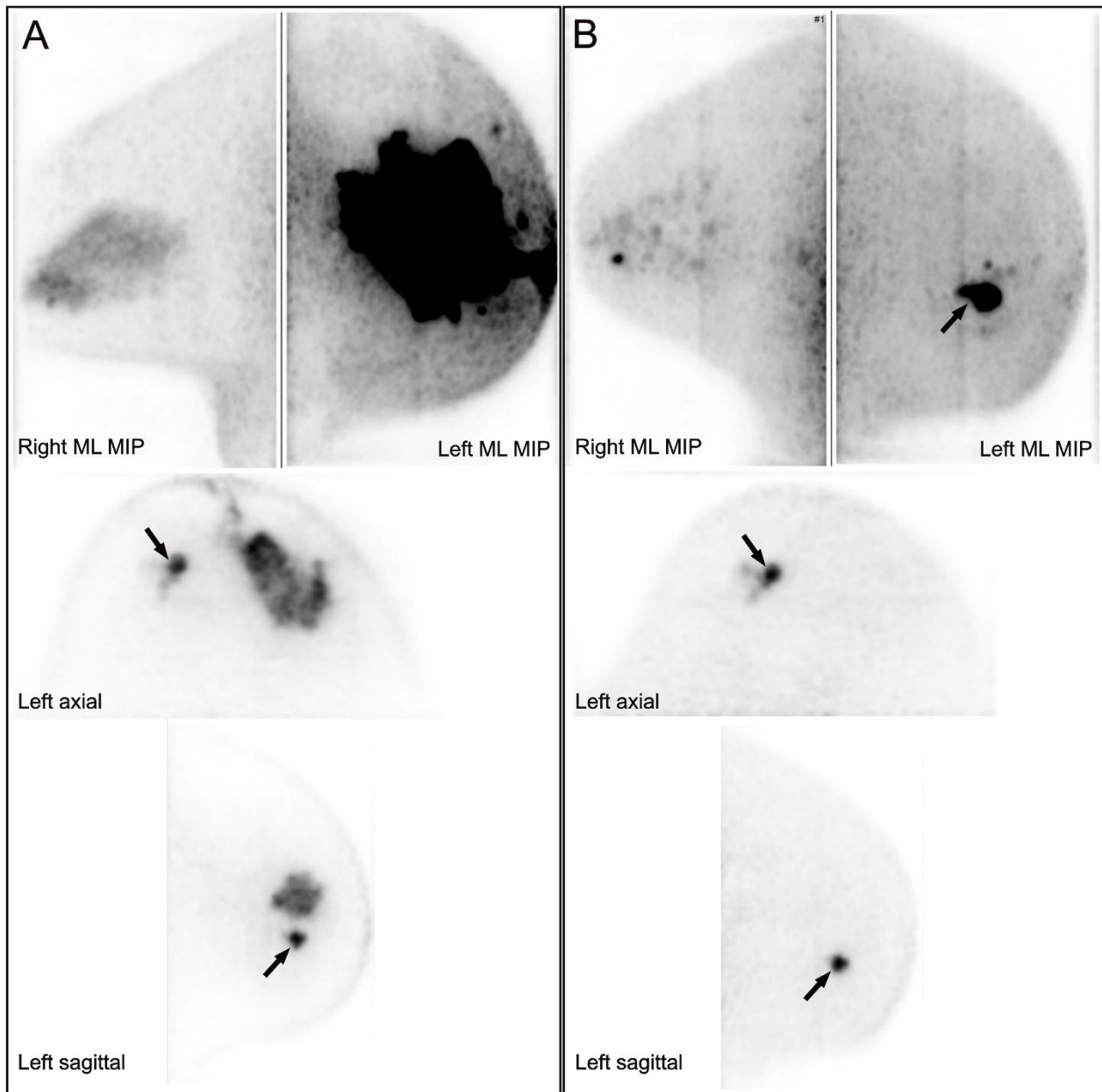


Figure 2.

Pre-treatment dedicated breast PET (dbPET) was performed using ^{18}F -FDG (A) and ^{18}F -FES (B). The ^{18}F -FDG dbPET demonstrated a large, irregular, multinodular mass with increased uptake in the left breast (SUVmax, 48.6). On the ^{18}F -FES dbPET, part of the tumor exhibited hyperintense uptake (SUVmax, 8.9) (arrows).

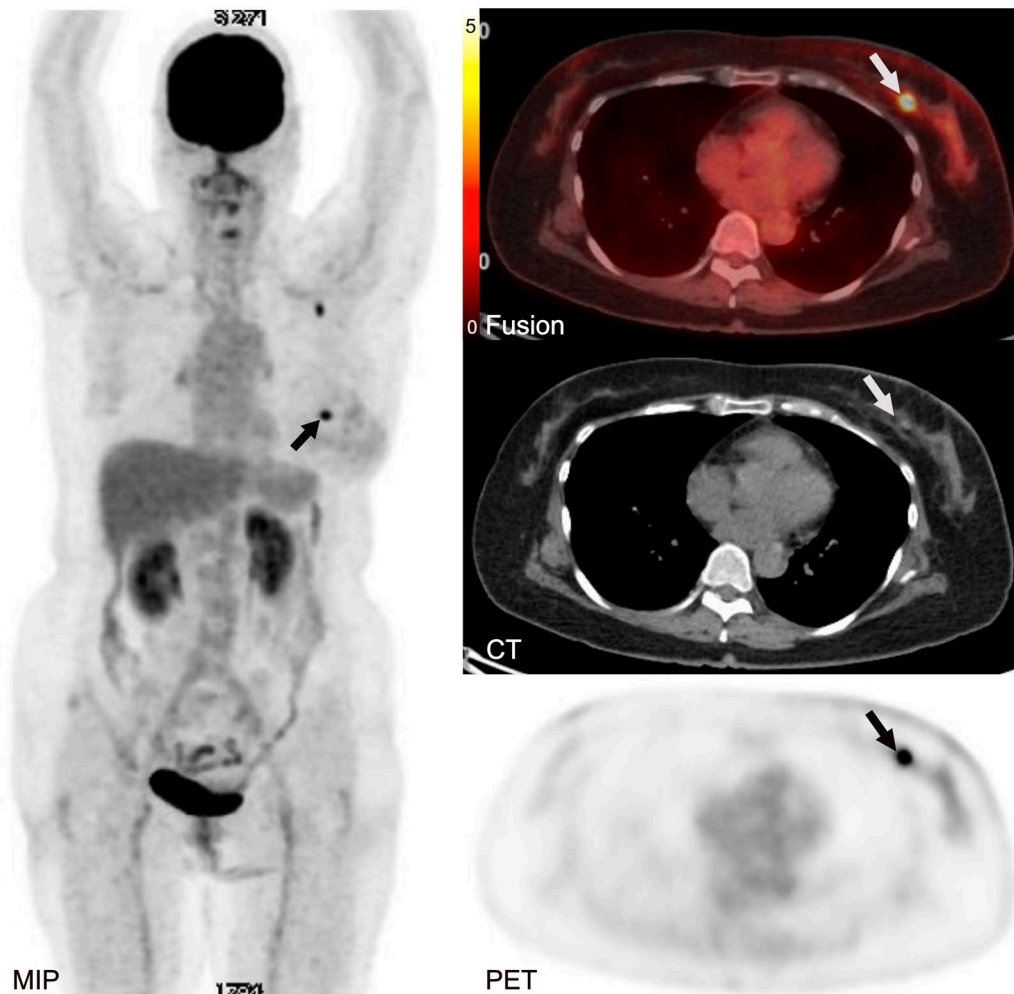


Figure 3.

Post-chemotherapy (paclitaxel and bevacizumab) ^{18}F -FDG PET/CT demonstrated a reduction in the primary tumor, lymph node metastases (except for a portion of the left axillary nodes), and lung metastases, suggesting an effective treatment response. However, a residual component exhibited hyperaccumulation on pre-treatment ^{18}F -FES images (**arrows**). The patient's treatment regimen was subsequently modified to include hormone therapy, a CDK4/6 inhibitor, and denosumab, but the disease progressed. The patient succumbed to the disease after one year and nine months.

ER status is crucial for predicting prognosis and treatment response in patients with breast cancer [1, 2]. High ER expression typically correlates with a favorable response to endocrine therapy and reduced efficacy of chemotherapy [3]. Immunohistochemistry on biopsy samples is used to assess pre-treatment ER status for treatment planning, but has limitations [4]. Biopsy samples represent a small portion of the tumor,

may not adequately represent the entire tumor's ER status. Breast cancer can exhibit intratumoral heterogeneity with diverse molecular subtypes [5]. Discrepancies in ER positivity between biopsy and surgical specimens occur in 5–11% of cases [5, 6]. Additionally, recent studies using next-generation sequencing have revealed genetic heterogeneity within breast cancers [7-9], with some reports indicating that approximately 38% of primary tumors demonstrating intratumoral genetic diversity [10].

¹⁸F-FES PET, an ER-targeted radiopharmaceutical, offers a non-invasive method to assess in vivo estrogen delivery, binding, and ER expression throughout the tumor and body [11-13]. While several reports have examined heterogeneity in primary and metastatic tumors using ¹⁸F-FES PET [14, 15], evidence on intratumor heterogeneity is limited. Yang *et al.* proposed using SUVmax/SUVmean on ¹⁸F-FES PET as a practical index for intratumoral heterogeneity [16]. Understanding intratumoral biomarker heterogeneity is crucial for identifying treatment-resistant populations and improving outcomes. Our case illustrated that ¹⁸F-FES PET can depict intratumoral heterogeneity, which may serve as a marker to predict a heterogeneous response to systemic therapy.

(442/500 words)

References:

1. Dowsett M, Forbes J, Bradley R, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386:1341-1352.
2. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;387:771-784.
3. Tamirisa N, Hunt K. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. *Ann Surg Oncol*. 2022;29:1489-1492.
4. Fisher E, Anderson S, Dean S, et al. Solving the dilemma of the immunohistochemical and other methods used for scoring estrogen receptor and progesterone receptor in patients with invasive breast carcinoma. *Cancer*. 2005;103:164-173.

5. Greer L, Rosman M, Mylander W, et al. Does breast tumor heterogeneity necessitate further immunohistochemical staining on surgical specimens? *J Am Coll Surg*. 2013;216:239-251.
6. Usami S, Moriya T, Amari M, et al. Reliability of prognostic factors in breast carcinoma determined by core needle biopsy. *Jpn J Clin Oncol*. 2007;37:250-255.
7. Martelotto LG, Ng CK, Piscuoglio S, et al. Breast cancer intra-tumor heterogeneity. *Breast Cancer Res*. 2014;16:210.
8. Zardavas D, Irrthum A, Swanton C, et al. Clinical management of breast cancer heterogeneity. *Nat Rev Clin Oncol*. 2015;12:381-394.
9. Rivenbark AG, O'Connor SM, Coleman WB. Molecular and cellular heterogeneity in breast cancer: challenges for personalized medicine. *Am J Pathol*. 2013;183:1113-1124.
10. Navin N, Krasnitz A, Rodgers L, et al. Inferring tumor progression from genomic heterogeneity. *Genome Res*. 2010;20:68-80.
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. 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.
14. Yang Z, Sun Y, Zhang Y, et al. Can fluorine-18 fluoroestradiol positron emission tomography-computed tomography demonstrate the heterogeneity of breast cancer in vivo? *Clin Breast Cancer*. 2013;13:359-363.
15. Liu C, Hu S, Xu X, et al. Evaluation of tumour heterogeneity by 18F-fluoroestradiol PET as a predictive measure in breast cancer patients receiving palbociclib combined with endocrine treatment. *Breast Cancer Res*. 2022;24(1):57.
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.