PET Imaging of ER and PR Receptors in Breast Cancer: New Insight

In breast cancer (BC) steroid hormone receptors like Estrogen Receptor (ER) and Progesterone Receptor (PR) are the established prognostic and predictive markers. These receptors act as ligand-activated nuclear transcription factor which regulate the gene expression.[1] ER and PR are expressed in about 75% of BC and their presence is used to predict prognosis and therapeutic response.[2] However, 15% of BC lack ER-α and PR (some with negative Human Epidermal Growth Factor type 2 receptor [HER-2] - triple negative cancer) with a dismal prognosis.[3,4] ER-α is the most important member of nuclear receptors that controls the replication or apoptotic death of selected populations of breast cancer cells. PR is an estrogen-regulated protein in breast cancer and present in 50-60% of ER-a positive and predicts hormone dependence of metastatic breast cancer.[5] All effective anti-hormonal agents like tamoxifen, fulvestrant and aromatase inhibitors act upon ER signal transduction pathway and prevent estrogen action in the tumor cell. Studies have shown that tumors expressing both receptors tend to be less aggressive and least likely to metastasize.[3] Compared to ERα+/PR+ patients, a smaller percentage of ERα+/PR-breast cancer patients respond to tamoxifen treatment, suggesting that PR plays an important role in endocrine therapy response.[7] Currently immuno-histochemistry remains the standard method for detecting ER-α and PR status although it is prone to sampling error from tissue biopsy.[8] Furthermore, not all metastatic sites are approachable to biopsy and variable receptor expression across disease sites within a patient during or after course of therapy.[8]

In current molecular imaging era, various ER-α and PR specific ligands labeled with positron emitters using PET/CT has provided a better insight for non-invasive assessment of ER and PR. This PET/CT based information could potentially guide oncologists about treatment strategy based on the presence and functionality of ER-α as a drug target. PET based ER-α and PR imaging can also provide longitudinal information regarding ER-α and PR status, which can change during course of treatment.[8]

For ER-α imaging ^{18}Flourine labelled 17 -estradiol (^{18}F-flouroestradiol) which binds to ER receptors in target cells. This was introduced by the University of Washington and University of Illinois and published trials[9,10] have shown (1) correlation between in-vitro ER-α assays and ^{18}F-fluoroestradiol uptake (Positive percentage agreement 76.6%; Negative percentage agreement was 100%); (2) heterogeneity of ER-α expression (28-45% patients have both (^{18}F-flouroestradiol positive and negative lesions); (3) dosing of ER-α antagonist for maximizing ER suppression and minimizing side effects; (4) predictive value for therapy response (patients with lower ^{18}F-flouroestradiol on baseline PET/CT indicate non-functional ER and neo-adjuvant chemotherapy could be superior to endocrine therapy while in patients with higher ^{18}F-flouroestradiol uptake endocrine therapy could be better than chemotherapy); (5) and also prognostic significance (high ^{18}FDG and high ^{18}F-flouroestradiol uptake favor better progression free survival while high 18FDG uptake and lower ^{18}F-flouroestradiol uptake favor shortest progression free survival).[8] However, currently ^{18}F-flouroestradiol imaging is clinically approved in France for determination of ER-a status in metastatic breast cancer for selection of endocrine therapy.[8]

PR is an estrogen-regulated target gene and can be an indicator of ER-α functionality. Therefore, when antagonists inhibit ER-α function, PR messenger RNA and protein decrease. The most studied PET tracer is ^{18}F labeled Fluorofuranyl norprogesterone (^{18}F-FFNP), a progestin analog which binds to PR receptor on target cell.[8] This was developed by the University of Washington and University of Illinois and first published clinical study revealed its safety and feasibility for human use.[11] Few preclinical studies have shown that decline in ^{18}F-FFNP after initiation of estrogen deprivation therapy in metastatic breast cancer indicates its importance as early biomarker for endocrine therapy response.[12,13]

Submitted 10 September 2020, Accepted 23 September 2020

In breast cancer steroid receptors (ER-α and PR) are important markers for predicting prognosis and response to therapy. Immunohistochemistry based methods for ER and PR detection are prone to sampling error, accessibility of lesion for biopsy and non-homogeneity in ER-a and PR expression in same patient. PET based imaging of these receptors (^{18}F-flouroestradiol and 18F labeled Fluorofuranyl norprogesterone) provides better insight for non-invasive assessment of ER-α and PR receptors and also longitudinal information about their status during therapy phase. Furthermore, clinical and preclinical studies have shown their potential role in selecting therapeutic strategies and therapy response.

Conflict of Interest: Declared none.

REFERENCE:

1. Beato M, Klug J. Steroid hormone receptors: an update. Hum Reprod Update. 2000; **6(3):** 225-36.

2. American Cancer Society. Cancer facts & figures 2016. Atlanta American Cancer Society; 2016.

3. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res. 2007; **9(1):** R6.

4. Pichon MF, Pallud C, Brunet M, Milgrom E. Relationship of presence of progesterone receptors to prognosis in early breast cancer. Cancer Res. 1980; **40(9):** 3357-60.

5. Carroll JS, Brown M. Estrogen receptor target gene: an evolving concept. Mol Endocrinol. 2006 **20(8):** 1707-14.

6. Maggie CL, Mary BS. Steroid hormone receptors as prognostic markers in breast cancer. Am J Cancer Res. 2017; **7(8):** 1617-36.

7. Bardou VJ, Arpino G, Elledge RM, Osborne CK, Clark GM. Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. J Clin Oncol. 2003; **21(10):** 1973-9.

8. Manoj K, Kelley S, Amye J. Tevaarwerk, Roberta MS, Amy MF. Recent Advances in Imaging Steroid Hormone Receptors in Breast Cancer. J Nucl Med 2020; **61:** 172-76.

9. Allott L, Smith G, Aboagye EO, Carroll L. PET imaging of steroid hormone receptor expression. Mol Imaging. 2015; **14:** 534-50.

10. Linden HM, Peterson LM, Fowler AM. Clinical potential of estrogen and progesterone receptor imaging. PET Clin. 2018; **13:** 415-22.

11. Dehdashti F, Laforest R, Gao F. Rebecca LA, Carmen SD, Dong Zhou, et al. Assessment of progesterone receptors in breast carcinoma by PET with 21-18F-fluoro-16a,17a-[(R)-(19-a-furylmethylidene) dioxy]-19-norpregn-4-ene-3,20-dione. J Nucl Med. 2012; **53:** 363-70.

12. Salem K, Kumar M, Yan Y, Justin JF, Kyle CK, Ciara JM, et al. Sensitivity and isoform specificity of 18Ffluorofuranylnorprogesterone for measuring progesterone receptor protein response to estradiol challenge in breast cancer. J Nucl Med. 2019; **60:** 220-6.

13. Chan SR, Fowler AM, Allen JA, Dong Z, Carmen SD, Dence, TL, et al. Longitudinal noninvasive imaging of progesterone receptor as a predictive biomarker of tumor responsiveness to estrogen deprivation therapy. Clin Cancer Res. 2015; **21:** 1063-70.

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