Imaging agents predict breast cancer response to endocrine therapy

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Research published in the July issue of *The Journal of Nuclear Medicine* shows imaging progesterone receptor (PR) status also may be able to identify responders and nonresponders to endocrine therapy at an early stage. Estrogen receptor-α (ERα) status is an important factor in determining the most appropriate treatment for breast cancer patients, especially for those who are ERα+ and likely to respond well to hormone-based, or endocrine, therapies.

Prominent professor and research chemist Michael J. Welch, PhD, who passed away in May, was a contributing author for this research. "Throughout his career, Dr. Welch specialized in the synthesis of new radiolabeled compounds for medical imaging, with a special emphasis on the growing numbers of applications in PET," said Dominique Delbeke, MD, PhD, editor of The Journal of Nuclear Medicine. Noted for his ability to see beyond the immediate aspects of basic work to potential future applications, Welch was both a prime mover and an integral part in the development of PET as it transitioned from a compelling investigative idea to widespread clinical acceptance. "Many of his discoveries and research will live on well into the future," said Delbeke.

The study, "Small-Animal PET of Steroid Hormone Receptors Predicts Tumor Response to Endocrine Therapy Using a Preclinical Model of Breast Cancer" was an example of his unique approach to research.

"Positron emission tomography, or PET, has typically been used to identify the target for endocrine therapy in breast cancer by

demonstrating that ER is present in tumors using F-18-fluoroestradiol (FES)-PET, or by monitoring for hormone-induced changes in tumor metabolism—'metabolic flare'— with F-18-fluorodeoxyglucose (FDG)-PET once therapy has begun. What is novel about our study is that we chose to image progesterone receptor levels to see how the estrogen signaling pathway is functioning in response to endocrine therapy," said Amy Fowler, MD, PhD, lead author of the study.

In the study, mice with mammary cell lines (SSM1, SSM2 and SSM3) derived from STAT1-deficient mammary tumors—which are ERα+/PR+ and similar to the majority of human breast cancers—were imaged. Small-animal PET/computed tomography (CT) was performed using F-18-FES to image estrogen receptor status, F-18-fluoro furanyl norprogesterone (F-18-FFNP) for progesterone receptor status, and FDG for glucose uptake.

Initial imaging of the cell lines showed that SSM3 tumors displayed the greatest F-18-FES and F-18-FFNP uptake, and therefore, the SSM3 cell line was used to test the response to estradiol, an ER agonist, and fulvestrant, a pure ER antagonist. Upon treatment with estradiol, it was determined that PR expression is estrogen-inducible and indicative of ERα signaling in the SSM3 tumors. Mice treated with fulvestrant showed early decreases in F-18-FFNP uptake after initiation of therapy, prior to measurable growth inhibition. SSM2 tumors, which were not growth-inhibited by fulvestrant despite also being ERα+/PR+, showed no change in F-18-FFNP uptake after initiation of therapy. These data support the potential use of PR imaging with F-18-FFNP PET of patients with ERα+ breast cancer at baseline and shortly after initiation of endocrine therapy to distinguish between responders and nonresponders, and thus help facilitate the selection of therapies most appropriate for individual patients.

"An important goal of molecular imaging in cancer research is to

noninvasively predict early responses to therapies in order to guide further management," noted Fowler. "Our work using a preclinical model of breast cancer helps support the notion that molecular imaging can achieve this goal by testing whether the target utilized for a specific therapy is not only present but also functional."

An estimated one in eight women will develop breast cancer in her lifetime. According to the American Cancer Society, an estimated 280,000 new cases of breast cancer were diagnosed among women in 2011, and nearly 40,000 died from the disease.

More information: "Small-Animal PET of Steroid Hormone Receptors Predicts Tumor Response to Endocrine Therapy Using a Preclinical Model of Breast Cancer," The *Journal of Nuclear Medicine*. jnm.snmjournals.org/

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