ER imaging for estrogen-related tumors is bothersome but useful.

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Recent development of molecular imaging (MI) methods has greatly contributed to the field of clinical nuclear medicine in terms of personalized cancer therapy as well as appropriate diagnosis of various diseases. Theranostics, the combination of therapy and diagnosis, is now not just a concept, but a fusion of biological diagnosis and its therapeutic application aiming at the goal of MI oncology. The basics of theranostics is to elucidate specific biological events or phenomena using molecular probes developed by MI technology. Conventional methods of assessing glucose metabolism and perfusion can be used to delineate the features of alteration in energy metabolism and blood flow; however, these are the results of pathophysiologic alterations caused by various diseases. Because the targets of MI are disease-specific biomarkers and phenotypic changes, the images delineate pathologic features of the disease. Imaging of amyloid and tau for diagnosis of Alzheimer's disease is a good example of molecular imaging for pathogenic substances. Prostate specific membrane antigen (PSMA) imaging and nuclear medicine therapy, a representative example of radiotheranostics, is now available in many hospitals and cancer centers for treatment of prostate cancer.

Estrogen receptor (ER) imaging, used for breast cancer and uterine tumors, is also a good example of molecular imaging which can well delineate features of cancers. In the breast cancer studies, ER expression in cancer is important information not only for diagnosis, but also for determining the suitability of hormone therapy (1). Conventional CT and MRI diagnosis can detect the size of lymph nodes, and [18F]fluorodeoxy glucose (FDG) PET can delineate glucose avidity of tumors and metastatic lesions, however, these images cannot differentiate lymph node metastases from reactive lymphadenopathy. 16α-[18F]-fluoro-17β-estradiol (FES) is a representative PET ligand for ER imaging and has been applied for decades in the diagnosis of breast cancers (2). Many studies have shown the usefulness of [18F]FES PET, and its accumulation correlated well with ER expression in tumor tissue (2-4). [18F]FES accumulation in enlarged lymph nodes indicates the presence of ER, i.e. metastatic lesions from an ER positive breast cancer, which improves the diagnostic ability in terms of staging of breast cancer. [18F]FES has a 6.3-fold absolute affinity preference for ERα over ERβ (5), which is important information to estimate the prognosis of ER-related malignancies.

[18F]FES PET is also very useful in diagnosis of uterine tumors such as endometrial cancer and leiomyosarcomas (4,6). Previous studies have shown its beneficial application for differential diagnosis as well as prediction of prognosis (3,4,6). Since [18F]FES accumulation correlates well with ER expression in endometrial cancer and sarcoma (3,4), SUV values can detect ER density in tumors. However, ER expression tends to be decreased in malignant tumors (4,6), and accumulation of [18F]FES alone cannot improve diagnostic ability of malignancies because negative accumulation cannot distinguish between normal tissue and high-grade malignancy. Since this tendency is the same as for metastatic lesions, diagnostic ability of [18F]FES PET for metastasis is not so sufficient. Furthermore, in the endometrial tissue of a normal uterus, substantial [18F]FES accumulation is observed in premenopausal women, and the intensity of accumulation varies according to menstrual cycles (7). Therefore, [18F]FES PET scans in premenopausal patients should be performed during the secretory phase of the menstrual cycle to minimize the effect of normal endometrial uptake (8). Another problem with [18F]FES PET in abdominal to pelvic scanning is the excretion of the tracer to the intestine. The tracer shows high accumulation in the liver where [18F]FES is metabolized and excreted into the bile ducts. PET scans are usually performed about 60 min after the tracer injection, as is the case with FDG PET scans. During this waiting time, [18F]FES is metabolized

and excreted into the intestine. Patients often show a strong intestinal accumulation of [^{18}F]FES due to excretion of metabolites which may sometimes prevent observation of abdominal and pelvic lesions. This [^{18}F]FES accumulation in the abdomen and pelvic cavity has made it difficult to apply the useful tracer to gynecologic tumors. However, in previous [^{18}F]FES PET studies for these tumors, scans were performed after a substantial fasting time, and clear images were obtained in the pelvic regions (3,4,6,8). The combination of FDG and [^{18}F]FES PET can provide useful information for evaluation of prognosis (8,9). In clinical practice, additional MRI scanning is essential to delineate features of the primary tumor (10), because it is difficult to make a correct radiological diagnosis of gynecologic tumors based on PET/CT findings alone.

In order to improve image quality and contrast for assessment of ER expression, a new PET ligand, 4-fluoro-11β-methoxy-16α-^{18}F-fluoroestradiol ([^{18}F]4FMFES), has been developed as a homolog of [^{18}F]FES and applied to diagnosis of breast cancer (11). Paquette, et al. compared [^{18}F]FES and [^{18}F]4FMFES PET images directly in a phase II clinical trial study for breast cancer, and found that SUV_{max} values were similar and image quality was better with [^{18}F]4FMFES PET than with [^{18}F]FES PET. Due to the improved tumor-to-background ratio with the new tracer, the image contrast has been improved compared with the conventional one. Therefore, the new tracer seemed to be promising for diagnosis of ER expression of breast cancer. They also applied [^{18}F]4FMFES PET to endometrial cancer of the uterus and assessed its diagnostic ability in comparison with FDG PET (12). After tumor biopsy, patients with ERα positive endometrial cancer were enrolled in the study and underwent FDG and [^{18}F]4FMFES PET within an interval of less than two weeks. They compared the diagnostic performance between [^{18}F]4FMFES and FDG PET. Since high-grade endometrial cancers tend to reduce or lose ERα expression (3,6), the diagnostic performance of FES/4FMFES PET alone is not expected to be superior to that of FDG PET. However, SUV values as well as diagnostic performance were preserved or surpassed in this study because they only enrolled the ERα+ cancers after tumor biopsy. If PET scans are performed without tumor biopsy, the FDG/4FMFES ratio would be the most sensitive parameter to determine the grade and prognostic value of the tumor (6,8,9,12). They added an evaluation of the effects of loperamide/butylbromide administration prior to tracer administration to reduce tracer excretion to the intestine. In the study of gynecologic tumors, the intense abdominal uptake may affect the diagnosis of uterine tumors including metastatic lesions as mentioned above. Taking a substantial fasting period before scanning may be a more effective and less invasive method for better image quality than administration of anti-motility medicine. The timing of the scan should also be chosen appropriately according to the patient's menstrual cycle so as to minimize the normal endometrial uptake which may disturb discrimination between normal tissue and cancer. Since breast cancer and gynecologic tumors have different features, the study protocol should be determined in accordance with the tumor characteristics. [^{18}F]4FMFES PET has shown good image quality in breast cancer studies, and it would be promising for uterine cancer/sarcoma studies with proper preparation and scanning protocols using PET/CT + MRI or PET/MRI. Information on the ERα expression is essential for application of hormonal therapy aimed at theranostics.

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