Journal of Biosciences and Medicines, 2024, 12, 105-114
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

^{18}F-FES PET/CT Research Progress in the Diagnosis and Treatment of Breast Cancer

Jiahang He, Hua Pang

Department of Nuclear Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: phua1973@163.com

How to cite this paper: He, J.H. and Pang, H. (2024) ^{18}F-FES PET/CT Research Progress in the Diagnosis and Treatment of Breast Cancer. *Journal of Biosciences and Medicines*, **12**, 105-114.
https://doi.org/10.4236/jbm.2024.121010

Received: December 14, 2023
Accepted: January 16, 2024
Published: January 19, 2024

Abstract

Estrogen receptor(ER) is a vital biomarker in the development and development of breast cancer, and its status has great clinical value in clinical treatment strategy, endocrine therapy efficacy prediction, and breast cancer prognosis. By specifically combining ^{18}F-FES with ER, ^{18}F-FES PET/CT imaging uses standard uptake value(SUV) to semi-quantitatively reflect the distribution of ER and its biological activity in patients, and assesses the expression of ER in breast cancer patients about primary and metastases before or after treatment, to provide a basis for personalized treatment of breast cancer. In this review, we will review the imaging principles of a new ER detection method ^{18}F-FES PET/CT, and the research progress in the clinical application of breast cancer, and compare its diagnostic and treatment value with non-specific tumor imaging ^{18}F-FDG PET/CT in breast cancer.

Keywords

^{18}F-FES, ^{18}F-FDG, PET/CT, Breast Cancer, ER

1. Introduction

Breast cancer is the most common cancer in women. According to the statistics of the World Health Organization, among the global new tumor cases in 2020, the number of breast cancer cases is 2.26 million, accounting for 11.7% of the total number of new tumors in the world. It has surpassed lung cancer (11.4%) to become the malignant tumor with the highest incidence in women [1]. Breast cancer is a hormone-dependent tumor. About 70% of breast cancer patients are positive for ER [2]. The treatments for breast cancer include surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, immunotherapy, etc., among which endocrine therapy is widely used because of its definite curative effect, low toxicity and low price [3]. According to the guidelines and norms for

breast cancer diagnosis and treatment of China Anti-Cancer Association (2021), breast cancer patients with positive ER and/or progesterone receptor (PR) should receive postoperative adjuvant endocrine therapy. So most breast cancer patients in China need endocrine therapy [4]. In terms of molecular mechanism, the expression activity of ER can regulate the expression of PR, and the endocrine therapeutic drugs used in clinic also take ER as the main therapeutic target [5]. Therefore, the expression status and expression rate of ER have become the most important factors affecting the efficacy of endocrine therapy for breast cancer. Thus it can be seen that the detection method and accuracy of ER are very important.

At present, the routine method of ER detection is puncture biopsy and immunohistochemistry (IHC). Its advantage is that a single biopsy can obtain multiple molecular phenotypes and provide multiple supporting information for treatment decision-making, but it also has some limitations: 1) Breast cancer is heterogeneous. About 20% to 35% of patients with metastatic breast cancer have phenotypic changes [6]. The puncture results can only reflect the pathological condition of a single lesion. 2) During the treatment, the epitope may be lost in the focus [7]. Therefore, it is necessary to dynamically evaluate the expression of ER, but it is difficult to achieve repeated biopsy in clinic. 3) Puncture biopsy is an invasive examination method, the tolerance of patients is poor, and affected by the location and size of the focus, it may be difficult to biopsy. 4) There may be some deviation in reflecting the true pathophysiological state of the focus due to sampling error, decalcification treatment and other factors. Therefore, we urgently need a new detection method to evaluate the expression of ER in patients more accurately, omni-directionally and dynamically. This article will describe the imaging principle of the new non-invasive ER detection method ^{18}F-FESPET/CT, and focus on its research progress in the diagnosis and treatment of breast cancer, and compare the value of ^{18}F-FESPET/CT and ^{18}F-FDGPET/CT in the diagnosis and treatment of breast cancer.

2. Imaging Principle of ^{18}F-FES PET/CT

^{18}F-FES is an estrogenic derivative, which is obtained by replacing the 16 α H of estradiol with ^{18}F. Fluorine is a small halogen, and its spatial structure and chemical properties will not be significantly changed after replacing H, so ^{18}F-FES has structural characteristics similar to estrogen and can specifically bind to ER. The metabolism and excretion pathway of ^{18}F-FES is also similar to that of estrogen. After being injected into the body, it is quickly absorbed by the liver and metabolized in a short time. The blood clearance rate is fast, about the stable level of 20 min - 30 min, and the background is basically stable after 30 min. The metabolites in the blood circulation cannot be combined with ER directly or indirectly, so it has little interference to the imaging. Metabolites are mainly eliminated through the kidney, some of them can enter the intestine with bile, excreted from feces, and a small amount can be reabsorbed through hepa-

tointestinal circulation. Therefore, its physiological uptake is mainly concentrated in the liver, kidney, bladder and intestinal tract [2] [8]. Radiation dose studies show that the organ dose of ^{18}F-FES PET is similar to that of other commonly used nuclear studies, and the potential radiation risk is within an acceptable range. The recommended injection dose is 6 mci or less [9] [10].

3. Research Progress of ^{18}F-FES PET/CT in Clinical Application of Breast Cancer

At present, ^{18}F-FES is the most widely used ER targeting probe. Non-invasive detection of ER expression in the whole body can be realized by ^{18}F-FES PET/CT, which provides a new basis for diagnosis, staging and curative effect prediction of breast cancer, and brings epoch-making significance for endocrine therapy of breast cancer [11].

3.1. The Value of ^{18}F-FES PET/CT in the Diagnosis of Breast Cancer

^{18}F-FES is a specific tracer for ER, while ER is highly expressed in 70% invasive breast cancer. Therefore, we can diagnose breast cancer by detecting ER [12]. In 2019, Sun Young Chae *et al.* verified the accuracy and safety of ^{18}F-FES PET/CT in evaluating the status of estrogen receptor in recurrent or metastatic breast cancer [13]. In 2021, Jin A Mo statistically analyzed the data of 7 studies. The comprehensive sensitivity and specificity of ^{18}F-FES PET in the diagnosis of ER+ breast cancer were 0.86 and 0.85 respectively [14]. As for false negative patients, they are usually patients with low expression of ER [13]. In this part of patients, due to the low expression of ER in the lesions, the radioactive intensity produced by binding with ^{18}F-FES will be lower, so false negative can be seen in ^{18}F-FES PET/CT imaging. It also shows that IHC is more sensitive than ^{18}F-FES PET/CT in detecting ER. Although the pathophysiological status of patients with low expression of ER is similar to that of patients with negative ER, endocrine therapy is still recommended [4]. Therefore, there may be blind spots in these patients with ^{18}F-FES PET/CT. The false positive patients account for relatively few benign lesions, such as breast fibroadenoma [15]. And as a specific imaging agent, ^{18}F-FES imaging can help identify the second primary tumor [16] [17]. And guide the treatment plan [18]. It is worth mentioning that ^{18}F-FES is a specific imaging agent for ER rather than breast cancer, so other estrogen-dependent tumors such as endometrial cancer and ovarian cancer should be excluded when used in breast cancer [19] [20]. Generally speaking, ^{18}F-FES PET/CT is a safe and reliable non-invasive *in vivo* ER detection method, which can provide omni-directional information about the distribution, density and activity of ER+ cancer cells in breast cancer foci. It is expected to fully reflect the expression of ER in breast cancer patients and provide help for the formulation of clinical individualized treatment. However, this imaging cannot recognize and distinguish ER− breast cancer and ER+ benign lesions, so there are still some shortcomings in the diagnosis of breast space occupying lesions alone.

3.2. Prediction of Therapeutic Effect of ^{18}F-FES PET/CT on Endocrine Therapy for Breast Cancer

The prediction of curative effect and the evaluation of prognosis are the key factors in deciding the treatment plan in clinical treatment, and the expression of ER is undoubtedly an important predictor for endocrine therapy of breast cancer. Therefore, as a targeted probe of ER, ^{18}F-FES PET/CT plays an important role in predicting the efficacy and prognosis of endocrine therapy for breast cancer. For patients with high expression of ER, endocrine therapy is often effective [21]. The high expression of ER on ^{18}F-FES PET/CT is mainly reflected by the increased radiouptake, that is, the SUVmax value of the foci. Therefore, we can predict the efficacy and prognosis of endocrine therapy by the SUVmax value of early ^{18}F-FES PET/CT imaging in patients [22] [23]. ER is not only the main target of endocrine therapy, but also the marker of hormone-dependent tumor cells. When the drug takes effect, it can lead to the decrease of physiological activity ER, so we can also compare the change of SUVmax value between baseline scan and treatment for a short time, that is, ΔSUVmax, to achieve the role of early efficacy evaluation and prognosis evaluation [24]. In addition to endocrine therapy, some scholars have also explored the role of ^{18}F-FES PET/CT in predicting the efficacy of neoadjuvant chemotherapy. Although ^{18}F-FESPET/CT is not directly related to the prediction of the efficacy of neoadjuvant chemotherapy, the results show that, contrary to endocrine therapy, patients with lower ^{18}F-FES SUVmax are more likely to benefit from neoadjuvant chemotherapy [25]. The study also found that patients with positive pathological ER but negative ^{18}F-FES PET/CT imaging were more likely to benefit from neoadjuvant chemotherapy than neoadjuvant endocrine therapy [26]. In other words, the effect of endocrine therapy in patients with low expression of ER is not as effective as that of adjuvant chemotherapy, which is consistent with previous studies. However, ^{18}F-FES PET/CT is not perfect, it cannot identify mutant ER, and gene mutation may cause endocrine drug resistance [27] [28] [29].

3.3. ^{18}F-FES PET/CT as a Pharmacodynamic Biomarker of Endocrine Therapy for Breast Cancer

ER is the main target of endocrine therapy for breast cancer. As a targeted probe of ER, ^{18}F-FES PET/CT plays an auxiliary role in the research and development of drugs targeting ER. First of all, for ER antagonists, when the drug acts on the focus, it can lead to the decrease of ER with physiologically active function, the metabolic activity decreases and the SUVmax value decreases on ^{18}F-FES PET/CT. Therefore, the time, intensity and scope of action of the drug can be directly reflected by ^{18}F-FESPET/CT [30]. Through the imaging of patients taking different doses of drugs, we can select the best treatment dose of drugs, so that patients can achieve the best treatment effect while minimizing the side effects caused by excessive drugs. For other types of agents, such as aromatase inhibitors and cyclin inhibitors, the drugs do not act directly on ER, so they cannot

achieve the effect of immediate imaging, but when the drugs take effect for a period of time, the pathophysiological changes of tumor cells can also be shown in ^{18}F-FES PET/CT. In summary, ^{18}F-FESPET imaging can be used as a biomarker of pharmacodynamics of ER-oriented drugs, which can show the performance of drugs reaching the target or taking effect in time, and provide an important basis for drug research and development, testing of the optimal therapeutic dose and duration of drug action [3] [30].

3.4. Effect of ^{18}F-FESPET/CT on Treatment Decision of Breast Cancer

The most important way to measure the clinical value of an examination lies in its impact on treatment decision-making. The main reasons for the influence of ^{18}F-FES PET/CT on treatment decision-making are: 1) reflecting the heterogeneity of lesions [31]. Heterogeneity of estrogen receptor expression in about 10% of 20% of breast cancer patients [32]. ^{18}F-FES PET/CT can reflect the expression of ER in patients with systemic lesions, so it can identify the heterogeneity of lesions, and the visual contrast effect is more obvious when combined with ^{18}F-FDG PET/CT imaging. Studies have shown that endocrine therapy is effective in patients with ER+, but not in patients with heterogeneity, and the effect is inversely proportional to the level of heterogeneity [32] [33]. Therefore, for patients with heterogeneity, the effect of single endocrine therapy is often not good. When ^{18}F-FES PET/CT finds the heterogeneity of patients' lesions, adjuvant chemotherapy can be recommended. 2) the effect on tumor staging of patients. Some studies have shown that ^{18}F-FESPET/CT is more sensitive than ^{18}F-FDG PET/CT for breast cancer lesions and can find more metastatic foci, so it can have a certain impact on the staging of the disease, thus further affecting the treatment plan [34] [35]. Generally speaking, the influence of ^{18}F-FES PET/CT on breast cancer treatment decision-making mainly comes from the identification of lesion heterogeneity and the influence on clinical stage.

4. Comparative Study on the Value of ^{18}F-FES PET/CT and ^{18}F-FDG PET/CT in the Diagnosis and Treatment of Breast Cancer

PET/CT is a new imaging technique which integrates anatomical imaging and functional imaging. It has been widely used in all kinds of tumor and non-tumor imaging. The commonly used tumor non-specific tracer is ^{18}F-FDG, which plays an important role in the diagnosis, clinical staging, guiding treatment and evaluating the curative effect of breast cancer [36]. As a specific tracer of ER, ^{18}F-FES may be comparable to or even better than ^{18}F-FDG in the diagnosis and treatment of breast cancer.

4.1. A Comparative Study of Diagnostic Efficiency

In previous studies, the comparative study of ^{18}F-FES and ^{18}F-FDG in the diagnosis of breast cancer is still controversial. Some studies have shown that

^{18}F-FES, as a specific tracer targeting ER, is more sensitive and can detect more lesions [34] [35]. Other studies have shown that the diagnostic efficacy of ^{18}F-FES and ^{18}F-FDG in breast cancer is almost the same, even slightly lower than that of ^{18}F-FDG [37]. According to the comprehensive analysis, the main reason is that ^{18}F-FES reflects the expression of ER, while ^{18}F-FDG reflects the level of glycolysis. When ER expression is high, ^{18}F-FES imaging is easier to find some subtle lesions, while when ER expression is low, it is close to ^{18}F-FDG, even due to the existence of tumor heterogeneity, only part of ER+ lesions are shown. For some subtypes of breast cancer, such as lobular adenocarcinoma, the level of glycolysis is low and the effect of ^{18}F-FDG imaging is poor, while ^{18}F-FES imaging shows relatively obvious advantages [38]. Therefore, the diagnostic efficacy of ^{18}F-FES and ^{18}F-FDG in breast cancer is affected by many factors and cannot be generalized. Therefore, we can try to combine the two and learn from each other's strengths to offset our weaknesses. For example, the physiological uptake of ^{18}F-FDG in the head is higher, while the uptake of ^{18}F-FES in the liver is extremely high, so the combination of the two can make up for their respective defects [39] [40] [41]. And due to the existence of ER-negative lesions, the information of ^{18}F-FESPET/CT imaging alone is limited, so it may be an inevitable trend to combine ^{18}F-FDGPET/CT at the first examination.

4.2. A Comparative Study on the Prediction of Curative Effect

Different imaging agents have different basis for predicting the prognosis of the disease. ^{18}F-FES imaging reflects the expression of ER in the lesions, and the expression of ER can predict the effect of endocrine therapy. If it is high expression, the ^{18}F-FES uptake will increase, indicating that the effect of endocrine therapy and prognosis of patients are good. ^{18}F-FDG imaging can reflect the invasiveness of the tumor, and the ^{18}F-FDG uptake is increased, indicating that the tumor has strong invasiveness and poor prognosis. However, studies have shown that patients with high ^{18}F-FDG uptake can also have high ^{18}F-FES uptake, and for these patients, progression-free survival is longer than those with high ^{18}F-FDG uptake and low ^{18}F-FES uptake [42]. To sum up, we can find that ^{18}F-FES and ^{18}F-FDG have different angles to evaluate the prognosis. ^{18}F-FDG imaging reflects the invasiveness of the tumor, which is a comprehensive situation, while ^{18}F-FES imaging predicts the effect of a single treatment (endocrine therapy), and the two evaluation angles are completely different. Therefore, in clinical practice, we should choose the corresponding examination scheme according to the actual needs, especially for patients with recurrent and metastatic breast cancer and multiple metastatic foci, it is of irreplaceable value to evaluate the expression of ER by ^{18}F-FESPET/CT before endocrine therapy.

5. Summary and Prospect

At present, the effective rate of endocrine therapy for breast cancer is far from perfect, and ^{18}F-FES PET/CT imaging, which is closely related to endocrine therapy, has become hot for a while [43] [44]. A large number of studies have

shown that ^{18}F-FES uptake is closely related to the pathological results of ER expression, which can be used to evaluate the systemic ER expression of patients. Based on this principle, ^{18}F-FES imaging can be used in breast cancer diagnosis, efficacy evaluation, prognosis evaluation, drug development and other, and has achieved good performance in clinical trials [45]. In addition, ^{18}F-FES imaging has unique advantages: reflecting the heterogeneity of lesions, so it is more in line with the needs of personalized treatment. With the research and application of ^{18}F-FES PET/CT imaging, it is expected to break through the bottleneck of endocrine therapy for breast cancer. However, with regard to the specific clinical application of ^{18}F-FESPET/CT imaging, there is no relevant guide recommendation and expert consensus, which may need to be studied and promoted on a larger scale.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Ding, Z., Xu, X., Li, T., *et al.* (2021) ZR-75-1 Breast Cancer Models to Study the Utility of ^{18}F-FES by PET Imaging. *Translational Cancer Research*, **10**, 1430-1438. https://doi.org/10.21037/tcr-20-3228

[3] Iqbal, R., Yaqub, M., Bektas, H.O., *et al.* (2023) [^{18}F]^{18}F-FDG and [^{18}F]^{18}F-FES PET/CT Imaging as a Biomarker for Therapy Effect in Patients with Metastatic ER+ Breast Cancer Undergoing Treatment with Rintodestrant. *Clinical Cancer Research*, **29**, 2075-2084. https://doi.org/10.1158/1078-0432.CCR-22-2720

[4] Breast Cancer Pro^{18}F-FESsional Committee of China Anti-Cancer Association (2021) Guidelines and Norms for Diagnosis and Treatment of Breast Cancer of China Anti-Cancer Association (2021 Edition). *Chinese Journal of Cancer*, **31**, 954-1040.

[5] Du, Y.R. (2021) Research Progress of Estrogen Receptor Negative and Progesterone Receptor Positive Breast Cancer. *Chinese Journal of Endocrine Surgery*, **15**, 202-204.

[6] Nienhuis, H.H., van Kruchten, M., Elias, S.G., *et al.* (2018) (18)F-Fluoroestradiol Tumor Uptake Is Heterogeneous and Influenced by Site of Metastasis in Breast Cancer Patients. *Journal of Nuclear Medicine*, **59**, 1212-1218. https://doi.org/10.2967/jnumed.117.198846

[7] Kurland, B.F., Wiggins, J.R., Coche, A., *et al.* (2020) Whole-Body Characterization of Estrogen Receptor Status in Metastatic Breast Cancer with 16alpha-^{18}F-Fluoro-17beta-Estradiol Positron Emission Tomography: Meta-Analysis and Recommendations for Integration into Clinical Applications. *Oncologist*, **25**, 835-844. https://doi.org/10.1634/theoncologist.2019-0967

[8] Grabher, B.J. (2020) Breast Cancer: Evaluating Tumor Estrogen Receptor Status with Molecular Imaging to Increase Response to Therapy and Improve Patient

Outcomes. *Journal of Nuclear Medicine Technology*, **48**, 191-201. https://doi.org/10.2967/jnmt.119.239020

[9] Mankoff, D.A., Peterson, L.M., Tewson, T.J., *et al.* (2001) [^{18}F]fltuoroestradiol Radiation Dosimetry in Human PET Studies. *Journal of Nuclear Medicine*, **42**, 679-684.

[10] Mathias, C.J., Welch, M.J., Katzenellenbogen, J.A., *et al.* (1987) Characterization of the Uptake of 16 alpha-([^{18}F]fluoro)-17 beta-Estradiol in DMBA-Induced Mammary Tumors. *International Journal of Radiation Applications and Instrumentation. Part B*, **14**, 15-25. https://doi.org/10.1016/0883-2897(87)90156-5

[11] Wang, M., Glick-Wilson, B.E. and Zheng, Q.H. (2020) Fully Automated Radiosynthesis and Quality Control of Estrogen Receptor Targeting Radiopharmaceutical 16alpha-[(18)F]fluoroestradiol ([(18)F]^{18}F-FES) for Human Breast Cancer Imaging. *Applied Radiation and Isotopes*, **160**, Article ID: 109109. https://doi.org/10.1016/j.apradiso.2020.109109

[12] Grabher, B. (2020) Addendum to Breast Cancer: Evaluating Tumor Estrogen Receptor Status with Molecular Imaging to Increase Response to Therapy and Patient Outcomes. *Journal of Nuclear Medicine Technology*, **48**, 191-201. https://doi.org/10.2967/jnmt.120.261889

[13] Chae, S.Y., Ahn, S.H., Kim, S.-B., *et al.* (2019) Diagnostic Accuracy and Safety of 16α-[^{18}F]fluoro-17β-Oestradiol PET-CT for the Assessment of Oestrogen Receptor Status in Recurrent or Metastatic Lesions in Patients with Breast Cancer: A Prospective Cohort Study. *The Lancet Oncology*, **20**, 546-555. https://doi.org/10.1016/S1470-2045(18)30936-7

[14] Mo, J.A. (2021) Safety and Effectiveness of F-18 Fluoroestradiol Positron Emission Tomography/Computed Tomography: A Systematic Review and Meta-Analysis. *Journal of Korean Medical Science*, **36**, e271. https://doi.org/10.3346/jkms.2021.36.e271

[15] Zhu, X., Wang, Y.M., Song, X.Y., *et al.* (2016) Analysis of the Value of F-^{18}F-FES PET/CT Examination in Diagnosis of Breast Cancer and Evaluation of Curative Effect. *Shandong Medicine*, **56**, 19-22.

[16] Lee, Y., Yoo, I.R. and Ha, S. (2022) ^{18}F-FES PET/CT for Characterization of Brain and Leptomeningeal Metastasis in Double Primary Cancer Patient. *Clinical Nuclear Medicine*, **47**, e554-e556. https://doi.org/10.1097/RLU.0000000000004197

[17] Kiatkittikul, P., Promteangtrong, C., Kunawudhi, A., *et al.* (2022) Discrepancy between [^{18}F]-^{18}F-FES and [^{18}F]-^{18}F-FDG PET/CT in ER-Positive Breast Cancer with Oesophageal Metastasis. *European Journal of Nuclear Medicine and Molecular Imaging*, **49**, 3297-3298. https://doi.org/10.1007/s00259-022-05759-z

[18] Yang, Z., Xie, Y., Liu, C., *et al.* (2021) The Clinical Value of (18)F-Fluoroestradiol in Assisting Individualized Treatment Decision in Dual Primary Malignancies. *Quantitative Imaging in Medicine and Surgery*, **11**, 3956-3965. https://doi.org/10.21037/qims-20-1364

[19] Yamada, S., Tsuyoshi, H., Yamamoto, M., *et al.* (2021) Prognostic Value of 16alpha-(18)F-Fluoro-17beta-Estradiol PET as a Predictor of Disease Outcome in Endometrial Cancer: A Prospective Study. *Journal of Nuclear Medicine*, **62**, 636-642. https://doi.org/10.2967/jnumed.120.244319

[20] Roze, J.F., van Meurs, H.S., Monroe, G.R., *et al.* (2021) [(18)F]^{18}F-FDG and [(18)F]^{18}F-FES Positron Emission Tomography for Disease Monitoring and Assessment of Anti-Hormonal Treatment Eligibility in Granulosa Cell Tumors of the Ovary. *Oncotarget*, **12**, 665-673. https://doi.org/10.18632/oncotarget.27925

[21] Peterson, L.M., Kurland, B.F., Yan, F., *et al.* (2021) (18)F-Fluoroestradiol PET Im-

aging in a Phase II Trial of Vorinostat to Restore Endocrine Sensitivity in ER+/HER2-Metastatic Breast Cancer. *Journal of Nuclear Medicine*, **62**, 184-190. https://doi.org/10.2967/jnumed.120.244459

[22] He, S., Wang, M., Zhang, Y., *et al.* (2019) Monitoring the Early Response of Fulvestrant plus Tanshinone IIA Combination Therapy to Estrogen Receptor-Positive Breast Cancer by Longitudinal (18)F-^{18}F-FES PET/CT. *Contrast Media Mol Imaging*, **2019**, Article ID: 2374565. https://doi.org/10.1155/2019/2374565

[23] Liu, S., Gu, B., Zhang, J., *et al.* (2018) The Feasibility of (18)F-^{18}F-FES and (18)F-^{18}F-FDG microPET/CT for Early Monitoring the Effect of Fulvestrant on Sensitizing Docetaxel by Downregulating ERalpha in ERalpha+ Breast Cancer. *Annals of Nuclear Medicine*, **32**, 272-280. https://doi.org/10.1007/s12149-018-1245-0

[24] He, M., Liu, C., Shi, Q., *et al.* (2020) The Predictive Value of Early Changes in (18)F-Fluoroestradiol Positron Emission Tomography/Computed Tomography during Fulvestrant 500 mg Therapy in Patients with Estrogen Receptor-Positive Metastatic Breast Cancer. *Oncologist*, **25**, 927-936. https://doi.org/10.1634/theoncologist.2019-0561

[25] Yang, Z., Sun, Y., Xue, J., *et al.* (2013) Can Positron Emission Tomography/Computed Tomography with the Dual Tracers Fluorine-18 Fluoroestradiol and Fluorodeoxyglucose Predict Neoadjuvant Chemotherapy Response of Breast Cancer?—A Pilot Study. *PLOS ONE*, **8**, e78192. https://doi.org/10.1371/journal.pone.0078192

[26] Chae, S.Y., Kim, S.B., Ahn, S.H., *et al.* (2017) A Randomized Feasibility Study of (18)F-Fluoroestradiol PET to Predict Pathologic Response to Neoadjuvant Therapy in Estrogen Receptor-Rich Postmenopausal Breast Cancer. *Journal of Nuclear Medicine*, **58**, 563-568. https://doi.org/10.2967/jnumed.116.178368

[27] Kumar, M., Salem, K., Michel, C., *et al.* (2019) (18)F-Fluoroestradiol PET Imaging of Activating Estrogen Receptor-alpha Mutations in Breast Cancer. *Journal of Nuclear Medicine*, **60**, 1247-1252. https://doi.org/10.2967/jnumed.118.224667

[28] Kumar, M., Salem, K., Jeffery, J.J., *et al.* (2021) Longitudinal Molecular Imaging of Progesterone Receptor Reveals Early Differential Response to Endocrine Therapy in Breast Cancer with an Activating ESR1 Mutation. *Journal of Nuclear Medicine*, **62**, 500-506. https://doi.org/10.2967/jnumed.120.249508

[29] Boers, J., Venema, C.M., de Vries, E.F.J., *et al.* (2020) Molecular Imaging to Identify Patients with Metastatic Breast Cancer Who Benefit from Endocrine Treatment Combined with Cyclin-Dependent Kinase Inhibition. *European Journal of Cancer*, **126**, 11-20. https://doi.org/10.1016/j.ejca.2019.10.024

[30] Besret, L., d'Heilly, S., Aubert, C., *et al.* (2020) Translational Strategy Using Multiple Nuclear Imaging Biomarkers to Evaluate Target Engagement and Early Therapeutic Efficacy of SAR439859, a Novel Selective Estrogen Receptor Degrader. *EJNMMI Research*, **10**, Article No. 70. https://doi.org/10.1186/s13550-020-00646-w

[31] Liu, C., Hu, S., Xu, X., *et al.* (2022) Evaluation of Tumour Heterogeneity by (18)F-Fluoroestradiol PET as a Predictive Measure in Breast Cancer Patients Receiving Palbociclib Combined with Endocrine Treatment. *Breast Cancer Research*, **24**, Article No. 57. https://doi.org/10.1186/s13058-022-01555-7

[32] Xie, Y., Du, X., Zhao, Y., *et al.* (2022) Chemotherapy Shows a Better Efficacy than Endocrine Therapy in Metastatic Breast Cancer Patients with a Heterogeneous Estrogen Receptor Expression Assessed by (18)F-^{18}F-FES PET. *Cancers* (*Basel*), **14**, Article No. 3531. https://doi.org/10.3390/cancers14143531

[33] Bottoni, G., Piccardo, A., Fiz, F., *et al.* (2021) Heterogeneity of Bone Metastases as

an Important Prognostic Factor in Patients Affected by Oestrogen Receptor-Positive Breast Cancer. The Role of Combined [^{18}F]Fluoroestradiol PET/CT and [^{18}F]Fluorodeoxyglucose PET/CT. *European Journal of Radiology*, **141**, Article ID: 109821. https://doi.org/10.1016/j.ejrad.2021.109821

[34] Tsujikawa, T., Makino, A., Mori, T., *et al.* (2022) PET Imaging of Estrogen Receptors for Gynecological Tumors. *Clinical Nuclear Medicine*, **47**, 481-488. https://doi.org/10.1097/RLU.0000000000004258

[35] Liu, C., Gong, C., Liu, S., *et al.* (2019) (18)F-^{18}F-FES PET/CT Influences the Staging and Management of Patients with Newly Diagnosed Estrogen Receptor-Positive Breast Cancer: A Retrospective Comparative Study with (18)F-^{18}F-FDG PET/CT. *Oncologist*, **24**, e1277-e1285. https://doi.org/10.1634/theoncologist.2019-0096

[36] Sadaghiani, M.S., Rowe, S.P. and Sheikhbahaei, S. (2021) Applications of Artificial Intelligence in Oncologic (18)F-^{18}F-FDG PET/CT Imaging: A Systematic Review. *Annals of Translational Medicine*, **9**, 823. https://doi.org/10.21037/atm-20-6162

[37] Chae, S.Y., Son, H.J., Lee, D.Y., *et al.* (2020) Comparison of Diagnostic Sensitivity of [(18)F]fluoroestradiol and [(18)F]fluorodeoxyglucose Positron Emission Tomography/Computed Tomography for Breast Cancer Recurrence in Patients with a History of Estrogen Receptor-Positive Primary Breast Cancer. *EJNMMI Research*, **10**, Article No. 54. https://doi.org/10.1186/s13550-020-00643-z

[38] Ulaner, G.A., Jhaveri, K., Chandarlapaty, S., *et al.* (2021) Head-to-Head Evaluation of (18)F-^{18}F-FES and (18)F-^{18}F-FDG PET/CT in Metastatic Invasive Lobular Breast Cancer. *Journal of Nuclear Medicine*, **62**, 326-331. https://doi.org/10.2967/jnumed.120.247882

[39] Ryu, J., Jeong, J.H., Moon, D.H., *et al.* (2022) Determination of the Estrogen Receptor Status of Leptomeningeal Metastasis in Patients with Metastatic Breast Cancer Using [(18)F]-^{18}F-FES PET/CT: A Case Report. *Nuclear Medicine and Molecular Imaging*, **56**, 105-109. https://doi.org/10.1007/s13139-022-00736-8

[40] Bodapati, S., Abraham, P., Chen, A., *et al.* (2022) ^{18}F-FES PET/CT Improves the Detection of Intraorbital Metastases in Estrogen-Receptor-Positive Breast Cancer: Two Representative Cases and Review of the Literature. *Tomography*, **8**, 1060-1065. https://doi.org/10.3390/tomography8020086

[41] Boers, J., Schroder, C.P., Hospers, G.A.P., *et al.* (2021) Detection of Dural Metastases before the Onset of Clinical Symptoms by 16alpha-[^{18}F]Fluoro-17beta-Estradiol PET in a Patient with Estrogen Receptor-Positive Breast Cancer. *Clinical Nuclear Medicine*, **46**, e165-e167. https://doi.org/10.1097/RLU.0000000000003382

[42] Kurland, B.F., Peterson, L.M., Lee, J.H., *et al.* (2017) Estrogen Receptor Binding (^{18}F-FES PET) and Glycolytic Activity (^{18}F-FDG PET) Predict Progression-Free Survival on Endocrine Therapy in Patients with ER+ Breast Cancer. *Clinical Cancer Research*, **23**, 407-415. https://doi.org/10.1158/1078-0432.CCR-16-0362

[43] Chudgar, A.V. and Mankoff, D.A. (2017) Molecular Imaging and Precision Medicine in Breast Cancer. *PET Clinics*, **12**, 39-51. https://doi.org/10.1016/j.cpet.2016.08.001

[44] Takahashi, M., Maeda, H., Tsujikawa, T., *et al.* (2021) ^{18}F-Fluoroestradiol Tumor Uptake Is Influenced by Structural Components in Breast Cancer. *Clinical Nuclear Medicine*, **46**, 884-889. https://doi.org/10.1097/RLU.0000000000003835

[45] Linden, H.M., Peterson, L.M. and Fowler, A.M. (2018) Clinical Potential of Estrogen and Progesterone Receptor Imaging. *PET Clinics*, **13**, 415-422. https://doi.org/10.1016/j.cpet.2018.02.005