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PICTORIAL REVIEW

Oestrogen-related tumour phenotype: positron emission tomography characterisation with ^{18}F-FDG and ^{18}F-FES

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ABSTRACT. This article outlines the role of 16α-[^{18}F]fluoro-17β-oestradiol (^{18}F-FES) positron emission tomography (PET) combined with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) in patients with oestrogen-related tumours for evaluating tumour phenotype. ^{18}F-FES-PET combined with ^{18}F-FDG is helpful in characterising the distinct phenotypic features of oestrogen-related tumours; that is, inter- and intrapatient tumour heterogeneity, which indicates its great potential as a determinant of individualised treatment and a prognostic predictor for patients with oestrogen-related tumours.

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Breast cancer was the most common female malignancy newly diagnosed in the UK in 2008 (n=47 693), and endometrial cancer was the most commonly diagnosed gynaecological malignancy affecting UK females in 2007 (n=7536) [1]. In the past few decades, positron emission tomography (PET) with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) has been used for diagnosis of breast cancer and gynaecological malignancies and is considered to be superior to conventional imaging methods in diagnostic accuracy for detecting metastatic lesions and local recurrence [2–5]. FDG-PET can also be useful in evaluating the response of metastatic breast cancer to systematic therapy [2, 3]. On the other hand, both breast and endometrial cancer are oestrogen-related tumours for which oestrogen is critical for their development and progression. 16α-[^{18}F]fluoro-17β-oestradiol (^{18}F-FES) is an ^{18}F-labelled compound of oestradiol, the most bioactive type of oestrogen, and ^{18}F-FES-PET has been well established for diagnosis, staging and post-therapeutic follow-up in patients with oestrogen receptor (ER)-positive breast cancer [6–11]. In particular, the ER status is the most important determinant of response to endocrine therapy in breast cancer patients. Compared with an *in vitro* assay of tumour biopsy material, PET imaging has the advantage of being able to measure *in vivo* tumour behaviour, characterise the entire tumour burden and capture the heterogeneity of the tumour phenotype [12, 13]. Recently, we applied ^{18}F-FES-PET imaging to the diagnosis of gynaecological tumours [14–19] and showed in particular that the uptake value of ^{18}F-FES combined with ^{18}F-FDG is associated with tumour aggressiveness in endometrial cancer; that is, endometrial carcinoma reduces oestrogen dependency with increased glucose metabolism as it progresses to a higher stage or grade, and the ^{18}F-FDG:^{18}F-FES uptake ratio is the most informative index reflecting tumour aggressiveness [17]. An imaging study combining ^{18}F-FES and ^{18}F-FDG-PET has the potential to characterise *in vivo* oestrogen-related tumour phenotypes. In this article, we review oestrogen-related tumour phenotyping by ^{18}F-FDG-PET and illustrate the role of ^{18}F-FES-PET combined with ^{18}F-FDG by showing representative cases.

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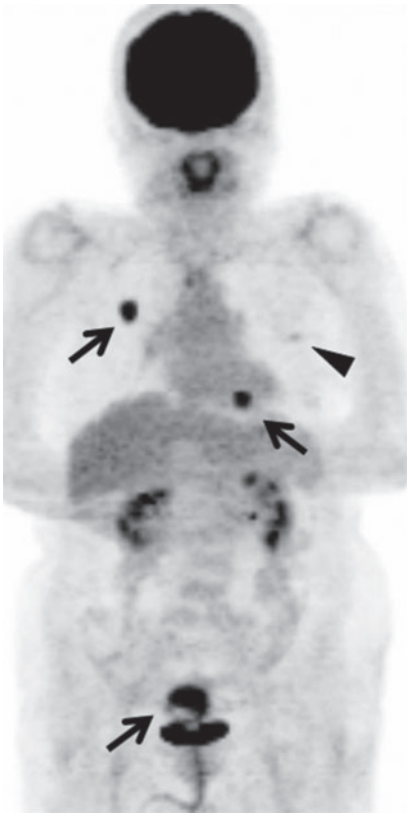
Tumour phenotyping by ^{18}F-FDG-PET

Several recent investigations reported the ability of ^{18}F-FDG-PET to characterise breast cancer tumour phenotype. They indicated that enhanced tumour ^{18}F-FDG uptake significantly correlates with ER negativity as a whole [20–24]. The latest report by Groheux et al [24] showed that ^{18}F-FDG uptake is highest in patients with poor prognostic features (high grade, hormone receptor negativity, triple negativity, metaplastic tumours). As for endometrial cancer, our recent study with a small sample size (n=19) did not show a significant correlation between tumour ^{18}F-FDG uptake and hormone receptor expression [18]. However, a recent report showed that ^{18}F-FDG accumulation by a primary endometrial cancer tumour significantly correlated with the differentiation grade, which still applies to the revised International Federation of Gynecology and Obstetrics staging classification 2009 [25]. Molecular imaging, including



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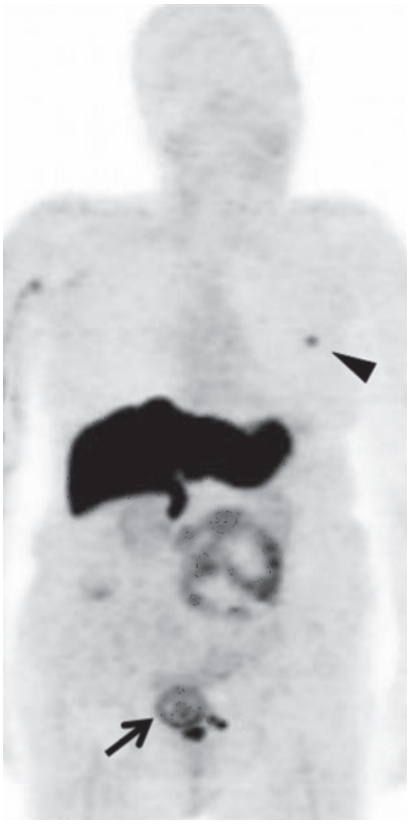

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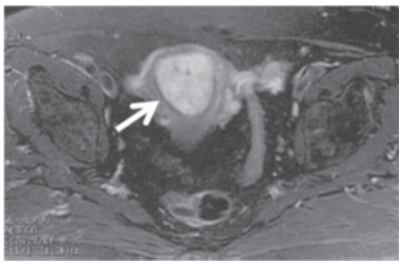

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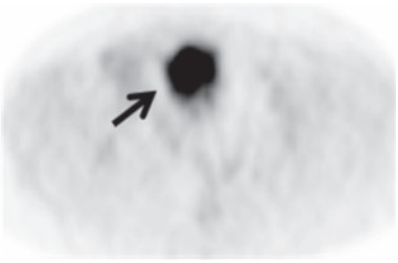

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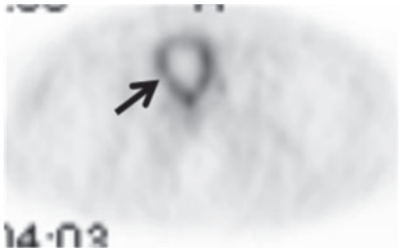

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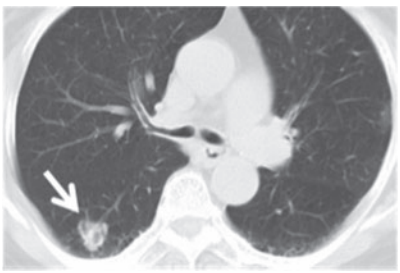

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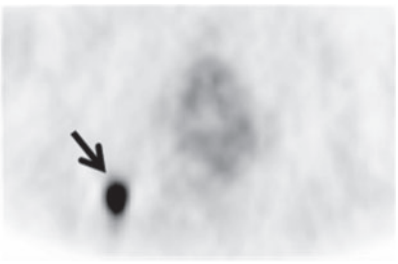

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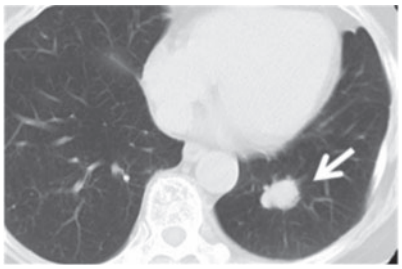

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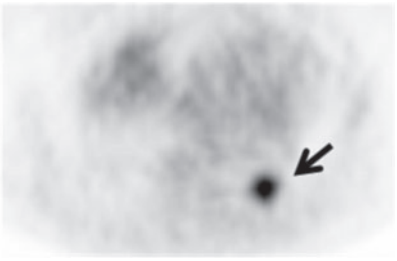

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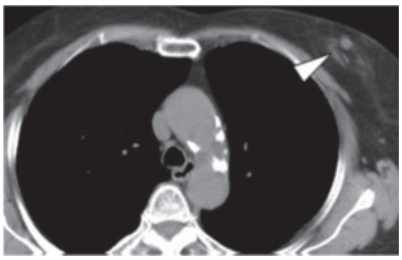

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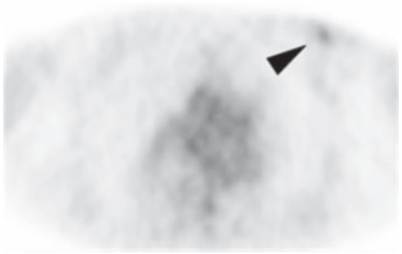

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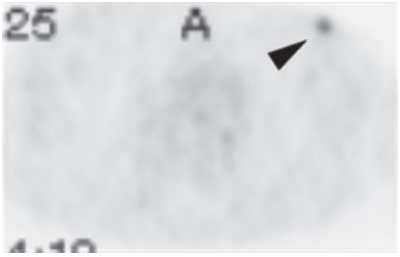


(l)

Figure 1. A 78-year-old female with advanced endometrial cancer and early-stage breast cancer. Maximum-intensity projection positron emission tomography (PET) images with (a) 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) and (b) 16α-[^{18}F]fluoro-17β-oestradiol (^{18}F-FES) demonstrated significantly higher accumulation of ^{18}F-FDG [standardised uptake value (SUV) mean, 9.5] than ^{18}F-FES (SUV mean, 1.7) in the primary uterine tumour (arrows). Although right and left lung tumours showed intense accumulation of ^{18}F-FDG (SUV mean, 10.1 and 5.7, respectively), almost no ^{18}F-FES accumulation was visually detected. The ^{18}F-FDG:^{18}F-FES SUV ratio was 5.6 in the primary tumour, whereas somewhat higher ^{18}F-FES uptake (SUV mean, 1.8) than ^{18}F-FDG uptake (SUV mean, 1.1) was incidentally detected in the left breast (arrowheads). This was determined as invasive ductal carcinoma by subsequent aspiration cytology. The ^{18}F-FDG:^{18}F-FES ratio was 0.6 in the breast tumour. (c) Transaxial contrast-enhanced T_1 weighted MRI, (d) ^{18}F-FDG and (e) ^{18}F-FES-PET images of the primary endometrial cancer arrows. Transaxial CT (f and h) and ^{18}F-FDG-PET (g and i) images of right and left lung tumours (arrows), respectively. Transaxial CT (j), ^{18}F-FDG (k) and ^{18}F-FES-PET (l) images of left breast cancer (arrow heads).

^{18}F-FDG-PET, which has hitherto been used mainly for tumour detection and staging, can play an important role in measuring tumour phenotype [13].

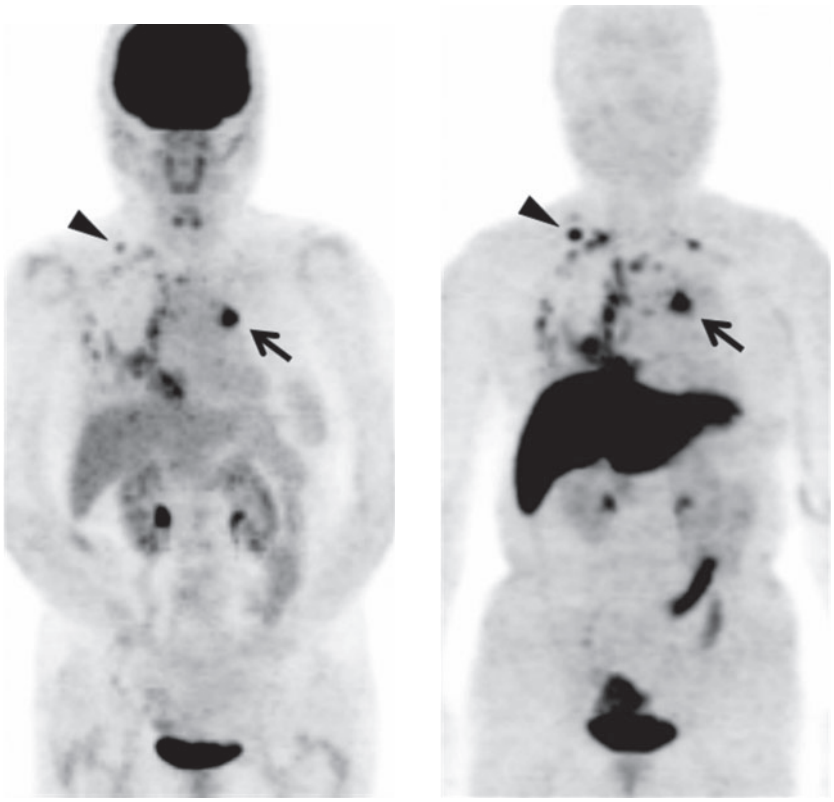
Tumour phenotyping by ^{18}F-FES-PET combined with ^{18}F-FDG

In this section we illustrate the role of ^{18}F-ES-PET combined with ^{18}F-DG for oestrogen-related tumour phenotyping by showing representative cases.

Case 1

A 78-year-old female was hospitalised with suspected endometrial cancer and lung metastases. Endometrial biopsy revealed the uterine tumour to be grade II endometrioid adenocarcinoma, and pelvic MRI indicated myometrial invasion. The patient underwent ^{18}F-ES-PET scan for evaluation of ER density and ^{18}F-FDG-PET scan to detect other metastatic lesions. PET images showed significantly higher accumulation of ^{18}F-FDG [standardised uptake value (SUV) mean, 9.5] than ^{18}F-FES (SUV mean, 1.7) in the primary tumour (Figure 1). Although right and left lung tumours showed intense accumulation of ^{18}F-FDG (SUV mean, 10.1 and 5.7, respectively), almost no ^{18}F-FES accumulation was detected visually and uptake values of ^{18}F-FES were not measurable in the lung tumours. The ^{18}F-FDG:^{18}F-FES SUV ratio was 5.6 in the primary tumour, whereas somewhat higher ^{18}F-FES uptake (SUV mean, 1.8) than ^{18}F-FDG uptake (SUV mean, 1.1) was incidentally detected in the left breast. This was determined to be invasive ductal carcinoma by subsequent aspiration cytology (Figure 1). The ^{18}F-FDG:^{18}F-FES SUV ratio was 0.6 in the breast tumour.

In this case of oestrogen-related tumours derived from two different organs, tracer accumulation patterns of ^{18}F-FES and ^{18}F-FDG were completely different between advanced endometrial cancer (^{18}F-FDG:^{18}F-FES ratio, 5.6 in the primary tumour) and early-stage breast cancer (^{18}F-FDG:^{18}F-FES ratio, 0.6). Although the patient was followed up without treatment by choice, multiple bone and liver metastases appeared besides the progression of



(a) (b)

Figure 2. A 64-year-old female with multiple metastases from breast cancer. Maximum-intensity projection positron emission tomography images with (a) 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) and (b) 16α-[^{18}F]fluoro-17β-oestradiol (^{18}F-FES) demonstrated almost the same degree of accumulation of ^{18}F-FDG [standardised uptake value (SUV) mean, 4.8] as ^{18}F-FES (SUV mean, 4.7) in left hilar lymphadenopathy (arrows), whereas higher ^{18}F-FES uptake (SUV mean, 3.2) than ^{18}F-FDG uptake (SUV mean, 1.3) was detected in right supraclavicular lymphadenopathy (arrowheads). The ^{18}F-FDG:^{18}F-FES SUV ratio was 1.0 and 0.4 in left hilar and right supraclavicular lymphadenopathy, respectively.

the primary tumour and she died within 1 year of the initial visit. During that time, no tendency for increased size was observed in the left breast tumour. Based on the opposite tracer accumulation pattern, combined ^{18}F-FES and ^{18}F-FDG-PET scan was considered a useful tool, providing supplementary information for *in vivo* phenotyping of two different oestrogen-related tumours.

Case 2

In patients with multiple metastases from breast cancer, the combination of ^{18}F-FES and ^{18}F-FDG-PET imaging studies has the potential to reflect tumour heterogeneity and characterise the *in vivo* tumour phenotype. A 64-year-old female with multiple metastases from breast cancer showed almost the same degree of accumulation of ^{18}F-FDG (SUV mean, 4.8) as ^{18}F-FES (SUV mean, 4.7) in left hilar lymphadenopathy, whereas higher ^{18}F-FES uptake (SUV mean, 3.2) than ^{18}F-FDG uptake (SUV mean, 1.3) was detected in right supraclavicular lymphadenopathy (Figure 2). The ^{18}F-FDG:^{18}F-FES SUV ratio was 1.0 and 0.4 in left hilar and right supraclavicular lymphadenopathy, respectively.

We previously reported that the ^{18}F-FDG:^{18}F-FES SUV ratio is the most informative index reflecting tumour aggressiveness in patients with endometrial cancer [17], which may also be applied to patients with other oestrogen-related tumours such as multiple metastases from breast cancer. The index of the ^{18}F-FDG:^{18}F-FES SUV ratio has the advantage of being able to cancel out the partial volume effect, which greatly influences the interpretation of tracer uptake by a lesion. In addition, the ratio could be used as a determinant of hormonal therapies such as tamoxifen and aromatase inhibitor for breast cancer and progestational agents and gonadotropin-releasing hormone agonists for gynaecological tumours. In fact, hormonal treatment was not effective in this case and the patient died of carcinomatous pleuritis; nevertheless, an optimal range of the ratio for prediction of therapeutic efficacy may exist. Future prospective studies with large sample sizes are required to prove the benefit of a combination of ^{18}F-FES and ^{18}F-FDG-PET imaging.

Conclusion

The combination of molecular imaging studies has considerable potential for *in vivo* tumour phenotyping, which helps move towards better and more individualised cancer treatment. As Mankoff and Dehdashti [13] put it, ''1 plus 1 is more than 2''.

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