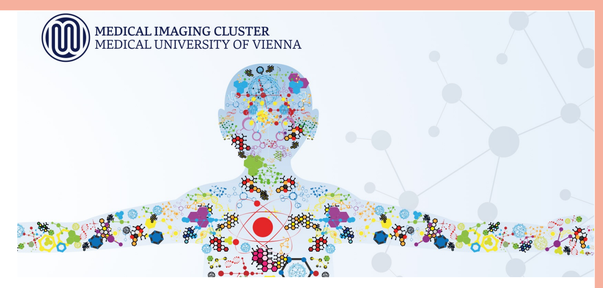
MEDICAL UNIVERSITY OF VIENNA



Simultaneous PET-MRI using ^{18}F-Fluoroethylcholine can provide accurate diagnosis and characterization of breast cancer

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Objective

Breast cancer is a leading cause of morbidity and mortality in women[1].
At present, diagnosis and treatment of breast cancer are largely based on histopathological and immunohistochemical analyses. There is a need for validated imaging biomarkers that could not only distinguish benign from malignant findings but also characterize breast cancer aggressiveness[2].
Increased activity of the choline kinase-α (CHKα) has been observed in breast cancer and is associated with malignant progression[3,4]. The assessment of CHKα activity and its effect on choline metabolism in vivo could thus provide valuable diagnostic and prognostic information for breast cancer diagnosis and treatment[5].
The aim of this prospective diagnostic pharmaceutical phase II validation study was to assess the role of [^{18}F]-Fluoroethylcholine (FEC) as a novel radiotracer in the characterization of breast lesions and breast cancer aggressiveness in simultaneous PET-MRI.

Patients and Methods

This prospective, monocentric study was approved by the ethic committee and patients gave their written informed consent.
Inclusion Criteria: Female patients with lesions classified as suspicious on mammography, tomosynthesis and/or ultrasound and no contraindications to contrast-enhanced magnetic resonance imaging (MRI) and PET.

Image Acquisition: The examinations were performed using a simultaneous whole-body combined PET-MRI device (Biograph mMR system, Siemens, Erlangen, Germany), characterized by an MRI-compatible PET detector integrated with a 3.0 Tesla MRI scanner. Exams were acquired with the patients in a prone position using a dedicated 16-channel breast coil (Rapid Biomedical, Rimpar, Germany).
Radiosynthesis of [^{18}F]-Fluoroethylcholine followed a two-step reaction procedure using a remote-controlled synthesizer (Nuclear Interface, GE Healthcare, Uppsala, Sweden). CE-MRI was obtained before and after intravenous administration of paramagnetic contrast agent (Dotarem: 0.2 ml/kg body weight), at a flow rate of 3.5 ml/s. All sequences were acquired in the axial plane. PET acquisition started immediately after the injection of 2.5–3.5 MBq/kg bodyweight of [^{18}F]-FEC.

Standard of reference: pathology obtained from image-guided biopsy samples. Immunohistochemical (IHC) analysis was available for malignant lesions.

Image Analysis: Suspicious lesions were identified on CE-MRI by an experienced breast radiologists. The maximum standardized uptake vale (SUVmax) of the MRI findings was subsequently measured by a board-certified nuclear medicine physician.

Statistical Analysis: Differences in SUVmax between benign and malignant lesions and between malignant lesion IHC analysis were evaluated with the Mann-Whitney-U-test. The area under the curve (AUC) was calculated.

Results

101 patients (mean age 52.3 years, standard deviation 12.0, range 30 - 84) with 117 histologically verified breast lesions were included in the analysis.
All patients tolerated [^{18}F]-FEC PET-MRI well, and no adverse events were noted.

Histology	Number (%)
Benign	30 (25.6)
Fibroadenoma	12 (10.2)
Adenosis, sclerosing adenosis	6 (5.1)
Papilloma	4 (3.4)
Fibrosis, fibrocystic changes	3 (2.6)
Others	5 (4.3)

Histology	Number (%)
Malignant	87 (74.4)
Invasive carcinoma NST	40 (34.2)
Invasive carcinoma NST with DCIS	35 (30.0)
Invasive lobular carcinoma	5 (4.3)
DCIS	7 (5.9)

Diagnostic Performance: Differential Diagnosis of Benign Vs Malignant Lesions

SUV_{max} of [^{18}F]-FEC was significantly higher in malignant than in benign breast lesions: mean SUV_{max} in benign lesion was 3.36 (Standard Deviation, SD, 2.22) and in malignant lesion was 10.5 (SD 0.79), p<0.001.
A significant difference in the SUV_{max} was found between:

- Invasive carcinomas and benign lesions (p<0.001)
- Invasive carcinomas and DCIS (p=0.009)

No significant difference was found between DCIS and benign lesions (p>0.227).
The AUC of SUV_{max} to distinguish benign from malignant lesions 0.846 (95% confidence interval 0.774 – 0.918).

Diagnostic Performance: Evaluation of Breast Cancer Aggressiveness

The evaluation was performed on the 80 invasive carcinomas.

Lesion Characteristics	Number (%)
Estrogen Receptor	
Positive	18 (22.5)
Negative	62 (77.5)
Progesteron Receptor	
Positive	28 (35.0)
Negative	52 (65.0)
HER-2 Status	
Positive	60 (75.0)
Negative	20 (35.0)
MIB-1	
Positive	29 (36.2)
Negative	51 (63.8)

Lesion Characteristics	Number (%)
Lesion Subtype	
Luminal A	23 (28.8)
Luminal B HER-2 negative	29 (36.3)
Luminal B HER-2 positive	13 (16.2)
HER-2	5 (6.2)
Triple Negative	10 (12.5)
Grade	
1	9 (11.3)
2	35 (43.7)
3	36 (45.0)

We found that (Figure 1):

- [^{18}F]-FEC SUV_{max} increased with tumor grade (p=0.013).
- SUV_{max} values were higher in carcinomas with a positive HER2 status (p=0.041).
- SUV_{max} values were higher in carcinomas with a high proliferation rate (MIB-1 > 20%) (p=0.011).
- SUV_{max} values did not differ in ER and PR receptor positive tumors compared to receptor negative carcinomas (p≥0.266).

The AUC of SUV_{max} to distinguish MIB-1 positive carcinomas from MIB1 negative ones was 0.672 (95% confidence interval 0.550 – 0.794).

More aggressive cancer subtypes (Luminal B-HER-2 positive, HER-2 positive, Triple Negative) showed a higher uptake (Figure 2).

There was a significant correlation between SUV_{max} and: grade (r=0.356, p=0.001); MIB-1 (r=0.434, p<0.001); lymph node status (r=0.333, p=0.015); tumor histology (r=-0.279, p=0.012) and tumor subtype (r=0.237, p=0.034).

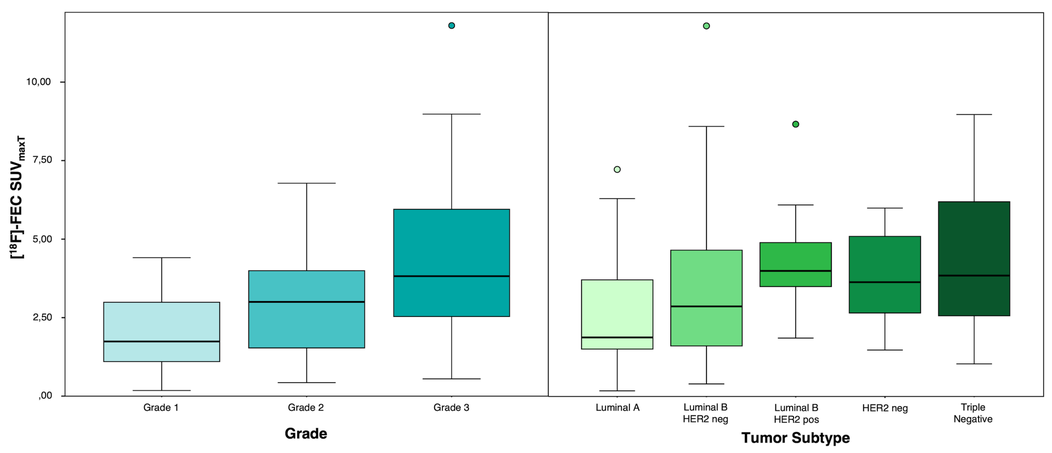

Figure 1: Boxplot showing the distribution of [^{18}F]-FEC SUV_{max} in malignant invasive carcinomas with different tumor grade and tumor subtype.

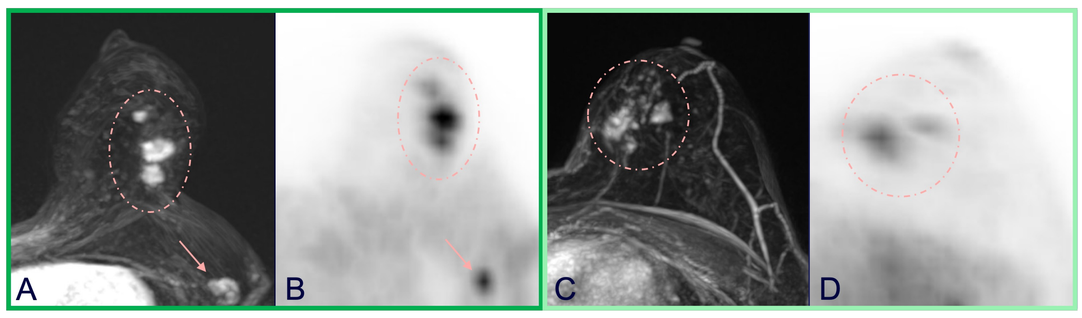

Figure 1: A (post-contrast subtracted MRI maximum intensity projection (MIP)) and B (PET): 42 years old woman with a palpable finding in the left breast. MRI revealed multiple suspicious lesions in the left breast and asymmetric lymph nodes (arrow). The lesions and the lymph node showed a strong [^{18}F]-FEC uptake (SUVmax tumor 3.52, SUVmax lymph node 2.69). Histology revealed an invasive carcinoma non-special type grade 3, Luminal B, HER2 positive, with a high proliferation rate and a metastatic lymph node.
C (MRI MIP) and D (PET): 51 years old woman with a palpable finding in the left breast. MRI revealed a multifocal tumor in the left breast. The lesion showed a weak [^{18}F]-FEC uptake (SUV_{max} tumor 1.74). Surgery revealed a multifocal invasive carcinoma non-special type grade 2, Luminal A with a low proliferation rate and no lymph node metastasis.

Conclusions

Simultaneous [^{18}F]-FEC PET-MRI of the breast is safe, and it allows an accurate characterization of benign and malignant breast lesions.
High [^{18}F]-FEC uptake was associated with histopathological features pointing at more aggressive cancer phenotypes.

References

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Funding Sources: This study has received funding by the Austrian National Bank (ÖNB) Jubiläumsfonds project number 17186.

The study is registered in the Clinical Trial Database EudraCT (Number 2017-003089-29)