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SHORT COMMUNICATION

^{18}F-FPPRGD$_2$ PET/CT in patients with metastatic renal cell cancer

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Abstract

Purpose The usefulness of positron emission tomography/computed tomography (PET/CT) using (^{18}F)-2-fluoropropionyl-labeled PEGylated dimeric arginine-glycine-aspartic acid peptide [PEG3-E{c(RGDyk)}2] (^{18}F-FPPRGD$_2$) in patients with metastatic renal cell cancer (mRCC) has not been evaluated; therefore, we were prompted to conduct this pilot study.

Methods Seven patients with mRCC were enrolled in this prospective study. ^{18}F-FPPRGD$_2$ and 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG) PET/CT images were evaluated in a per-lesion analysis. Maximum standardized uptake value (SUV$_{max}$) and tumor-to-background ratio (T/B) were measured for all detected lesions, both before and after starting antiangiogenic therapy.

Results Sixty lesions in total were detected in this cohort. SUV$_{max}$ from ^{18}F-FPPRGD$_2$ PET/CT was lower than that from ^{18}F-FDG PET/CT (4.4 ± 2.9 vs 7.8 ± 5.6, $P < 0.001$). Both SUV$_{max}$ and T/B from ^{18}F-FPPRGD$_2$ PET/CT decreased after starting antiangiogenic therapy (SUV$_{max}$, 4.2 ± 3.2 vs 2.6 ± 1.4, $P = 0.003$; T/B, 3.7 ± 3.2 vs 1.5 ± 0.8, $P < 0.001$). Average changes in SUV$_{max}$ and T/B were − 29.3 ± 23.6% and − 48.1 ± 28.3%, respectively.

Conclusions ^{18}F-FPPRGD$_2$ PET/CT may be an useful tool for monitoring early response to antiangiogenic therapy in patients with mRCC. These preliminary results need to be confirmed in larger cohorts.

Keywords Renal cell cancer · ^{18}F-FPPRGD$_2$ · ^{18}F-FDG · PET/CT · Antiangiogenic therapy

Introduction

Antiangiogenic therapies that target vascular endothelial growth factor (VEGF) and VEGF receptor are the mainstay of treatment for patients with metastatic RCC (mRCC) [1]. Although effect of anticancer drugs in solid tumors is generally evaluated by changes in size, molecular targeted therapies may not cause significant tumor shrinkage despite efficacy at the molecular level.

(^{18}F)-2-fluoropropionyl-labeled PEGylated dimeric arginine-glycine-aspartic acid (RGD) peptide [PEG3-E{c(RGDyk)}2] (^{18}F-FPPRGD$_2$) is a ligand targeting integrin $\alpha_v\beta_3$ on sprouting endothelial cells, which allows imaging tumor angiogenesis [2–4]. Withofs et al. showed positron emission tomography/computed tomography (PET/CT) using ^{18}F-FPRGD$_2$ reflects the expression of tumor associated integrin $\alpha_v\beta_3$ activity in RCC [5]. There are a few studies indicating the potential of ^{18}F-FPPRGD$_2$ PET/CT for evaluation of response to antiangiogenic drugs [2, 3].

In this study, we evaluated the detectability of mRCC lesions using ^{18}F-FPPRGD$_2$ PET/CT in comparison with 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG) PET/CT and the usefulness of ^{18}F-FPPRGD$_2$ PET/CT for early assessment of response to antiangiogenic therapy.

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Material and methods

Patients

Seven patients (4 men and 3 women, mean age 64.1 ± 14.0 years) with mRCC were enrolled in this prospective study approved by our institutional review board. Informed consent was obtained from all individual participants included in the study. All patients had undergone both ^{18}F-FPPRGD$_2$ and ^{18}F-FDG PET/CT within a month prior to starting systemic antiangiogenic therapy. Five patients had a follow-up ^{18}F-FPPRGD$_2$ PET/CT at 7–11 days (mean 8.4 ± 1.7 days) after initiation of therapy. Patients' characteristics are shown in Table 1.

PET/CT protocol

PET/CT studies were performed using Discovery 600 or Discovery 690 PET/CT scanners (GE Healthcare, Waukesha, WI, USA). The details of PET/CT imaging protocols in our hospital have been described previously [3]. In brief, for ^{18}F-FDG PET/CT, patients fasted for at least 6 h before scanning. Blood glucose levels at the time of injection were less than 150 mg/dl in all patients. 60 min after intravenous administration of 365–503 MBq (mean 421 ± 51 MBq) of ^{18}F-FDG, non-contrast CT data for attenuation correction and anatomical localization was acquired. Thereafter, a whole-body PET scan from skull base to the mid-thighs was performed. For ^{18}F-FPPRGD$_2$ PET/CT, 60 min after intravenous administration of 223–374 MBq (mean 298 ± 45 MBq) of ^{18}F-FPPRGD$_2$, non-contrast CT data acquisition was performed, followed by a whole-body PET scan from vertex to mid-thighs. Image reconstruction was performed using ordered subsets expectation maximization (OSEM) method.

Image analysis

Two nuclear medicine physicians evaluated all ^{18}F-FPPRGD$_2$ and ^{18}F-FDG PET/CT images by consensus with reference to conventional CT and/or MRI findings. Radiotracer uptakes above the background that did not correspond to physiological uptake was considered significant. Maximum standardized uptake value (SUV$_{max}$) and tumor-to-background ratio (T/B) were measured in each lesion. When calculating T/B, background was regarded as mean SUV in the region of interest (ROI) with a diameter of 2 cm in the ascending aorta. For the follow-up ^{18}F-FPPRGD$_2$ PET/CT, ROIs were put in the same location for lesions that were initially ^{18}F-FPPRGD$_2$ positive but showed complete resolution in the course of therapy.

Table 1 Patients' characteristics

Patient number	Age (years)	Sex	Pathology	Newly diagnosed or recurrent	Treatment (line)	Renal primary	Number of lesions	Days on the treatment at the second PET/CT	Best response to treatment	Outcome
1	77	Male	Unknown[a]	Newly diagnosed	Pazopanib (1)	Present[b]	3	7	SD at 2 months (Shrinkage of kidney mass)	Died (OS = 186 days)
2	73	Male	CCC	Recurrent	Pazopanib (1)	Absent	13	–	SD at 16 months	Alive (OS = 898 days)
3	46	Male	CCC	Newly diagnosed	Pazopanib[c] (1)	Present[b]	28	8	Unevaluable (Discontinued from toxicity)	Died (OS = 464 days)
4	81	Female	Chromophobe	Recurrent	Sunitinib (1)	Absent	1	7	SD at 2 months (Shrinkage of pancreatic mass)	Died (OS = 545 days)
5	67	Male	CCC	Recurrent	Bevacizumab (5)	Absent	1	11	SD at 3 months (No significant change in bone metastasis)	Alive (OS = 763 days)
6	57	Female	CCC	Newly diagnosed	Pazopanib (1)	Present[b]	3	–	SD at 11 months	Alive (OS = 735 days)
7	48	Female	Unclassified	Recurrent	Lenvatinib + Everolimus (7)	Absent	11	9	PR at 8 months (Shrinkage of metastases)	Alive (OS = 689 days)

CCC clear cell carcinoma, *^{18}F-FDG* 2-deoxy-2-(^{18}F)fluoro-D-glucose, *^{18}F-FPPRGD$_2$* (^{18}F)-2-fluoropropionyl-labeled PEGylated dimeric arginine-glycine-aspartic acid (RGD) peptide [PEG3-E{c(RGDyk)}2], *OS* overall survival, *PET/CT* positron emission tomography/computed tomography, *PR* partial response, *SD* stable disease

[a] Patient was diagnosed as renal cell carcinoma based on imaging findings

[b] Patients had inoperable synchronous metastatic lesions at diagnosis

[c] Pazopanib therapy was discontinued after 12 days due to bleeding complication, and followed by additional therapies including nivolumub, axitinib, and tumor debulking surgery

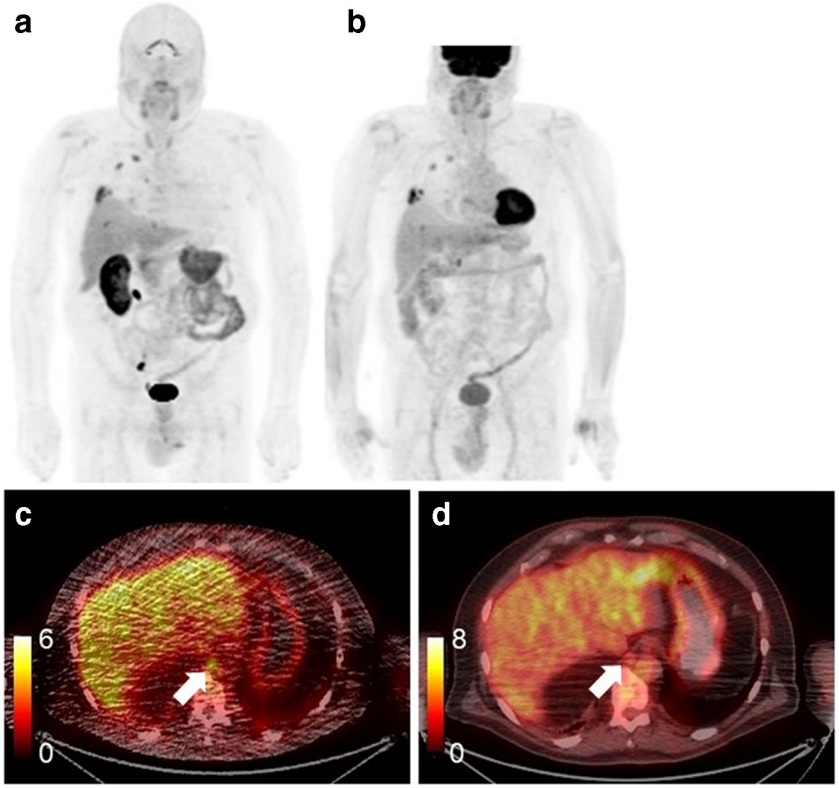

Fig. 1 A 73-year-old male patient with mRCC (patient no. 2). This patient had multiple pleural and paraaortic lymph node metastases that were identified on CT. Maximum intensity projection images of ^{18}F-FPPRGD$_2$ (**a**) and ^{18}F-FDG PET/CT (**b**) showed significant radiotracer uptake in multiple pleural metastases. ^{18}F-FPPRGD$_2$ PET/CT showed uptake in a paraaortic lymph node metastasis with a short diameter of 12 mm (**c**, *white arrow*) that was not seen on ^{18}F-FDG PET/CT (**d**, *white arrow*)

Statistical analysis

We used the EZR software for statistical analyses [6]. Comparison of SUV$_{max}$ and T/B in detected lesions on ^{18}F-FPPRGD$_2$ and ^{18}F-FDG PET/CT was performed using Mann-Whitney U test and Spearman's rank correlation coefficient. Evaluation of significance in change of SUV$_{max}$ and T/B between the initial and follow-up ^{18}F-FPPRGD$_2$ PET/CT was performed using Mann-Whitney U test. $P < 0.05$ was considered statistically significant.

Results

A total of 60 lesions (3 primary and 57 metastatic) were identified prior to the start of antiangiogenic therapy as shown in Table 1 and Supplemental Table 1. Seven lesions were found to only have uptake on ^{18}F-FPPRGD$_2$ PET/CT and four only on ^{18}F-FDG PET/CT (Fig. 1). In one patient, neither ^{18}F-FPPRGD$_2$ nor ^{18}F-FDG PET/CT showed uptake in the primary tumor due to urinary excretion of radiotracers.

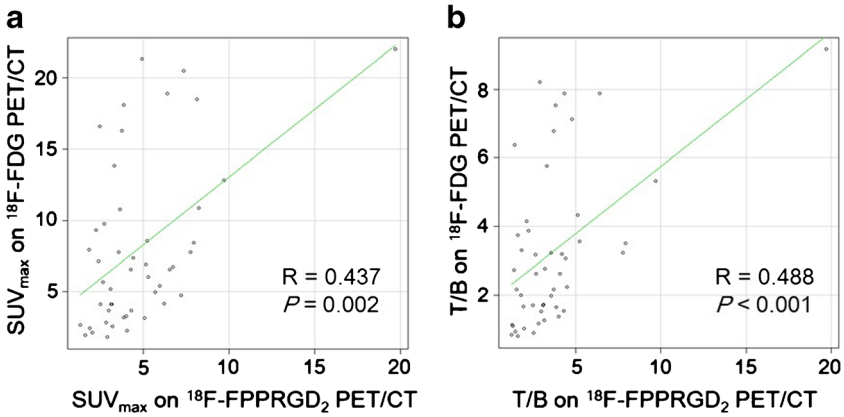

Fig. 2 Correlation of uptake between ^{18}F-FPPRGD$_2$ and ^{18}F-FDG PET/CT. Both SUV$_{max}$ (**a**) and T/B (**b**) showed moderate positive correlation between ^{18}F-FPPRGD$_2$ and ^{18}F-FDG PET/CT

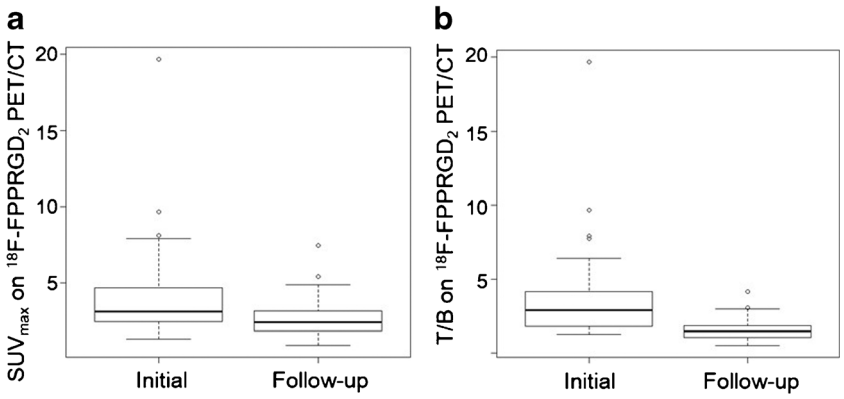

Fig. 3 Comparison of ^{18}F-FPPRGD$_2$ uptake between the initial and follow-up PET/CT after initiation of antiangiogenic therapy. Both SUV$_{max}$ (**a**) and T/B (**b**) significantly decreased in these lesions after antiangiogenic therapy

Supplemental Table 1 shows SUV$_{max}$ and T/B measured on ^{18}F-FPPRGD$_2$ and ^{18}F-FDG PET/CT in each lesion. SUV$_{max}$ from ^{18}F-FPPRGD$_2$ PET/CT was significantly lower than that from ^{18}F-FDG PET/CT (4.4 ± 2.9 vs 7.8 ± 5.6, $P < 0.001$). Both SUV$_{max}$ and T/B showed moderate correlation between ^{18}F-FPPRGD$_2$ and ^{18}F-FDG PET/CT (SUV$_{max}$, R = 0.437, $P = 0.002$; T/B, R = 0.488, $P < 0.001$) (Fig. 2).

Among five patients who had a follow-up ^{18}F-FPPRGD$_2$ PET/CT, four patients had a total of 40 lesions with significant ^{18}F-FPPRGD$_2$ uptake before systemic therapy. Supplemental Table 2 shows the changes in SUV$_{max}$ and T/B between the initial and follow-up ^{18}F-FPPRGD$_2$ PET/CT for all detected lesions. Both SUV$_{max}$ and T/B significantly decreased in these lesions after antiangiogenic therapy (SUV$_{max}$, 4.2 ± 3.2 vs 2.6 ± 1.4, $P = 0.003$; T/B, 3.7 ± 3.2 vs 1.5 ± 0.8, $P < 0.001$) (Figs. 3 and 4). Average changes in SUV$_{max}$ and T/B were − 29.3 ± 23.6% and − 48.1 ± 28.3%, respectively. Three of the patients (patients 1, 3, and 7) had decrease of ^{18}F-FPPRGD$_2$ uptake in mRCC lesions on the follow-up PET/CT. Patient 1 had stable disease based on tumor diameter measurements 2 months after initiating pazopanib. Patient 3 showed expansion of necrosis in the tumor on contrast-enhanced CT that correlated with decrease of ^{18}F-FPPRGD$_2$ uptake (Fig. 5). However, this patient had severe bleeding from pazopanib and required a change in therapy after 2 weeks of treatment; therefore, clinical response could not be fully assessed. Patient 7 had long-term tumor control with the combination of lenvatinib and everolimus for more than 2 years, achieving a partial response based on tumor diameter measurements at 8 months after initiating treatment. Patient 5 had bone metastasis with an increase in SUV$_{max}$ and T/B in the follow-up ^{18}F-FPPRGD$_2$ PET/CT. However, after he received 3 months of bevacizumab, he has had excellent tumor control in the single lesion for more than 2 years without requiring additional treatment. As a limitation of this pilot study, heterogeneity of treatment, RCC subtype and tumor location precluded complete correlation of changes in ^{18}F-FPPRGD$_2$ with clinical response.

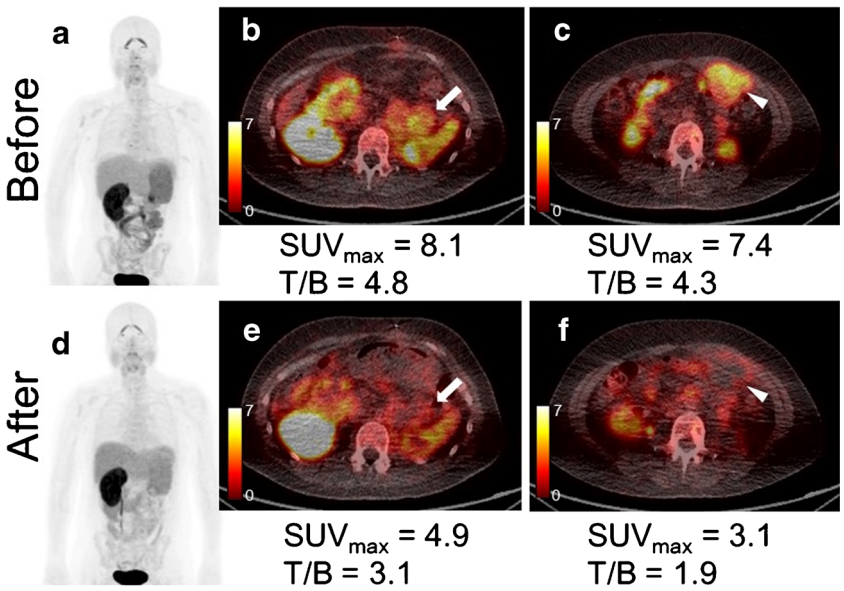

Fig. 4 A 48-year-old woman with mRCC (patient no. 7). Two ^{18}F-FPPRGD$_2$ PET/CT studies are shown (**a**–**c**, baseline; **d**–**f**, after starting antiangiogenic therapy). The largest mass in the left retroperitoneum (**b**, *white arrow*) and abdominal wall (**c**, *white arrowhead*) showed high ^{18}F-FPPRGD$_2$ uptake before therapy. Both lesions showed decrease in ^{18}F-FPPRGD$_2$ uptake after initiation of antiangiogenic therapy

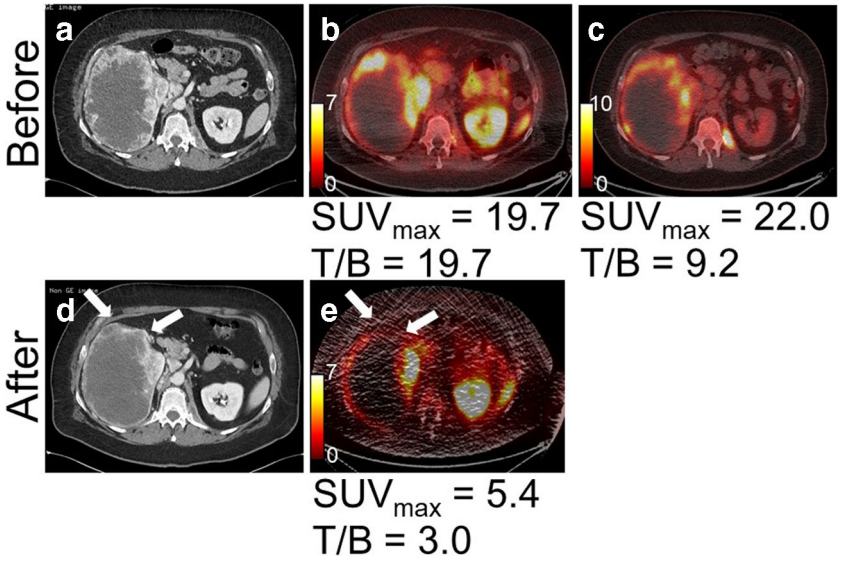

Fig. 5 A 46-year-old man with newly diagnosed mRCC lesions (patient no. 3). Contrast-enhanced CT (**a**), ^{18}F-FPPRGD$_2$ PET/CT (**b**), and ^{18}F-FDG PET/CT (**c**) before systemic therapy showed the primary tumor with necrosis and elevated radiotracer uptake in the peripheral tumor tissue in the right kidney. After initiation of antiangiogenic drug, expansion of necrosis in the tumor was observed on contrast-enhanced CT (**d**, *white arrows*) in concordance with decrease of ^{18}F-FPPRGD$_2$ uptake (**e**, *white arrows*)

Discussion

We evaluated the possible clinical utility of ^{18}F-FPPRGD$_2$ PET/CT in patients with mRCC in terms of lesion detectability and monitoring response to antiangiogenic therapy.

Several studies have shown that SUV$_{max}$ from ^{18}F-FDG PET/CT was significantly higher than that from ^{18}F-FPPRGD$_2$ PET/CT in various cancers [2, 3, 7–9]. One possible reason for this difference is that there is only a small number of endothelial cells expressing integrin $\alpha_v\beta_3$ in each lesion as opposed to many tumor cells with an increased number of glucose transporters [7, 8]. ^{18}F-FPPRGD$_2$ PET/CT detected more mRCC lesions than ^{18}F-FDG PET/CT, consistent with a previous study in breast cancer patients [4]. In this study, while all lesions had CT or MRI correlates, lesions were not all histopathologically confirmed as mRCC, particularly in pleural or lung nodules. Thus, we could not calculate sensitivity, specificity and accuracy, nor statistically compare their diagnostic ability. However, based on these preliminary results, ^{18}F-FPPRGD$_2$ PET/CT may have comparable detectability for mRCC lesions with ^{18}F-FDG PET/CT.

Significant positive correlation between ^{18}F-FPPRGD$_2$ and ^{18}F-FDG uptake has already been shown in other malignant tumors [7–9]. One possible explanation for the correlation between angiogenesis and glycolysis in RCC is a mutation of von Hippel-Lindau (VHL) tumor suppressor gene. Loss of VHL activity leads to activation of the hypoxia-inducible factor pathway, followed by increase of anaerobic glycolysis and enhanced transcription of hypoxia-inducible genes including vascular endothelial growth factor [10].

Our pilot study revealed a decrease of ^{18}F-FPPRGD$_2$ uptake in mRCC lesions after starting antiangiogenic therapy. Taken together with the results of previous studies [2, 3], the early follow-up ^{18}F-FPPRGD$_2$ PET/CT may help evaluate response to antiangiogenic therapy. However, our study is limited by the small patient cohort with heterogeneous treatment and histological subtypes of RCC. As such, we could not evaluate correlation between the change in ^{18}F-FPPRGD$_2$ uptake, clinically best response to treatment, or patient survival. To determine the usefulness of ^{18}F-FPPRGD$_2$ PET/CT for evaluating clinical benefit of antiangiogenic therapy in patients with mRCC, further studies enrolling a larger number of patients with well-defined histology and treatment cohorts are needed.

In conclusion, ^{18}F-FPPRGD$_2$ PET/CT may be an useful tool for monitoring early response to antiangiogenic therapy in patients with mRCC. These preliminary results need to be confirmed in larger cohorts.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Conflict of interest Alice C. Fan receives funding support from ASCO Conquer Cancer Foundation Career Development Award and is a founder of Molecular Decisions Inc.

Andrei Iagaru receives institutional research support from GE Healthcare (unrelated to this study).

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