

Somatostatin Receptor Imaging with [¹⁸F]FET-βAG-TOCA PET/CT and [⁶⁸Ga]Ga-DOTA-Peptide PET/CT in Patients with Neuroendocrine Tumors: A Prospective, Phase 2 Comparative Study

Suraiya Dubash*¹, Tara D. Barwick*^{1,2}, Kasia Kozlowski¹, Andrea G. Rockall¹, Sairah Khan², Sameer Khan², Siraj Yusuf³, Angela Lamarca^{4,5}, Juan W. Valle^{4,5}, Richard A. Hubner^{4,5}, Mairéad G. McNamara^{4,5}, Andrea Frilling¹, Tricia Tan⁶, Florian Wernig⁶, Jeannie Todd⁶, Karim Meeran⁶, Bhavesh Pratap¹, Saleem Azeem⁷, Michael Huiban⁷, Nicholas Keat⁷, Jingky P. Lozano-Kuehne^{1,8}, Eric O. Aboagye¹, and Rohini Sharma¹

¹Department of Surgery and Cancer, Imperial College London, London, United Kingdom; ²Department of Imaging, Imperial College Healthcare NHS Trust, London, United Kingdom; ³Radiology and Nuclear Medicine Department, Royal Marsden NHS Foundation Trust, London, United Kingdom; ⁴Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom; ⁵Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; ⁶Department of Endocrinology, Imperial College Healthcare NHS Trust, London, United Kingdom; ⁷Invicro-London, Imperial College London, London, United Kingdom; and ⁸Population Health Sciences Institute, Faculty of Medical Sciences, University of Newcastle, Newcastle, United Kingdom

There is a clinical need for ¹⁸F-labeled somatostatin analogs for the imaging of neuroendocrine tumors (NET), given the limitations of using [⁶⁸Ga]Ga-DOTA-peptides, particularly with regard to widespread accessibility. We have shown that [¹⁸F]fluoroethyl-triazole-[Tyr³]-octreotate ([¹⁸F]FET-βAG-TOCA) has favorable dosimetry and biodistribution. As a step toward clinical implementation, we conducted a prospective, noninferiority study of [¹⁸F]FET-βAG-TOCA PET/CT compared with [⁶⁸Ga]Ga-DOTA-peptide PET/CT in patients with NET. **Methods:** Forty-five patients with histologically confirmed NET, grades 1 and 2, underwent PET/CT imaging with both [¹⁸F]FET-βAG-TOCA and [⁶⁸Ga]Ga-peptide performed within a 6-mo window (median, 77 d; range, 6–180 d). Whole-body PET/CT was conducted 50 min after injection of 165 MBq of [¹⁸F]FET-βAG-TOCA. Tracer uptake was evaluated by comparing SUV_{max} and tumor-to-background ratios at both lesion and regional levels by 2 unblinded, experienced readers. A randomized, blinded reading of both scans was also then undertaken by 3 experienced readers, and consensus was assessed at a regional level. The ability of both tracers to visualize liver metastases was also assessed. **Results:** A total of 285 lesions were detected on both imaging modalities. An additional 13 tumor deposits were seen in 8 patients on [¹⁸F]FET-βAG-TOCA PET/CT, and [⁶⁸Ga]Ga-DOTA-peptide PET/CT detected an additional 7 lesions in 5 patients. Excellent correlation in SUV_{max} was observed between both tracers ($r = 0.91$; $P < 0.001$). No difference was observed between median SUV_{max} across regions, except in the liver, where the median tumor-to-background ratio of [¹⁸F]FET-βAG-TOCA was significantly lower than that of [⁶⁸Ga]Ga-DOTA-peptide (2.5 ± 1.9 vs. 3.5 ± 2.3 ; $P < 0.001$). **Conclusion:** [¹⁸F]FET-βAG-TOCA was not inferior to

[⁶⁸Ga]Ga-DOTA-peptide in visualizing NET and may be considered in routine clinical practice given the longer half-life and availability of the cyclotron-produced fluorine radioisotope.

Key Words: [¹⁸F]FET-βAG-TOCA; [⁶⁸Ga]Ga-DOTA-peptide; PET; neuroendocrine tumors; somatostatin receptor

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Neuroendocrine neoplasms (NEN) are a heterogeneous group of malignancies arising from cells of the diffuse neuroendocrine system. Accurate diagnosis of primary lesion and staging the extent of disease dictates both management and prognosis, whereby patients with limited disease can undergo radical locoregional therapy, including surgery or ablation with curative intent, whereas systemic therapy is reserved for those with metastatic disease given with palliative intent (1). Accurate imaging is crucial. As 20%–50% of patients with NEN will have metastatic disease at presentation (2), there is a need for an imaging methodology that is both sensitive and widely accessible.

A unique characteristic of NEN is the expression of somatostatin receptors (SSTRs) on the tumor surface (3). The presence of SSTRs has long been exploited for imaging NEN initially with planar or SPECT imaging using [¹¹¹In]In-diethylenetriaminepentaacetic acid-octreotide and, more recently, with PET/CT using radiolabeled somatostatin analogs (SSAs). PET imaging has greater sensitivity, enhanced resolution, and better accuracy in detecting NEN compared with SPECT imaging (4,5). The most commonly used PET tracers used for the visualization of NEN are SSAs labeled with [⁶⁸Ga]Ga-DOTA-peptides, including [⁶⁸Ga]Ga-DOTA-0-Tyr3-octreotate ([⁶⁸Ga]Ga-DOTATATE) and [⁶⁸Ga]Ga-DOTA-0-Phe1-Tyr3-octreotide ([⁶⁸Ga]Ga-DOTATOC). Defining the presence of SSTRs on the tumor surface is also important for therapeutic decision making, whereby patients with SSTR-positive NEN on [⁶⁸Ga]Ga-DOTA PET may be candidates for [¹⁷⁷Lu]Lu-

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For correspondence or reprints, contact Rohini Sharma (r.sharma@imperial.ac.uk).

*Contributed equally to this work.

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DOTA0-Tyr3-octreotate ($[^{177}\text{Lu}]\text{Lu-DOTATATE}$), a targeted radiotherapeutic that significantly improves progression-free survival in patients with metastatic disease (6).

Although $[^{68}\text{Ga}]\text{Ga-DOTA}$ analogs have good resolution, the availability and scalability of production is limited due to the necessity of an on-site generator pertaining to the short half-life of $[^{68}\text{Ga}]\text{Ga}$. Furthermore, the $[^{68}\text{Ga}]\text{Ga}$ -radiometal may accumulate within the uroteric process of the pancreas, leading to a false-positive diagnosis (7). Clinically, a $[^{18}\text{F}]\text{F}$ -radioligand would overcome the limited capacity of $[^{68}\text{Ga}]\text{Ga-DOTA}$ production while exploiting existing worldwide cyclotron manufacturing. We developed a novel $[^{18}\text{F}]\text{F}$ -octreotate radioligand, $[^{18}\text{F}]\text{fluoroethyl-triazole-[Tyr}^3\text{]-octreotate}$ ($[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$) (8), to obviate these limitations of $[^{68}\text{Ga}]\text{Ga-DOTA}$ ligands. Previously, we showed that tumor uptake of $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$ was superior to that of $[^{68}\text{Ga}]\text{Ga-DOTATATE}$ in vivo with good spatial resolution (9). Clinically, $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$ has favorable dosimetry and biodistribution (8). We therefore performed a prospective study, the primary objective of which was to assess uptake of $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$ both at lesion and regional levels. Evaluation of interreader agreement between $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$ and $[^{68}\text{Ga}]\text{Ga-DOTA-peptide PET}$ was assessed as a secondary endpoint.

MATERIALS AND METHODS

Study Design and Participants

A prospective, multicenter, open-label, single-arm comparative imaging study consisting of an initial safety run phase (part A) followed by a noninferiority phase (part B) was conducted. The safety and biodistribution study (part A) has been reported (8). Patients from part A ($n = 9$) were included in the noninferiority analysis. Key eligibility criteria include histologically confirmed diagnosis of locally advanced or metastatic grade 1 or 2 neuroendocrine tumors (NET), measurable disease with at least 1 lesion with longest diameter ≥ 10 mm on conventional imaging, and positive SSTR imaging within 6 mo of study enrollment with $[^{68}\text{Ga}]\text{Ga-DOTA-peptide PET}$. Patients were not required to stop SSAs before either PET scan. Patients were recruited from 2 U.K. European Neuroendocrine Tumor Society Centers of Excellence, Imperial College Health Care NHS Trust and Christie NHS Foundation Trust, Manchester. All diagnostic tissue samples underwent central pathology review to assess eligibility. The study was approved by the Leeds East, Yorkshire and Humber National Research Committee (13/YH/0281). The administration of radioactivity was approved by the Administration of Radioactive Substances Advisory Committee (United Kingdom) (RPC 630/2892/30595). The Medicines and Health Care Products Regulatory Agency (United Kingdom) gave permission to administer the investigational medicinal product (European Clinical Trials no. 2013-003152-20). All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and registered with EudraCT (2013-003152-20).

Procedures

PET Imaging Protocol. At Imperial College Health Care NHS Trust, clinical PET/CT imaging was performed using $[^{68}\text{Ga}]\text{Ga-DOTATATE}$, as previously described (10) (mean dose injected, 134.1 MBq; mean uptake period, 37.7 min [range, 27–82 min]). At Christie NHS Foundation Trust, imaging was performed using $[^{68}\text{Ga}]\text{Ga-DOTANOC PET}$ (mean dose injected: 136.2 MBq and mean uptake period of 65.2 min (range, 30–82 min) and a single case $[^{68}\text{Ga}]\text{Ga-DOTATOC}$ (dose, 143 MBq; uptake time, 75 min).

No clinically significant differences in DOTA tracers have been reported (11,12), and these patients were all included for the primary analysis. Imaging with $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$ was conducted after $[^{68}\text{Ga}]\text{Ga-DOTA-peptide PET}$ in most cases.

$[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$ was synthesized by Invicro-London (8); the mean dose injected was 157.7 MBq, with a mean uptake period of 37.4 min (range, 30–51 min). Images were acquired on a Siemens Biograph 6 TruePoint PET/CT scanner (with TrueV; extended field of view) at 50 min after injection (8). An attenuation CT scan was obtained from vertex to midthigh, immediately followed by a PET emission study at 4 min per bed position (CT settings: tube potential, 130 kV; exposure, 15 effective mAs; pitch, 1.5; slice thickness, 5 mm; rotation time, 0.6 s). Images were reconstructed using the ordered-subsets expectation maximization algorithm (4 iterations and 8 subsets) with corrections for dead time, scatter, attenuation, and radioactive decay. All images were viewed on a dedicated PET workstation (Hermes Medical Solutions).

Image Interpretation. Images were reviewed by 2 observers: a radiation oncologist with greater than 15 y of experience in imaging and tumor outlining and an experienced radiologist (with dual accreditation in radiology and nuclear medicine) with greater than 20 y of experience. To ensure a methodical and consistent approach, comparison of $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$ with $[^{68}\text{Ga}]\text{Ga-DOTA-peptide PET/CT}$ on a patient-by-patient and lesion-by-lesion analysis was performed. Due to the large number of metastases, lesions were analyzed within the context of anatomic regions. Seven regions were defined as being the most common sites for both primary tumors and metastases: head and neck, lung, liver, pancreas, abdomen/pelvis, bone and lymph nodes. Any organ with greater than 5 lesions were truncated at 5 target lesions as in previous studies (13,14). SUV measurements (SUV_{max} , SUV_{mean} , and tumor-to-background ratio [TBR]) were obtained for lesion-by-lesion analysis by manually outlining whole tumor volumes on side-by-side analysis of both studies to ensure, in cases with innumerable lesions, that the same lesions were selected for comparative quantitative analysis. For comparative SUV analysis, only those lesions that were visible on both $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA}$ and $[^{68}\text{Ga}]\text{Ga-DOTA-peptide PET/CT}$ were included reference (normal background) tissue were outlined using a spheric reference volume of interest (3 cm^3 for background liver; 2 cm^3 for spleen, bone, and mediastinal blood pool); 1 cm^3 for spheric volumes in the pancreas and sum of 3 slices manually drawn around each adrenal gland). TBR was calculated using tumor lesion $\text{SUV}_{\text{max}}/\text{background tissue SUV}_{\text{mean}}$ using background liver for liver metastases, background bone marrow for bone metastases, and background mediastinal blood pool for soft-tissue, nodal, and pulmonary metastases.

As the presence of liver metastases is an independent prognostic factor (15), subgroup analysis of SUV and TBR measurements of the liver lesions based on tumor size was performed.

Independent Reader Evaluations. PET/CT scans were reviewed by 3 independent imaging experts to obtain an objective interreader lesion detection rate between $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA PET/CT}$ and $[^{68}\text{Ga}]\text{Ga-DOTA-peptide PET/CT}$ scans. To avoid recall bias, $[^{18}\text{F}]\text{FET-}\beta\text{AG-TOCA PET/CT}$ and $[^{68}\text{Ga}]\text{Ga-DOTA-peptide PET/CT}$ scans for each subject were reviewed at least 4 wk apart in random order. Readers were blinded to clinical details, type of scan and results of other imaging modalities. Readers documented the presence or absence of lesions in each of the 7 previously defined areas. Comparison was made between individual readers across both imaging modalities for interobserver agreement. After locking findings, readers then performed a final side-by-side visual analysis of the 2 sets of scans to document any discordant lesions

detected on 1 scan and not the other, to arrive at consensus between the 3 readers.

Clinical cross-sectional imaging (contrast-enhanced CT or MRI) performed within 3 mo of [¹⁸F]FET-βAG-TOCA was reviewed by a single experienced observer with more than 20 y of experience.

Statistical Analysis

A total of 56 patients were required based on a hypothesized 90% sensitivity, a noninferiority margin of 10%, power of 80%, and a level of significance of 5%. Descriptive statistics such as the median and interquartile range were calculated for numeric outcomes. Wilcoxon test was used for comparison of results. Pearson linear correlation test was used to evaluate correlation between SUV_{max} values. Groups were compared using the χ^2 test. The Cohen κ and the Fleiss κ were used to determine the level of agreement among 2 and more than 2 readers of [¹⁸F]FET-βAG-TOCA and [⁶⁸Ga]Ga-DOTA-peptide PET/CT, respectively. A *P* value lower than 0.05 was taken to be significant. All statistical analyses were performed using SPSS version 27.0 (IBM Inc.) and Stata 16 (StataCorp LLC).

RESULTS

Baseline Characteristics

A total of 56 patients were enrolled to the study. Eleven patients were excluded from the primary analysis: 2 patients underwent octreotide scan, 6 patients did not have a [⁶⁸Ga]Ga-DOTA-peptide PET/CT within 6 mo of [¹⁸F]FET-βAG-TOCA PET/CT and in a further 3 patients, central pathology review after [⁶⁸Ga]Ga-DOTA-peptide and [¹⁸F]FET-βAG-TOCA imaging reported high-grade neuroendocrine carcinoma. A total of 45 patients were included in the final analysis. Four patients had a [⁶⁸Ga]Ga-DOTANOC PET/CT and 1 patient had [⁶⁸Ga]Ga-DOTATOC PET/CT. All remaining patients underwent [⁶⁸Ga]Ga-DOTATATE PET/CT. The median age of the enrolled population was 57 y (range, 29–81 y) and most had a diagnosis of small-bowel (44%) NET. All patients had either locally advanced (9%) or metastatic disease (91%), the commonest site of metastases being the liver (58%). Demographics and clinical characteristics of the study population are presented in Table 1. The median interval between [¹⁸F]FET-βAG-TOCA and [⁶⁸Ga]Ga-DOTA PET/CT was 77 d (range, 6–180 d).

Comparison of [¹⁸F]FET-βAG-TOCA and [⁶⁸Ga]Ga-DOTA-Peptide PET

Lesion Analysis. On per-lesion analysis, 285 lesions were seen both on [¹⁸F]FET-βAG-TOCA PET/CT and [⁶⁸Ga]Ga-DOTA-peptide PET/CT. Most lesions were within the liver (38.6% for both imaging modalities) followed by nodal involvement (16.8%) and bone metastases (17.1%). After unblinding of readers, side-by-side visual analysis illustrated 20 discordant lesions in 11 patients; in 6 patients additional lesions were detected on [¹⁸F]FET-βAG-TOCA in comparison to [⁶⁸Ga]Ga-DOTA-peptide, conversely additional lesions were detected on [⁶⁸Ga]Ga-DOTA-peptide in 3 patients compared with [¹⁸F]FET-βAG-TOCA and in 2 patients there was a mixture with some lesions detected by 1 tracer and not the other and vice versa (Table 2). [¹⁸F]FET-βAG-TOCA detected an additional 13 lesions (6 liver metastases, 4 bone metastases, 2 nodes, and 1 small-bowel lesion) in 8 patients and [⁶⁸Ga]Ga-DOTA-peptide PET/CT detected an additional 7 lesions (4 liver, 1 bone, 1 pancreas, and 1 node) in 5 patients (Fig. 1B).

TABLE 1

Baseline Characteristics of Patient Cohort (*n* = 45)

Variable	Value*
Age (y)	
Median	57
Range	29–81
Sex	
Male	23 (51)
Female	22 (49)
Stage	
Locally advanced	4 (9)
Metastatic	41 (91)
Site of primary tumor	
Pancreas	15 (33)
Small bowel	20 (44)
Lung	3 (7)
Other	7 (16)
Grade	
1	15 (33)
2	21 (47)
Unknown	9 (20)
Site of metastatic disease	
Liver	27 (60)
Bone	12 (27)
Nodes	10 (22)
Lung	3 (7)
Other	17 (38)
Median Ki-67 (%)	3 (7) [†]
Chromogranin A (ng/mL)	72 (92) [†]
Previous treatment	
Surgery	24 (53)
Somatostatin analogs	20 (44)
Chemotherapy	9 (20)
PRRT	7 (16)
RFA	6 (13)
Other	3 (7)

*Data are reported as numbers of patients, with percentages of patients in parentheses.

[†]Value in parentheses is interquartile range.

PRRT = peptide receptor radiotherapy; RFA = radiofrequency ablation.

For comparative SUV analysis, 285 lesions were included. Excellent correlation in lesion SUV_{max} between imaging modalities was observed (*r* = 0.91; *P* < 0.001) (Fig. 2). We then assessed the impact of the use of SSAs on tracer uptake. Twenty-three patients (51%) were receiving monthly injections with SSAs. No difference was observed in median SUV_{max} (\pm SD) of [¹⁸F]FET-βAG-TOCA of those receiving SSAs (19.2 \pm 21.1) compared with those who were not (15.8 \pm 15.9) (*P* = 0.06).

Regional Analysis. No significant difference was noted in the median SUV_{max} across all tumor regions between the 2 imaging

TABLE 2
Discordant Lesions Between [¹⁸F]FET-βAG-TOCA (FETO) and [⁶⁸Ga]Ga-DOTA-peptide (DOTA) PET/CT

Patient	Time between scans (mo)	Congruent site(s)	Lesion	Discordant lesion site	Lesion size (mm)	Scan
1	4.6	Liver	1	Liver	7	FETO
2	0.2	Liver, nodal	2	Node	5	FETO
			3	Node	5	FETO
3	4.8	Liver, peritoneal	4	Liver	7	FETO
4	0.6	Bone	5	Bone	3	FETO
5	4.3	Liver, nodal	6	Liver	10	DOTA
6	2.5	Gastric, liver	7	Liver	8	DOTA
			8	Liver	8	DOTA
7	0.2	Liver, nodal	9	Liver	12	DOTA
			10	Pancreas	13	DOTA
8	1.6	Bone, nodal	11	Bone	10	FETO
			12	Bone	4	FETO
			13	Bone	4	FETO
			14	Small bowel	5	FETO
			15	Node	15	DOTA
9	1.1	Liver	16	Liver	9	FETO
			17	Liver	9	FETO
10	3.7	Liver, nodal	18	Liver	5	FETO
11	4.4	Liver, bone	19	Bone	3	DOTA
			20	Liver	8	FETO

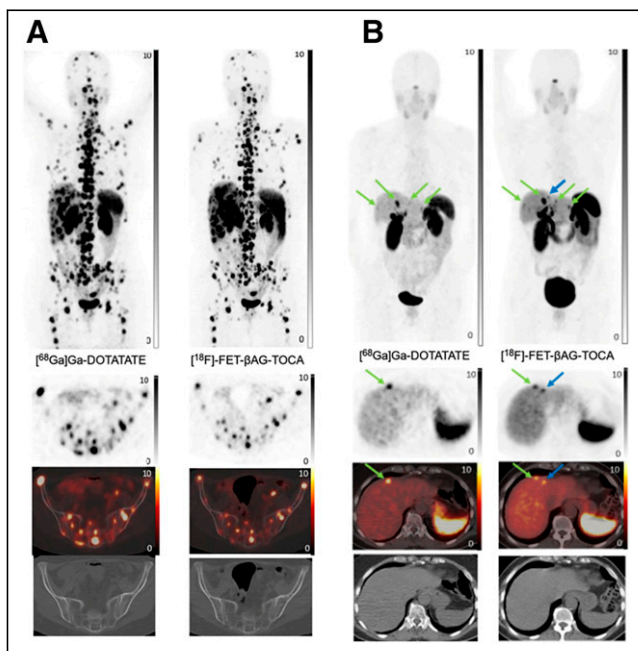


FIGURE 1. (A) Congruent imaging: [⁶⁸Ga]Ga-DOTATATE imaging and [¹⁸F]FET-βAG-TOCA imaging (maximum-intensity projection [MIP], axial PET, fused and CT images) in metastatic small-bowel NEN with widespread liver and bone metastases. (B) Incongruent imaging: [⁶⁸Ga]Ga-DOTATATE imaging and [¹⁸F]FET-βAG-TOCA imaging (MIP, axial PET, fused and CT images) performed 4 wk apart in metastatic ileal NEN with liver metastases (green arrows), which are more visible on [¹⁸F]FET-βAG-TOCA. Additional lesion is detected on [¹⁸F]FET-βAG-TOCA (blue arrow).

modalities (Table 3). The highest median [¹⁸F]FET-βAG-TOCA SUV_{max} was observed in pancreatic lesions (median SUV_{max}, 24.5 ± 24.9) and the lowest was observed in bone (median SUV_{max}, 9.7 ± 8.8).

Both tracers demonstrated comparable distribution in background organs (spleen, pancreas, adrenals, bone) except for increased background hepatic activity on [¹⁸F]FET-βAG-TOCA PET/CT (Supplemental Fig. 1) (supplemental materials are available at <http://jnm.snmjournals.org>). Low physiologic uptake of [¹⁸F]FET-βAG-TOCA was observed, as previously described in the pituitary, salivary glands, spleen and thyroid gland (8). There

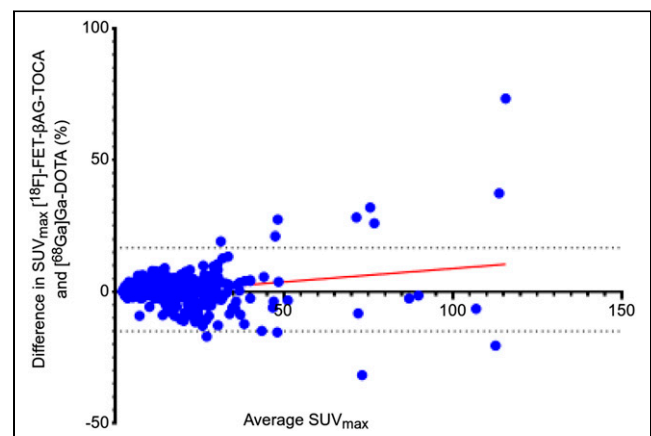


FIGURE 2. Bland-Altman plot of difference in SUV_{max} between [¹⁸F]FET-βAG-TOCA and [⁶⁸Ga]Ga-DOTA-peptide.

TABLE 3
Median Tumor Uptake (SUV_{max}) and Tumor-to-Background Ratio (TBR) of [¹⁸F]FET-βAG-TOCA and [⁶⁸Ga]Ga-DOTA-peptide per Anatomic Region

Region	No. of lesions	[¹⁸ F]FET-βAG-TOCA		[⁶⁸ Ga]Ga-DOTA-peptide		P	Median TBR with:		
		Median SUV _{max}	Range	Median SUV _{max}	Range		[¹⁸ F]FET-βAG-TOCA	[⁶⁸ Ga]Ga-DOTA-peptide	P
Head and neck	3	12.4	10.4–27.7	6.9	6.4–23.4	0.5	29.8	12.2	0.3
Liver	110	19.59	7.2–132.4	20.6	6.7–95.1	0.5	2.5	3.5	<0.001
Bone	49	9.7	2.2–37.0	7.2	1.9–38.8	0.5	12.5	10.1	0.5
Lung	11	10.4	5.3–42.1	9.4	2.2–38.0	0.9	14.6	15.4	0.4
Pancreas	28	24.5	4.2–85.8	21.9	6.4–88.4	0.8	35.2	36.6	0.6
Abdomen/pelvis	36	18.8	2.7–152.3	21.2	4.1–110.3	0.6	23.5	23.6	0.1
Lymph nodes	48	18.0	3.4–102.4	17.0	3.1–122.9	0.7	21.1	29.7	0.5

was a statistical difference observed in median TBR for liver lesions with [¹⁸F]FET-βAG-TOCA compared with [⁶⁸Ga]Ga-DOTA-peptide PET/CT (2.52 ± 1.88 vs. 3.50 ± 2.35; *P* < 0.001). No other differences in regional TBR were observed (Table 3).

Interreader Agreement

Interreader agreement across tumor sites was considered. It was possible to estimate with 95% confidence a κ-agreement of 86% with an SE of 10% assuming 90% positive ratings among raters for a total of 45 subjects. Agreement was significantly higher in the liver with [⁶⁸Ga]Ga-DOTA-peptide (κ = 0.3) than with [¹⁸F]FET-βAG-TOCA (κ = 0.05) (*P* < 0.001). In particular, when considering the liver, discrepancies in reads were noted in 4 patients on [¹⁸F]FET-βAG-TOCA imaging, 3 of whom did not have liver metastases but were thought to be present by 1 of the 3 readers. In contrast, only 1 patient was felt to have liver metastases on [⁶⁸Ga]Ga-DOTA-peptide PET, where none were present by 1 of the 3 readers. No significant differences in agreement were observed across other sites (Table 4).

Liver Metastases

As the presence of liver metastases is an independent prognostic factor, we performed subgroup analysis of uptake in the liver lesions based on lesion size (<1 cm, 1.0–2 cm, >2.1 cm). Of the 110 liver metastases, 28 lesions were smaller than 1 cm, 52 were 1–2 cm, and 30 were larger than 2.1 cm. When considering SUV_{max}, no significant difference in uptake was observed with [¹⁸F]FET-βAG-TOCA in lesions smaller than 1 cm (15.1 ± 7.9) and those 1–2 cm (22.7 ± 19.9) compared with [⁶⁸Ga]Ga-DOTA-peptide (<1 cm, 12.2 ± 6.9 [*P* = 0.2]; 1–2 cm, 22.4 ± 14.5 [*P* = 0.4]). A significantly lower median TBR was observed for lesions 1–2 cm with [¹⁸F]FET-βAG-TOCA (3.3 ± 2.1) compared with [⁶⁸Ga]Ga-DOTA-peptide (4.5 ± 2.4) (*P* = 0.050). No difference was observed in median TBR for lesions smaller than 1 cm ([¹⁸F]FET-βAG-TOCA, 1.9 ± 0.8; [⁶⁸Ga]Ga-DOTA-peptide, 2.3 ± 1.3) (*P* = 0.4). Overall, the [¹⁸F]FET-βAG-TOCA median TBR was significantly lower in the liver than the [⁶⁸Ga]Ga-DOTA-peptide median TBR (2.5 ± 1.9 vs. 3.5 ± 2.3; *P* < 0.001).

DISCUSSION

The superiority of [⁶⁸Ga]Ga-DOTA-peptide PET/CT over [¹¹¹In]In-octreotide SPECT/CT and contrast CT imaging for the

visualization of NET is well established (4,5). However, the use of [⁶⁸Ga]Ga necessitates the presence of an onsite (limited life span) generator, limiting the scalability and availability of [⁶⁸Ga]Ga-DOTA-peptide radioligands, such that many patients are not able to access [⁶⁸Ga]Ga-DOTA-peptide for diagnosis, treatment planning or assessment of disease progression. To alleviate these issues, we developed a GMP compliant [¹⁸F]F-octreotate radiopharmaceutical, [¹⁸F]FET-βAG-TOCA. We have previously reported [¹⁸F]FET-βAG-TOCA to be safe, with good dosimetry and biodistribution, that highlights tumor lesions with high contrast (8). In this prospective study, we have shown that [¹⁸F]FET-βAG-TOCA is excellent in detecting lesions and is not inferior to [⁶⁸Ga]Ga-DOTA-peptide- PET/CT for the detection of NET. We have also shown the ability of [¹⁸F]FET-βAG-TOCA in detecting small liver lesions, an important consideration given the prognostic impact of liver metastases (15).

We observed no significant difference in tumoral SUV_{max} both on lesion and regional bases between scan types confirming the noninferiority of [¹⁸F]FET-βAG-TOCA for imaging NET. Observed SUV_{max} values of [¹⁸F]FET-βAG-TOCA are consistent with the high affinity of [¹⁸F]FET-βAG-TOCA for SSTR2 binding (IC₅₀, 1.6 ± 0.2 nM) (16). The use of SSAs had no impact on [¹⁸F]FET-βAG-TOCA SUV_{max}, an important consideration, given the widespread use of these agents. Moreover, there was excellent correlation between the 2 tracers as confirmed by interobserver agreement across most regions.

The liver is the commonest site of metastases and is an independent prognostic factor in patients with NET (15). Background liver uptake was significantly lower with [¹⁸F]FET-βAG-TOCA compared with [⁶⁸Ga]Ga-DOTA-peptide. This difference in uptake can be attributed to differences in elimination. [¹⁸F]FET-βAG-TOCA is eliminated by both the biliary and renal system, whereas [⁶⁸Ga]Ga-DOTA-peptide is eliminated predominantly through the kidneys. Hepatic clearance and slow clearance through the common bile duct may contribute to the higher background uptake observed on [¹⁸F]FET-βAG-TOCA imaging. As a result of this difference in background uptake, a significant difference in TBR in the liver between the 2 tracers was observed. The higher liver background activity may have contributed to the difference observed on interreader agreement within the liver, whereby observers were less confident in 3 cases about the absence of metastases in “normal liver”, a concept that needs exploring in future work. However, of the 20 discordant lesions, 10 were in the

TABLE 4
Interrater Agreement for [¹⁸F]FET-βAG-TOCA and [⁶⁸Ga]Ga-DOTA-peptide per Anatomic Region Between All 4 Raters

Scan site	[¹⁸ F]FET-βAG-TOCA		[⁶⁸ Ga]Ga-DOTA-peptide		P	P for [¹⁸ F]FET-βAG-TOCA vs. [⁶⁸ Ga]Ga-DOTA-peptide
	Agreement (%)	κ*	Agreement (%)	κ*		
Head and neck	97.4	0.2 (-0.01 to 0.3)	97.8	-0.01 (-0.02 to -0.006)	0.6	0.04
Lung	97.8	-0.01 (-0.02 to -0.01)	98.9	-0.01 (NC)	0.5	NC
Liver	94.4	-0.03 (-0.05 to -0.006)	98.5	0.3 (NC)	<0.001	<0.001
Pancreas	89.3	0.2 (0.1 to 0.3)	91.5	0.1 (-0.03 to 0.3)	0.05	0.2
Abdomen/pelvis	88.5	0.0005 (-0.07 to 0.2)	95.2	0.1 (-0.02 to 0.3)	0.04	0.3
Bone	98.5	0.3 (NC)	100.0	NC	NC	NC
Lymph nodes	97.4	0.3 (-0.01 to 0.3)	96.3	0.2 (-0.02 to 0.3)	0.008	0.7

*Values in parentheses are 95% CIs.
NC = noncalculable.

liver, 6 were only detected on [¹⁸F]FET-βAG-TOCA and 4 with [⁶⁸Ga]Ga-DOTA-peptide imaging. The management in these cases did not change as the patients already had multiple liver metastases.

Since ¹⁸F has a shorter positron range and higher positron yield than ⁶⁸Ga, one might postulate that [¹⁸F]FET-βAG-TOCA imaging could detect smaller lesions compared with [⁶⁸Ga]Ga-DOTA-peptide imaging. On the 20 discordant lesions, 13 were detected only on [¹⁸F]FET-βAG-TOCA, and all were less than or equal to 10 mm in size, whereas 7 were detected only on [⁶⁸Ga]Ga-DOTA-peptide imaging, of which all were greater than or equal to 8 mm in size except for 1 (Table 2). The latest digital PET detector technology may improve detection of small lesions.

The use of [¹⁸F]FET-βAG-TOCA PET/CT may be considered in the clinical setting where difficulties accessing [⁶⁸Ga]Ga-DOTA-peptide have led to longer waiting times for patients, particularly where delivery of [⁶⁸Ga]Ga-DOTA-peptide is limited to those centers within close proximity to the gallium generator. Delivery of low yields of [⁶⁸Ga]Ga-DOTA-peptide is also a common problem and can lead to last minute cancellation of scanning slots with an ever-increasing burden on nuclear medicine departments. Recent work has explored the utility of [¹⁸F]F-AIF-1,4,7-triazacyclononane-1,4,7-tri-acetate-octreotide ([¹⁸F]F-AIF-NOTA-octreotide compared with [⁶⁸Ga]Ga-DOTATATE/NOC in patients with NET (17). In this study the noninferiority of ¹⁸F-labeled AIF-NOTA-octreotide was illustrated; the authors reported high physiologic uptake in the pancreas, necessitating the need for additional cross-sectional imaging to delineate any pancreatic lesion, a feature not observed with [¹⁸F]FET-βAG-TOCA (8). Moreover, SUV_{max} was lower than [⁶⁸Ga]Ga-DOTATATE and TBR within the bone was particularly lower, which may have implications in assessing disease response to therapy within the bone. [⁶⁴Cu]Cu-DOTATATE has also recently been studied, with comparable results to [⁶⁸Ga]Ga-DOTATOC, albeit with a higher radiation burden, which may not be acceptable to users, particularly as patients typically undergo multiple PET/CT studies during their disease journey (18).

However, there are some key limitations. As [¹⁸F]FET-βAG-TOCA imaging was performed after [⁶⁸Ga]Ga-DOTA-peptide imaging in most patients, potential sequence effects cannot be excluded, but most were performed within 6 mo and no change in treatment occurred between both scans. Moreover, due to the variation in time interval between the 2 scans, changes in tumor composition or size and the possible change in SSTR density cannot be excluded (14). Although most patients underwent [⁶⁸Ga]Ga-DOTATATE imaging, a number were imaged with other [⁶⁸Ga]Ga-DOTA-peptide radioligands, the impact of which remains unclear. Finally, PET findings were not validated by a reference imaging standard such that sensitivity or specificity cannot be established.

CONCLUSION

In this prospective head-to-head comparison of [¹⁸F]FET-βAG-TOCA PET/CT and [⁶⁸Ga]Ga-DOTA-peptide PET/CT we have shown excellent tumoural uptake and noninferiority at both lesion and regional levels. [¹⁸F]FET-βAG-TOCA could potentially be used clinically as an alternate to [⁶⁸Ga]Ga-DOTA-peptide. Further developments could lead to its use as a theranostic agent in locally advanced and metastatic NET.

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KEY POINTS

QUESTION: How does the novel fluorine-labeled PET tracer [¹⁸F]FET-βAG-TOCA compare with [⁶⁸Ga]Ga-DOTA-peptide PET/CT for the detection of NET?

PERTINENT FINDINGS: In a prospective, noninferiority study in 45 patients with histologically confirmed NET, we observed excellent correlations between both tracers with no difference across median SUV_{max}.

IMPLICATIONS FOR PATIENT CARE: [¹⁸F]FET-βAG-TOCA may be considered in routine clinical practice for imaging NET.

REFERENCES

- Pavel M, Oberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31:844–860.
- Yao JC, Hassan M, Phan A, et al. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26:3063–3072.
- Klöppel G, Couvelard A, Perren A, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. *Neuroendocrinology*. 2009;90:162–166.
- Sadowski SM, Neychev V, Millo C, et al. Prospective study of ⁶⁸Ga-DOTATATE positron emission tomography/computed tomography for detecting gastroenteropancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol*. 2016;34:588–596.
- Krausz Y, Freedman N, Rubinstein R, et al. ⁶⁸Ga-DOTA-NOC PET/CT imaging of neuroendocrine tumors: comparison with ¹¹¹In-DTPA-octreotide (OctreoScan®). *Mol Imaging Biol*. 2011;13:583–593.
- Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ¹⁷⁷Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125–135.
- Mapelli P, Tam HH, Sharma R, Aboagye EO, Al-Nahhas A. Frequency and significance of physiological versus pathological uptake of ⁶⁸Ga-DOTATATE in the pancreas: validation with morphological imaging. *Nucl Med Commun*. 2014;35:613–619.
- Dubash SR, Keat N, Mapelli P, et al. Clinical translation of a click-labeled ¹⁸F-octreotate radioligand for imaging neuroendocrine tumors. *J Nucl Med*. 2016;57:1207–1213.
- Iddon L, Leyton J, Indrevoll B, et al. Synthesis and in vitro evaluation of [¹⁸F]fluoroethyl triazole labelled [Tyr3]octreotate analogues using click chemistry. *Bioorg Med Chem Lett*. 2011;21:3122–3127.
- Sharma R, Wang WM, Yusuf S, et al. ⁶⁸Ga-DOTATATE PET/CT parameters predict response to peptide receptor radionuclide therapy in neuroendocrine tumours. *Radiother Oncol*. 2019;141:108–115.
- Koopmans KP, de Vries EG, Kema IP, et al. Staging of carcinoid tumours with ¹⁸F-DOPA PET: a prospective, diagnostic accuracy study. *Lancet Oncol*. 2006;7:728–734.
- Wild D, Bomanji JB, Benkert P, et al. Comparison of ⁶⁸Ga-DOTANOC and ⁶⁸Ga-DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors. *J Nucl Med*. 2013;54:364–372.
- Koopmans KP, Neels ON, Kema IP, et al. Molecular imaging in neuroendocrine tumors: molecular uptake mechanisms and clinical results. *Crit Rev Oncol Hematol*. 2009;71:199–213.
- Poeppel TD, Binse I, Petersenn S, et al. ⁶⁸Ga-DOTATOC versus ⁶⁸Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med*. 2011;52:1864–1870.
- Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335–1342.
- Leyton J, Iddon L, Perumal M, et al. Targeting somatostatin receptors: preclinical evaluation of novel ¹⁸F-fluoroethyltriazole-Tyr3-octreotate analogs for PET. *J Nucl Med*. 2011;52:1441–1448.
- Pauwels E, Cleeren F, Tshibangu T, et al. ¹⁸F-AIF-NOTA-octreotide outperforms ⁶⁸Ga-DOTATATE/NOC PET in neuroendocrine tumor patients: results from a prospective, multicenter study. *J Nucl Med*. 2023;64:632–638.
- Johnbeck CB, Knigge U, Loft A, et al. Head-to-head comparison of ⁶⁴Cu-DOTATATE and ⁶⁸Ga-DOTATOC PET/CT: a prospective study of 59 patients with neuroendocrine tumors. *J Nucl Med*. 2017;58:451–457.