Choice Is Good at Times: The Emergence of [^{64}Cu]Cu-DOTATATE–Based Somatostatin Receptor Imaging in the Era of [^{68}Ga]Ga-DOTATATE

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Somatostatin receptor (SSTR) imaging has brought about impactful changes in clinical management of neuroendocrine tumors (NETs), including pheochromocytoma and paraganglioma (PPGL) (*1,2*). It allows tumor detection and disease characterization and is mandatory for selecting patients who are likely to benefit from peptide receptor radionuclide therapy (commonly referred to as theranostics). In 2016, [^{68}Ga]Ga-DOTATATE (Netspot; Advanced Accelerator Applications) received Food and Drug Administration approval. Recently in 2020, the Food and Drug Administration approved the radiopharmaceutical [^{64}Cu]Cu-DOTATATE (Detectnet; Curium) as an SSTR imaging option.

[^{68}Ga]Ga-SSTR PET/CT has been increasingly evaluated in PPGLs of various genetic backgrounds (*3,4*). A recent metaanalysis showed the pooled PPGL detection rate of [^{68}Ga]Ga-SSTR PET/CT in patients with unknown genetic status to be 93%, which was significantly higher than that of [^{18}F]-fluorodihydroxyphenylalanine ([^{18}F]-FDOPA) PET/CT (80%), [^{18}F]-FDG PET/CT (74%), and [$^{123/131}$I]-metaiodobenzylguanidine scintigraphy [(38%), $P < 0.001$ for all] (*5*). These studies reflect the clinical utility of [^{68}Ga]Ga-SSTR in PPGL imaging. However, [^{18}F]-FDOPA is the preferred radiopharmaceutical of choice in cluster 1B (pseudohypoxia-related: *VHL/HIF2A/PHD1/2*) or cluster 2 (kinase signaling–related: *RET/NF1/TMEM127/MAX*) mutated PPGLs (*3,4*).

Recently, DOTATATE was radiolabeled with Copper-64, which should be inspected from a clinical perspective. In a prospective head-to-head comparison between [^{64}Cu]Cu-DOTATATE and [^{68}Ga]Ga-DOTATOC PET/CT in 59 NET patients, Johnbeck et al. reported a slightly higher detection rate for the former (99.1% vs. 95.6%), with 701 concordant lesions on both scans (*6*). Of 40 additional true-positive lesions detected on either scan, significantly more true-positive lesions were detected by [^{64}Cu]Cu-DOTATATE ($n = 33$) than by [^{68}Ga]Ga-DOTATOC (82.5% vs. 17.5%, $P < 0.0001$). Although the authors attributed the better detection rate to the shorter positron range of Copper-64 (*6*), one must consider that the study used different peptides (DOTATATE vs. DOTATOC) linked to Copper-64 versus Gallium-68, respectively. In a prospective phase III clinical trial from the United States on 42 NET patients and 21 healthy volunteers, Delpassand et al. determined that PET/CT images of diagnostic quality can be acquired with a dose of 148 MBq of [^{64}Cu]Cu-DOTATATE, achieving a sensitivity of 100.0% with 96.8% specificity by masked readers (*7*). In another study, on 112 NET patients, when [^{64}Cu]Cu-DOTATATE was compared with [^{111}In]In-diethylenetriamine pentaacetate-octreotide the former detected more lesions (1,213 vs. 603) and more organ involvement (in 36% of patients) (*8*). These 2 studies led to approval of [^{64}Cu]Cu-DOTATATE by the Food and Drug Administration in September 2020 for the localization of NETs (*8*).

Tumor detectability also depends on the radionuclide's physical properties, which can have a significant impact on diagnostic performance (*6*). Gallium-68 has a lower positron energy than Copper-64 (0.65 vs. 1.90 MeV), resulting in a lower positron range (0.56 vs. 3.5 mm) that provides superior spatial resolution, improved imaging quality, and enhanced detection of small lesions (*7*). Since Copper-64 suffers from a lower positron yield than Gallium-68 (17% vs. 88%), Copper-64 would theoretically require a higher injected activity to achieve the same positron count as Gallium-68 (*6*). However, PET/CT images of diagnostic quality were acquired with a dose of 148 MBq of [^{64}Cu]Cu-DOTATATE (*7*). Nevertheless, the radiation exposure associated with 200 MBq of [^{68}Ga]Ga-DOTATATE (4.3 mSv) is lower than that associated with 148 MBq of [^{64}Cu]Cu-DOTATATE (4.7 mSv), per the package inserts. Furthermore, the long half-life of Copper-64 (12.7 h) has potential advantages over Gallium-68 (1.1 h). This longer half-life allows a scanning window of at least 1–3 h after injection, potentiating a better tumor-to-background ratio and offering logistic benefits in coordinating radiochemical production and patient arrival (*6*). Additionally, serial multiple-time-point imaging is possible with a longer half-life, enabling dosimetric calculations. Lastly, this longer half-life along with centralized production of Copper-64 allows for easier distribution of Copper-64 to remote geographic areas. The physical properties, including other characteristics of both [^{68}Ga]Ga-DOTATATE and [^{64}Cu]Cu-DOTATATE, are summarized in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org).

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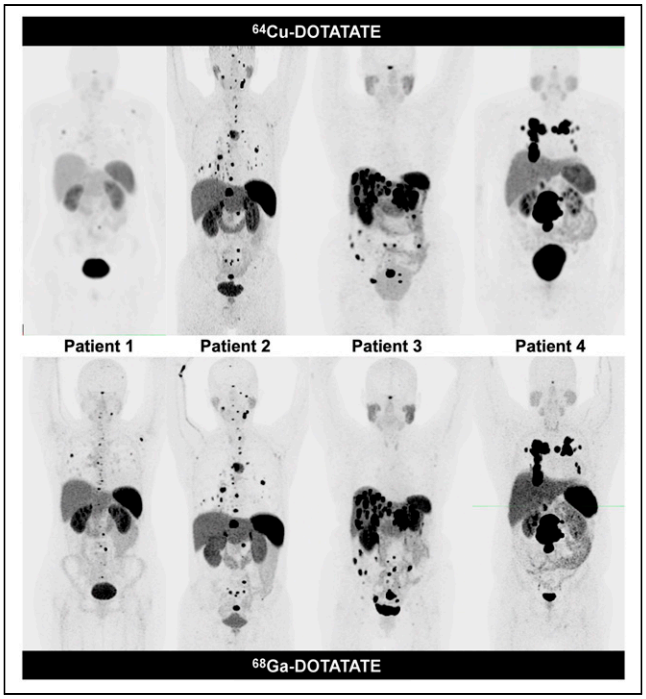

FIGURE 1. SSTR imaging with [^{64}Cu]Cu-DOTATATE and [^{68}Ga]Ga-DOTATATE in PPGL. Figure shows maximum-intensity projection images in 4 patients who underwent imaging with both [^{64}Cu]Cu-DOTATATE (top panel) and [^{68}Ga]Ga-DOTATATE (bottom panel). Leveling of all maximum-intensity projection images is at same SUV_{max}, ranging from 0 to 14.

Five patients (4 new, 1 follow-up) who had undergone [^{64}Cu]Cu-DOTATATE at outside institutions presented to us and underwent [^{68}Ga]Ga-DOTATATE scans prospectively at the National Institutes of Health. The institutional review board of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (clinical trial number NCT00004847) approved this study, and all subjects gave written informed consent. Four of these 5 patients (2 women, 2 men; mean age, 52.3 ± 21.0 y; range, 32–75 y; 1 *SDHB*, 1 *SDHD*, and 2 sporadic) did not receive any new antitumor intervention between the 2 scans. The median interval between the [^{64}Cu]Cu-DOTATATE scan (mean activity, 148 ± 11.1 MBq; mean uptake time, 71.8 ± 10.9 min) and the [^{68}Ga]Ga-DOTATATE scan (mean activity, 199.8 ± 7.4 MBq; mean uptake time, 60.3 ± 1.3 min) was 2 mo (range, 1–4 mo). Details on the PET/CT imaging techniques, scanner, and protocol are summarized in Supplemental Tables 2 and 3. All 4 patients were positive on both scans (Fig. 1). In patient 1, who was undergoing cold somatostatin analog therapy with lanreotide, [^{68}Ga]Ga-DOTATATE seemed to detect more lesions than [^{64}Cu]Cu-DOTATATE, and one might conclude that there had been progression of disease despite therapy. However, this observation could also be attributable to a difference in spatial resolution between scanners, differences in image acquisition and reconstruction methods, or a combination of these factors. Therefore, it is also important to optimize [^{64}Cu]Cu-DOTATATE image acquisition and reconstruction methods, using protocols optimized for the physical properties of Copper-64.

Intraindividual head-to-head comparison between [^{64}Cu]Cu-DOTATATE and [^{68}Ga]Ga-DOTATATE is lacking in PPGLs. It is too early to answer the question of whether Copper-64 or Gallium-68 should be used for PPGL imaging, especially in the widespread landscape of functional imaging options available ([^{18}F]-FDOPA, [^{18}F]-FDG, and [^{123}I]-metaiodobenzylguanidine) (*4,9*). Until we gather more evidence, both [^{68}Ga]Ga-DOTATATE and [^{64}Cu]Cu-DOTATATE should be considered interchangeable; however, we do suggest remaining consistent with the SSTR imaging choice for follow-up imaging. This is vital in those patients who are in a watch-and-wait scheme (stable for a considerable time because of their slow progression), and the incorrect determination could lead to an unwarranted change in management. Seamless availability and distribution of SSTR imaging to the users is necessary to adequately meet an increasing and broader geographic demand.

In conclusion, despite the theoretic advantages of each radiopharmaceutical over the other, currently available comparison data are not conclusive about the superiority of one over the other. Therefore, until definitive data emerge, both [^{68}Ga]Ga-DOTATATE and [^{64}Cu]Cu-DOTATATE can be used interchangeably, if one remains consistent with the SSTR imaging choice for follow-up imaging. The future looks bright for SSTR theranostics with the advent of novel promising radionuclides that will substantially expand their use in NETs, including PPGLs.

DISCLOSURE

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REFERENCES

1. Barrio M, Czernin J, Fanti S, et al. The impact of somatostatin receptor-directed PET/CT on the management of patients with neuroendocrine tumor: a systematic review and meta-analysis. *J Nucl Med.* 2017;58:756–761.
2. Kong G, Schenberg T, Yates CJ, et al. The role of ^{68}Ga-DOTA-octreotate PET/CT in follow-up of SDH-associated pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab.* 2019;104:5091–5099.
3. Taïeb D, Hicks RJ, Hindié E, et al. European Association of Nuclear Medicine practice guideline/Society of Nuclear Medicine and Molecular Imaging procedure standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging.* 2019;46:2112–2137.
4. Taïeb D, Jha A, Treglia G, Pacak K. Molecular imaging and radionuclide therapy of pheochromocytoma and paraganglioma in the era of genomic characterization of disease subgroups. *Endocr Relat Cancer.* 2019;26:R627–R652.
5. Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of ^{68}Ga-DOTA-conjugated somatostatin receptor-targeting peptide PET in detection of pheochromocytoma and paraganglioma: a systematic review and metaanalysis. *J Nucl Med.* 2019;60:369–376.
6. Johnbeck CB, Knigge U, Loft A, et al. Head-to-head comparison of ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC PET/CT: a prospective study of 59 patients with neuroendocrine tumors. *J Nucl Med.* 2017;58:451–457.
7. Delpassand ES, Ranganathan D, Wagh N, et al. Cu-DOTATATE PET/CT for imaging patients with known or suspected somatostatin receptor-positive neuroendocrine tumors: results of the first U.S. prospective, reader-masked clinical trial. *J Nucl Med.* 2020;61:890–896.
8. Pfeifer A, Knigge U, Binderup T, et al. ^{64}Cu-DOTATATE PET for neuroendocrine tumors: a prospective head-to-head comparison with ^{111}In-DTPA-octreotide in 112 patients. *J Nucl Med.* 2015;56:847–854.
9. Carrasquillo JA, Chen CC, Jha A, et al. Imaging of pheochromocytoma and paraganglioma. *J Nucl Med.* 2021;62:1033–1042.