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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, the [^{68}Ga]Ga-DOTATATE (Netspot®) received Food and Drug Administration (FDA) approval. Recently in 2020, the FDA approved the radiopharmaceutical, [^{64}Cu]Cu-DOTATATE (Detectnet®) as an SSTR imaging option.

[^{68}Ga]Ga-SSTR positron emission tomography/computed tomography (PET/CT) has been increasingly evaluated in PPGLs of various genetic background (*3*,*4*). A recent meta-analysis showed the pooled PPGL detection rate of [^{68}Ga]Ga-SSTR PET/CT in patients with unknown genetic status was 93%, which was significantly higher than that of [^{18}F]-fluorodihydroxyphenylalanine ([^{18}F]-FDOPA) PET/CT (80%), [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) PET/CT (74%), and [$^{123/131}$I]-metaiodobenzylguanidine ([$^{123/131}$I]-MIBG 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 signalling 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 (99.1% vs 95.6%, respectively) with 701 concordant lesions on both scans. Out of 40 additional true-positive lesions detected on either scan, significantly more true-positive lesions were detected by [^{64}Cu]Cu-DOTATATE (n=33) compared to [^{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 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 US in 42 NET patients and 21 healthy volunteers, Delpassand et al. determined that diagnostic-quality PET/CT images can be acquired with a dose of 148 MBq of [^{64}Cu]Cu-DOTATATE basis achieving a sensitivity of 100.0% with 96.8% specificity by masked-readers (*7*). Another study in 112 NET patients, [^{64}Cu]Cu-DOTATATE compared to ^{111}In-DTPA-octreotide detected more lesions (1213 vs 603) and organ involvement (in 36% patients) (*8*). These 2 studies led to approval of ^{64}Cu-DOTATATE by the FDA in September 2020 for the localization of NETs (*8*).

Tumor detectability also depends upon the physical properties of the radionuclide which can have a significant impact on diagnostic performance (*6*). Copper-64 compared to Gallium-68 has a lower positron energy (0.65 vs 1.90 MeV) that results in lower positron range (0.56 vs 3.5 mm) providing superior spatial resolution, improved imaging quality, and enhanced detection of small lesions (*7*). Since Copper-64 suffers from a lower positron yield compared to Gallium-68 (17% vs 88%), it would theoretically require a higher injected activity to achieve the same positron count as Gallium-68 (*6*). However, diagnostic-quality PET/CT images were acquired with a dose of 148 MBq of [^{64}Cu]Cu-DOTATATE as mentioned above (*7*). Nevertheless, the radiation exposure associated with 200 MBq of [^{68}Ga]Ga-DOTATATE (4.3 mSv) is lower compared to that with 148 MBq of [^{64}Cu]Cu-DOTATATE (4.7 mSv) per their package inserts. Furthermore, the long half-life of Copper-64 (12.7 hours) has potential advantages over Gallium-68 (1.1 hours). This longer half-life allows a scanning window of at least 1-3 hours post injection potentiating a better tumor to background ratio and offering the logistical benefit 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 geographical areas. The physical properties including other characteristics of both [^{68}Ga]Ga-DOTATATE and [^{64}Cu]Cu-DOTATATE are summarized in Supplementary Table 1.

Five patients (4 new, 1 follow-up) presented to us with [^{64}Cu]Cu-DOTATATE performed at outside institutions and underwent [^{68}Ga]Ga-DOTATATE scans prospectively at the NIH. The institutional review board of *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (Clinical Trial number: NCT00004847) approved this study and all subjects signed a written informed consent. Four of these 5 patients (2 females, 2 males; mean age 52.3±21.0, range 32-75 years; 1 *SDHB*, 1 *SDHD*, and 2 sporadic) did not receive any new anti-tumor intervention between the two scans. The median duration between the [^{64}Cu]Cu-DOTATATE (mean activity 148±11.1 MBq, mean uptake time 71.8±10.9 minutes) and [^{68}Ga]Ga-DOTATATE (mean activity 199.8±7.4 MBq, mean uptake time 60.3±1.3 minutes) PET/CT scans was 2 months (range 1-4 months). The detailed PET/CT imaging techniques, scanner, and protocol information are summarized in Supplementary Tables 2 and 3. All four patients were found to be positive on both scans (Figure 1). In patient 1, who is undergoing cold somatostatin analog therapy with lanreotide, [^{68}Ga]Ga-DOTATATE seems 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, image acquisition and reconstruction methods or combination of these factors. Therefore, it is also important to optimize [^{64}Cu]Cu-DOTATATE scan image acquisition and reconstruction methods, protocols optimized for the physical properties of Copper-64.

Intraindividual head-to-head comparison comparisons 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]-MIBG) (*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 "*wait and watch*" scheme (stable for considerable period of time due to 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 geographical demand.

In conclusion, despite the above-discussed theoretical advantages of each radiopharmaceutical over the other, currently available comparison data is not conclusive of the superiority of one over the other. Therefore, until the definitive data emerges, both [^{68}Ga]Ga-DOTATATE and [^{64}Cu]Cu-DOTATATE could be utilized interchangeably, remaining 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.

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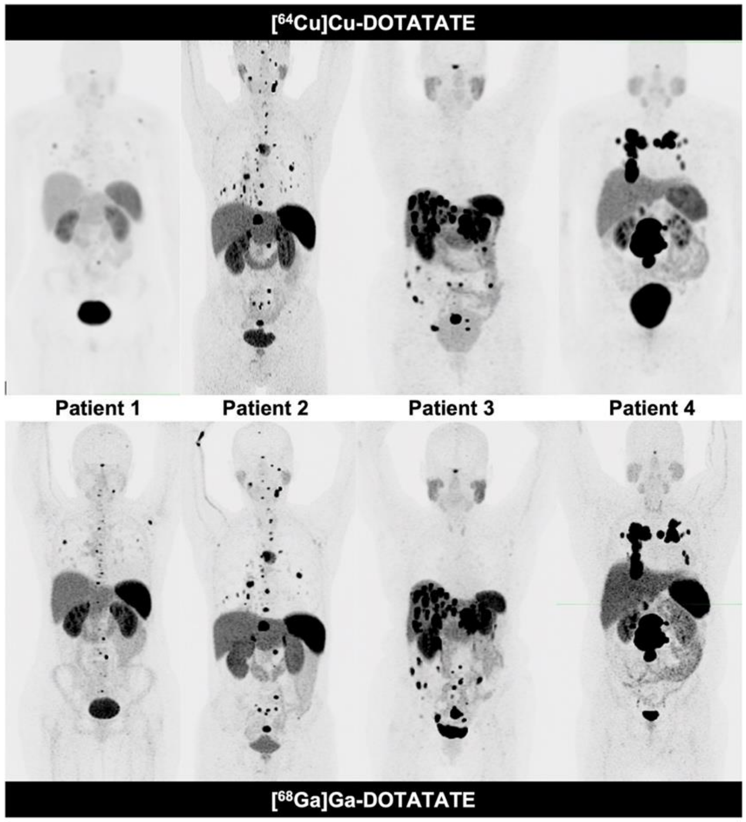
Figure 1. Somatostatin receptor imaging with [^{64}Cu]Cu-DOTATATE and [^{68}Ga]Ga-DOTATATE in pheochromocytoma/paraganglioma



The figure shows the maximum intensity projection images in 4 patients who underwent both [^{64}Cu]Cu-DOTATATE (top panel) and [^{68}Ga]Ga-DOTATATE (bottom panel). The leveling of all maximum intensity projection images are at the same SUVmax ranging from 0 to 14.

Supplementary Table 1. PET/CT based somatostatin receptor imaging in pheochromocytoma/paraganglioma

	$[^{68}Ga]$Ga-DOTATATE	$[^{64}Cu]$Cu-DOTATATE
Physical properties		
• **Half-life (hours)**	1.13	12.7
• **Type of emission**	β^+	$\beta^+/\gamma/\beta^-$
• **Maximum positron energy (mega electron-volt)**	1.90	0.65
• **Positron range (millimeter)**	3.5	0.56
• **Positron yield (%)**	88	17
• **Production**	Generator/cyclotron	Cyclotron
• **Dose [megabecquerel (MBq)]**	200 (max); 2 MBq/kg	148
• **Radiation exposure [millisievert (mSv)]**	4.3 mSv/200 MBq	4.7 mSv/148 MBq
• **Time to PET/CT scan (hours)**	1	1-3
Other characteristics		
• **Background image noise**	-	Higher
• **Acquisition times required to get comparable quality**	-	Higher
• **Distribution/Availability**	Nearby locations to generators, limiting availability	Easier nationwide distribution
• **Scheduling of scans**	Immediate imaging (1 hour)	Delayed imaging possible (1-3 hours)
• **Coordination between radiochemistry and patient scheduling personnel**	Close	Relaxed
• **Quality control**	Variable	Comparable due to centralized production
• **Dosimetric calculation**	Not possible	Possible
Insurance coverage and costs		
• **FDA approval for pheochromocytoma/paraganglioma**	No (used off label)	No (used off label)
• **FDA approval for neuroendocrine tumors**	Yes	Yes
• **Approximate cost of radiopharmaceutical (US dollars/dose)**	3500	3800
Preference based on clinical scenario		
• **Initial evaluation**	Either	Either
• **Follow-up imaging**	As prior	As prior
• **PRRT eligibility**	Either	Either

Supplementary Table 2. Clinical characteristics of the patient cohort

Pt. No.	Age (d)	Age (s)	Duration of disease (yr)	Duration between two scans (mo)	Location of Primary	Size of primary (cm)	Time to metastasize (mo)	LOM	Family History	Mutation al status	Hypersecretion (Plasma)	Treatment received before scans	Treatment instituted after scans
1	22	32	10	2	L carotid body	3.7	1	Lungs, Bones	Neg	***SDHB***	WNL	Surgical resection, Octreotide, Lanreotide, Zometa	Lanreotide, Zometa
2	30	64	34	4	L Carotid body, L Glomus vagale	L Carotid body (6.0), L Glomus vagale (<1.0)	424	Mediastinum, Bones	Pos	***SDHD***	NE, NMN, DA, MTY	Surgical resection, Stereotactic radiation therapy	^{177}Lu-DOTATATE
3	68	75	7	2	L Adrenal	6.0	0	Liver, Pancreas, Abdomen, Pelvis	Neg	Sporadic	NE, NMN, MN, DA, CgA	Surgical resection, Lanreotide,	Temozolomide
4	27	38	11	1	L Adrenal	14.0	0	Lungs, Abdomen	Neg	Sporadic	NE NMN, DA, CgA	Surgical resection	Temozolomide and Olaparib

*mutations highlighted in bold is the pathogenic/likely pathogenic mutation.

Abbreviations: Age (d), age in years at diagnosis; Age (s), age in years at the time of scans; CgA, chromogranin A; Cm, centimeter; DA, dopamine; L, left; LOM, Mo, months; location of metastasis; MTY, methoxytyramine; Neg, negative; NE, norepinephrine; NMN, normetanephrine; Pos, positive; R, right; WNL, within normal limit; Yr, year

Supplementary Table 3: Scan protocol of [^{64}Cu]Cu-DOTATATE and [^{68}Ga]Ga-DOTATATE

Radiopharmaceutical	**[^{64}Cu]Cu-DOTATATE**				**[^{68}Ga]Ga-DOTATATE***
Patients	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patients 1-4**
Dose (MBq)	148	148	129.5	159.1	188.7, 203.5, 196.1, 207.2
Uptake Time	67	67	88	65	60, 59, 62, 60
Frame duration (minutes)	5.0	2.8	4.0	5.0	7.3
Camera Model	Siemens Biograph Horizon	Siemens Biograph128_Vision 600 Edge	GE Discovery MI DR	Siemens Biograph40_mCT	Siemens Biograph128_mCT
Reconstruction Method	OSEM3D+TOF 2i10s	PSF+TOF 4i5s	VPFXS	OSEM3D+TOF 2i21s	PSF+TOF 3i21s
****Additional Corrections**	-	-	DCAL, SLSENS	-	PGC
Post-filter	XYZ Gauss 8mm	All-Pass	Unknown ("Edge enhancing")	XYZ Gauss 8mm	All-Pass
Voxel Size (mm)	4.11, 4.11, 5.0	1.65, 1.65, 5.0	2.73, 2.73, 3.27	4.07, 4.07, 5.0	3.18, 3.18, 3.0

*The dose and uptake time post ^{68}Ga-DOTATATE injection in all the four patients are mentioned.
**All the patients received the following correction: NORM, DTIM, ATTN, SCAT, RAN and DECY. The additional corrections are identified as PGC= prompt-gamma correction, DCAL=Calibrated to Dose Calibrator