

⁶⁸Ga-DOTATATE PET/CT for Neuroblastoma Staging: Utility for Clinical Use

Ata Ur Rehman Maaz¹, Jim O'Doherty², and Mehdi Djekidel³

¹Division of Hematology Oncology, Department of Pediatrics, Sidra Medicine, Doha, Qatar; ²Siemens Healthineers, Charleston, South Carolina; and ³Division of Nuclear Medicine and Molecular Imaging, Department of Diagnostic Imaging, Sidra Medicine, Doha, Qatar

Metaiodobenzylguanidine (MIBG) imaging has been the standard for neuroblastoma staging for many decades. Novel agents such as ¹⁸F-DOPA and ⁶⁸Ga-DOTATATE are being used nowadays in academic centers. During the coronavirus disease 2019 (COVID-19) pandemic, procurement of ¹²³I-MIBG has proved particularly challenging, necessitating the use of ⁶⁸Ga-DOTATATE PET. ⁶⁸Ga-DOTATATE is Food and Drug Administration–approved for imaging of somatostatin receptor–positive gastroenteropancreatic neuroendocrine tumors. **Methods:** ⁶⁸Ga-DOTATATE PET/CT imaging was performed for staging of 3 pediatric patients with neuroblastoma at our institution. A review of the literature was also completed. **Results:** ⁶⁸Ga-DOTATATE PET/CT scans were successfully performed on all patients. All patients showed ⁶⁸Ga-DOTATATE–avid disease. PET scans showed an excellent spatial resolution and demonstrated high accuracy in concordance with current European Association of Nuclear Medicine guidelines. **Conclusion:** We have presented ⁶⁸Ga-DOTATATE PET/CT imaging for staging of neuroblastoma and believe it can reliably be used as an alternative to ¹²³I-MIBG. It has technical, clinical, and practical advantages making it an attractive option. Further multicenter studies are required before it can be recommended for standard clinical use.

Key Words: neuroblastoma imaging; MIBG; ⁶⁸Ga-DOTATATE; COVID-19

J Nucl Med Technol 2021; 49:265–268

DOI: 10.2967/jnmt.120.258939

Neuroblastoma, the most common extracranial solid tumor in the pediatric age group, accounts for about 10% of all solid tumors. It varies in presentation from self-resolving disease to the highly malignant variant associated with an extremely poor prognosis. The staging evaluation of neuroblastoma requires both anatomic and nuclear medicine imaging to look for skeletal metastatic deposits (1,2). ¹²³I-metaiodobenzylguanidine (MIBG) can be used for localization of neural crest tumors such as neuroblastoma, pheochromocytoma, and other neuroendocrine tumors. MIBG with ¹³¹I and more recently ¹²³I has been the standard for

neuroblastoma staging since its utility was first reported by Geatti et al. in 1985 (3,4).

The reported sensitivity and specificity of ¹²³I-MIBG are approximately 90% (2,5). However, because 10% of neuroblastomas are not ¹²³I-MIBG–avid, alternate imaging techniques have been investigated, including PET with ¹⁸F-FDG and ¹⁸F-DOPA, as well as PET/CT with DOTA-conjugated peptides such as ⁶⁸Ga-DOTATATE. Early evidence suggests that these modalities may be superior in sensitivity and specificity to MIBG, thus having the potential of replacing MIBG (6–9).

Somatostatin receptors are variably expressed in neuroblastoma (10,11). Somatostatin analogs such as ⁶⁸Ga-DOTATATE have been in clinical use for nearly a decade. Their role is most established in imaging and treatment of adult neuroendocrine tumors and pheochromocytoma but has also been studied in neuroblastoma in limited settings (7,8). ⁶⁸Ga-DOTATATE PET has been studied at the time of recurrence and at the therapeutic planning phase within a theragnostic paradigm. However, there are very few reports of its role at diagnosis for staging (5,12).

Because MIBG production is limited globally, the severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) pandemic has resulted in unacceptable delays in performing MIBG scans due to interruption in international air traffic. Its availability became particularly challenging at our institution, and we therefore decided to perform ⁶⁸Ga-DOTATATE PET scans for 3 newly diagnosed patients with neuroblastoma. This PET agent is locally produced in a nearby center, obviating the delivery logistics. Here, we report our results and review the literature.

MATERIALS AND METHODS

At the beginning of the COVID 19 pandemic, 3 patients were diagnosed with neuroblastoma at Sidra Medicine. MIBG scintigraphy had to be cancelled for patient 1 when the radiopharmaceutical did not arrive on the scheduled date because of flight cancellations. In a discussion with the clinical team, we decided to perform ⁶⁸Ga-DOTATATE PET/CT imaging instead. For subsequent patients, ⁶⁸Ga-DOTATATE PET was done electively to avoid delays and hazards during the pandemic.

A local ⁶⁸Ge/⁶⁸Ga generator was used to produce ⁶⁸Ga, which was used to radiolabel DOTATATE. Required quality control tests were performed before injecting the patient, in accordance with good manufacturing practices. After radiopharmaceutical injection, an

Received Oct. 20, 2020; revision accepted Feb. 16, 2021.
For correspondence or reprints, contact Mehdi Djekidel (mdjekidel@sidra.org).

Published online April 5, 2021.

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uptake phase of 45–60 min took place before the patient was scanned. All 3 patients were scanned on a GE Healthcare Discovery 690 PET/CT scanner with an axial field of view of 15.7 cm. A low-dose CT scan (80 kVp, mA dose modulation, adaptive statistical iterative reconstruction, 0.5-s rotation time, 40-mm collimation) was performed for attenuation correction and anatomic localization, followed by a whole-body PET scan at 4 min per bed position with an 11-slice overlap. Images were reconstructed using a time-of-flight iterative reconstruction algorithm with a correction for point-spread function (VUE Point FX [GE Healthcare]: 2 iterations, 28 subsets), and a 3.4-mm postreconstruction gaussian filter. The final pixel size was 1.56×1.56 mm, with a slice thickness of 3.27 mm. All 3 patients were scanned under general anesthesia. The need for sedation was independent of the type of study, as the patients would have required general anesthesia for MIBG as well. The administered activities were weight-based according to the guidelines of the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine (74 MBq [2 mCi], 101.75 MBq [2.75 mCi], and 45.88 MBq [1.24 mCi] in the first, second, and third patients, respectively) (2).

RESULTS

Patient 1

A 23-mo-old boy presented with lower back pain, ataxia, and leg weakness for 5 d. Physical examination rapidly progressed from normal to lower-limb weakness and frank paraplegia. His work-up included an MRI scan showing a paravertebral mass at the level of the T2–T4 vertebrae, causing spinal cord compression and edema. He underwent emergency laminotomy and laminoplasty by the neurosurgeons and a debulking procedure resulting in return of lower-limb function over the next 48 h.

Patient 2

A 6-y-old girl presented with an intermittent limp over 2 mo. There were no other symptoms. On physical examination, she was unable to stand straight because of pain in the left leg and had mild tenderness on the left side of the abdomen. MRI of her abdomen and pelvis demonstrated a large mass in the left adrenal gland and numerous bony metastatic lesions.

Patient 3

A 3.5-y-old girl presented with weight loss, swelling of the left eye, body aches, and constitutional symptoms over several months. She was severely malnourished and had left-sided proptosis. MRI showed a right-sided adrenal mass, numerous liver metastases, and multiple vertebral lesions.

The clinical and imaging findings are summarized in Table 1, Supplemental Table 1, and Figures 1–4 (supplemental materials are available at <http://jnm.tnmjournals.org>).

DISCUSSION

The COVID-19 pandemic has posed many unanticipated and unprecedented health-care challenges worldwide, including challenges in the care of cancer patients (13). Before the pandemic, establishing a cancer diagnosis and performing the standard staging investigation were not seen to be a potential problem. Faced with the logistic difficulty of ^{123}I -MIBG procurement, ^{68}Ga -DOTATATE PET scans were performed in the light of limited but compelling evidence of their utility for initial staging of neuroblastoma. Our results will add to the evidence base for future studies.

TABLE 1
Patient Characteristics

Characteristic	Patient 1	Patient 2	Patient 3
Age	23 mo	6 y	3.5 y
Sex	Male	Female	Female
Clinical presentation	Ataxia, irritability, progressing to paraparesis	Limp, discomfort on left side of abdomen	Body pain, swelling of left eye, weight loss, cachexia
Histopathology	Poorly differentiated neuroblastoma	Poorly differentiated neuroblastoma	Not done
Cytogenetics			Not done
N-Myc	Not amplified	Not amplified	
SCA (1p ⁻ , 11q ⁺ , any other, LOH)	Not seen	1q ⁺ , 11q ⁻ , 17q ⁺ , X ⁻ , no LOH	
Alk	No rearrangement	No rearrangement	
NCA	Not seen	Not seen	
Bone marrow	No evidence of infiltration	Infiltrated by nonhematopoietic tumor, neuroblastoma	Infiltrated by nonhematopoietic tumor, neuroblastoma
Urinary catecholamines			
VMA/creatinine ratio	14.1 (0–6.3)	90.7 (0–4.7)	209.8 (0–6.3)
HVA/creatinine ratio	9.9 (0–13.6)	95.6 (0–9.4)	191.0 (0–13.6)

SCA = segmental chromosomal abnormalities; LOH = loss of heterozygosity; NCA = numerical chromosomal abnormalities; 1p⁻ = 1 p deletion; 11q⁻ = 11q deletion; 17q⁺ = gain of 17q; X⁻ = deletion of X-chromosome; N-Myc = N-Myc oncogene; Alk = anaplastic lymphoma kinase; VMA = vanillylmandelic acid; HVA = homovanillic acid.

Data in parentheses represent reference range.

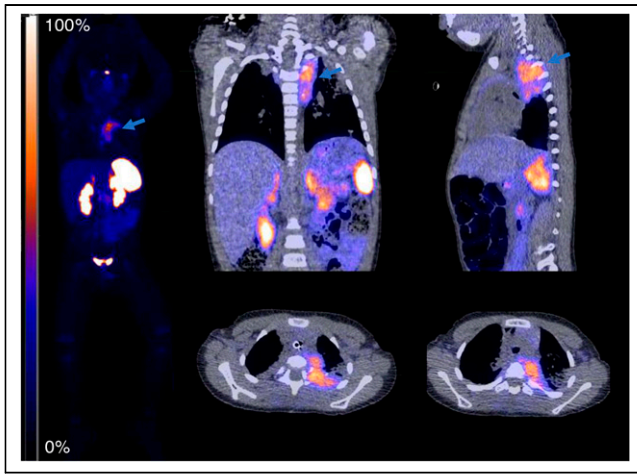


FIGURE 1. Increased uptake in left-sided paravertebral mass and invading the spinal canal and adjacent vertebral body of T3 (blue arrows).

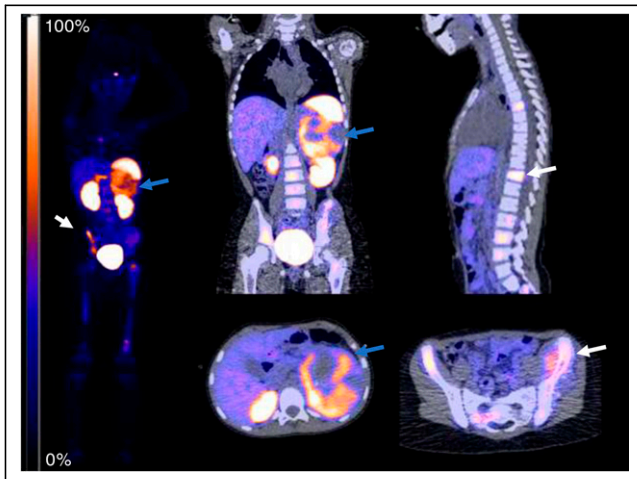


FIGURE 2. Uptake in left suprarenal mass, with areas of necrosis (blue arrows) and evidence of skeletal metastasis (white arrows) and bone marrow infiltration.

^{68}Ga -DOTATATE scans in our patients showed a high spatial resolution and high accuracy in concordance with reports in the literature (5,12,14).

In neuroblastoma management, the role of MIBG scintigraphy is established in staging, prognosis, and response evaluation (15,16). However, several logistic disadvantages make this form of imaging less attractive. These include a lengthy acquisition process, a protracted imaging schedule requiring repeated visits to the nuclear medicine department, and an occasional need for inpatient admission for younger patients. Another disadvantage is the need for thyroid blockade with Lugol solution, as MIBG can result in the accumulation of unbound iodine in the thyroid gland. Finally, MIBG uptake is affected by other medications affecting the sensitivity and accuracy of the study (17,18). On the other hand, ^{68}Ga -DOTATATE can be produced locally using a generator and the patient is injected and imaged on the same day. No special

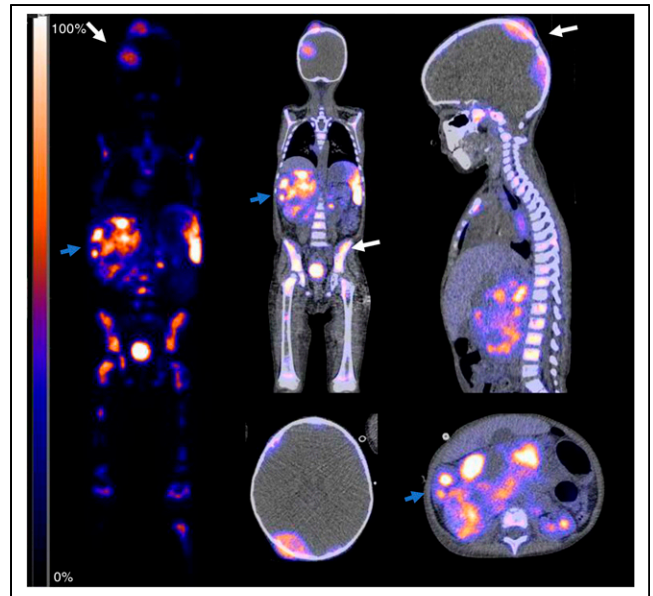


FIGURE 3. Heterogeneous uptake in lobulated right suprarenal mass (blue arrows), with diffuse skeletal metastasis, including in skull and pelvis (white arrows), and diffuse bone marrow infiltration.

preparation is required other than avoiding somatostatin analogs.

The role of ^{68}Ga -DOTATATE PET has previously been studied at the time of recurrence and at the therapeutic planning phase within a theranostic paradigm. However, there are very few reports of its role for staging at diagnosis (5,12). Maurice et al. found that in their series of 15 adults with pheochromocytoma and paraganglioma, ^{68}Ga -DOTATATE was positive in 5 patients in whom MIBG was negative, whereas the converse was true for only 2 patients (19). Similarly Naji et al. found that in adults with neural crest tumors, ^{68}Ga -DOTATATE showed 10 of 12 lesions, versus 5 shown by MIBG (20). Krois et al. compared the sensitivity and specificity of ^{68}Ga -DOTATATE with those of MIBG and morphologic imaging in their series of 11 patients (a mixed pediatric and adult cohort). Although only 5 of 11 patients had a diagnosis of neuroblastoma, ^{68}Ga -DOTATATE had a sensitivity of 97%, versus 90% for MIBG (5). In a case report, Agrawal et al. reported the utility of ^{68}Ga -DOTATATE PET/CT in diagnosis and response evaluation in a 12-y-old child with neuroblastoma (12).

All lesions evaluable on MRI scans were also avid on ^{68}Ga -DOTATATE PET/CT imaging, affirming the hypothesis that it is highly sensitive for neuroblastoma.

The effective radiation doses for ^{123}I -MIBG and ^{68}Ga -DOTATATE are 0.013 mSv/MBq (0.481 mSv/mCi) and 0.021 mSv/MBq (0.777 mSv/mCi), respectively (21). Depending on the activity schedule for a 20-kg pediatric patient using the standardized European Association of Nuclear Medicine weight-based activity calculator (62 MBq [1.7 mCi] for ^{68}Ga -DOTATATE and 136 MBq [3.7 mCi]

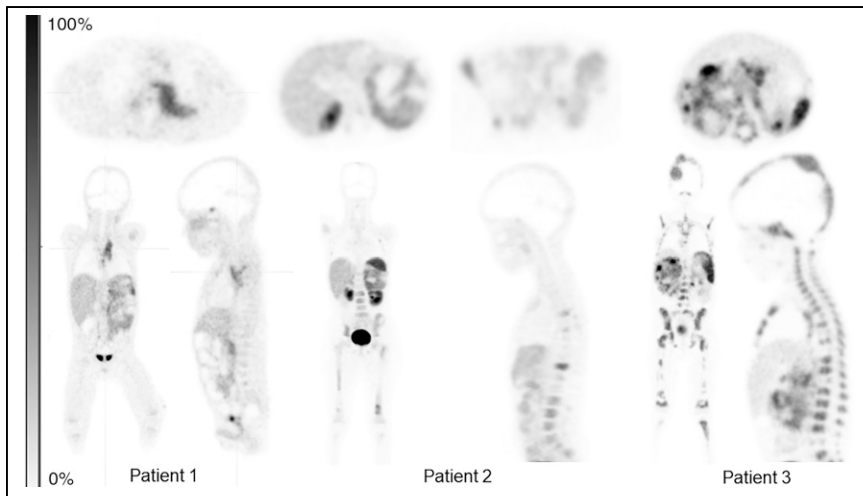


FIGURE 4. Summary of PET images for patients 1–3.

for ^{123}I MIBG), an approximately 25% lower radiation dose is possible with ^{68}Ga -DOTATATE (14,21,22). Reducing the radiation exposure is especially relevant in low-stage tumors for which radionuclide therapy is not required.

Advantages of ^{68}Ga -DOTATATE PET/CT include high image quality and better spatial resolution than with SPECT. Practical advantages also include more rapid imaging requiring less sedation, as well as no specific patient preparation requirements. Considering that ^{68}Ga -DOTATATE has been Food and Drug Administration–approved for use with PET for localization of somatostatin receptor–positive neuroendocrine tumors in pediatric patients, and that it is relatively easy to acquire for clinical use, it should be considered for routine use in staging of neuroblastoma patients.

CONCLUSION

^{68}Ga -DOTATATE PET/CT imaging can reliably be used as an alternative to MIBG for staging evaluation. It has numerous advantages over MIBG, including higher sensitivity, higher spatial resolution from PET, better image contrast, better tumor-to-background ratio, easier patient flow, easier patient preparation, and a more favorable dosimetry profile. Pooled data from multiple institutions may bring forth recommendations for its standard clinical use.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We thank Cyclomedica-HMC in facilitating the provision of ^{68}Ga -DOTATATE and Dr. William Mifsud (pathology department at Sidra Medicine) for provision of histopathology images used in the graphical abstract.

REFERENCES

1. Monclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. *J Clin Oncol.* 2009;27:298–303.
2. Bar-Sever Z, Biassoni L, Shulkin B, et al. Guidelines on nuclear medicine imaging in neuroblastoma. *Eur J Nucl Med Mol Imaging.* 2018;45:2009–2024.
3. Smets LA, Janssen M, Metwally E, Loesberg C. Extraganular storage of the neuron blocking agent meta-iodobenzylguanidine (MIBG) in human neuroblastoma cells. *Biochem Pharmacol.* 1990;39:1959–1964.
4. Geatti O, Shapiro B, Sisson JC, et al. Iodine-131 metaiodobenzylguanidine scintigraphy for the location of neuroblastoma: preliminary experience in ten cases. *J Nucl Med.* 1985;26:736–742.
5. Kroiss A, Putzer D, Uprimny C, et al. Functional imaging in pheochromocytoma and neuroblastoma with ^{68}Ga -DOTA-Tyr3-octreotide positron emission tomography and ^{123}I -metaiodobenzylguanidine: a clarification. *Eur J Nucl Med Mol Imaging.* 2012;39:543.
6. Bleeker G, Tytgat GA, Adam JA, et al. ^{123}I -MIBG scintigraphy and ^{18}F -FDG-PET imaging for diagnosing neuroblastoma. *Cochrane Database Syst Rev.* 2015;2015:CD009263.
7. Kong G, Hofman MS, Murray WK, et al. Initial experience with gallium-68 DOTA-octreotate PET/CT and peptide receptor radionuclide therapy for pediatric patients with refractory metastatic neuroblastoma. *J Pediatr Hematol Oncol.* 2016;38:87–96.
8. Gains JE, Bomanji JB, Fersht NL, et al. ^{177}Lu -DOTATATE molecular radiotherapy for childhood neuroblastoma. *J Nucl Med.* 2011;52:1041–1047.
9. Shulkin BL, Wieland D, Baro M, et al. Neuroblastoma: positron emission tomography with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose compared with metaiodobenzylguanidine scintigraphy. *Radiology.* 1996;199:743–750.
10. O'Doriso MS, Chen F, O'Doriso TM, et al. Characterization of somatostatin receptors on human neuroblastoma tumors. *Cell Growth Differ.* 1994;5:1–8.
11. Albers AR, O'Doriso MS, Balster DA, et al. Somatostatin receptor gene expression in neuroblastoma. *Regul Pept.* 2000;88:61–73.
12. Agrawal K, Kumar R, Shukla J, Bhattacharya A, Mittal BR. Ga-68 DOTATATE positron emission tomography/computer tomography in initial staging and therapy response evaluation in a rare case of primary neuroblastoma in neck. *Indian J Nucl Med.* 2014;29:175–176.
13. Sullivan M, Bouffet E, Rodriguez-Galindo C, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI and St Jude Global. *Pediatr Blood Cancer.* 2020;67:e28409.
14. Alexander N, Vali R, Ahmadzadehfah H, Shammas A, Baruchel S. Review: the role of radiolabeled DOTA-conjugated peptides for imaging and treatment of childhood neuroblastoma. *Curr Radiopharm.* 2018;11:14–21.
15. Suc A, Lumbroso J, Rubie H, et al. Metastatic neuroblastoma in children older than one year: prognostic significance of the initial metaiodobenzylguanidine scan and proposal for a scoring system. *Cancer.* 1996;77:805–811.
16. Lewington V, Lambert B, Poetschger U, et al. ^{123}I -mIBG scintigraphy in neuroblastoma: development of a SIOPEN semi-quantitative reporting method by an international panel. *Eur J Nucl Med Mol Imaging.* 2017;44:234–241.
17. Van Vickle SS, Thompson RC. ^{123}I -MIBG imaging: patient preparation and technologist's role. *J Nucl Med Technol.* 2015;43:82–86.
18. Sharp SE, Trout AT, Weiss BD, Gelfand MJ. MIBG in neuroblastoma diagnostic imaging and therapy. *Radiographics.* 2016;36:258–278.
19. Maurice JB, Troke R, Win Z. A comparison of the performance of ^{68}Ga -DOTATATE PET/CT and ^{123}I -MIBG SPECT in the diagnosis and follow-up of pheochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging.* 2012;39:1266–1270.
20. Naji M, Zhao C, Welsh SJ, et al. ^{68}Ga -DOTA-TATE PET vs. ^{123}I -MIBG in identifying malignant neural crest tumours. *Mol Imaging Biol.* 2011;13:769–775.
21. Bombardieri E, Giammarile F, Aktolun C, et al. $^{131}\text{I}/^{123}\text{I}$ -metaiodobenzylguanidine (mIBG) scintigraphy: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging.* 2010;37:2436–2446.
22. Walker RC, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured human dosimetry of ^{68}Ga -DOTATATE. *J Nucl Med.* 2013;54:855–860.