^{68}Ga-DOTATATE PET in Restaging and Response to Therapy in Neuroblastoma: A Case Series and a Mini Review

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^{68}Ga-DOTATATE PET/CT is widely used for the evaluation of neuroendocrine tumors. Some reports exist on its use in the management of neuroblastoma. Building on the prior reports as well as our previous experience in using this technique for initial staging, we propose to describe its practical benefits in restaging and response to therapy. We describe different aspects including supply logistics, preparation, spatial resolution, and other practical applications. **Methods:** We reviewed the medical records for 8 patients who were evaluated with ^{68}Ga-DOTATATE PET/CT at our institution over 2 y. A note was made of the patient and disease characteristics and the indication for PET imaging, and the results were retrospectively analyzed for feasibility, logistics, radiation exposure, and utility in answering the clinical question. **Results:** Eight children (5 girls and 3 boys; age range, 4–60 mo; median age, 30 mo) diagnosed with neuroblastoma were imaged with ^{68}Ga-DOTATATE PET/CT and 5 with ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) SPECT/CT over 2 y. Three ^{68}Ga-DOTATATE PET scans were done for staging, 10 for response evaluation, and 2 for restaging. ^{68}Ga-DOTATATE PET accurately identified neuroblastoma lesions suspected or seen on anatomic imaging. It has been shown to be more specific and more sensitive than ^{123}I-MIBG and at times also MRI. It had better spatial and contrast resolution than ^{123}I-MIBG. ^{68}Ga-DOTATATE PET was better than ^{123}I-MIBG SPECT/CT, CT, and MRI in the detection of early progression and viable tumor delineation for response assessment, as well as in target volume definition for external-beam radiotherapy and proton-beam radiotherapy. ^{68}Ga-DOTATATE PET was also better at assessing bony and bone marrow disease changes with time. **Conclusion:** ^{68}Ga-DOTATATE PET/CT offers added value and a superior edge to other imaging modalities in restaging and response assessment in neuroblastoma patients. Further multicenter evaluations in larger cohorts are needed.

Key Words: neuroblastoma; DOTATATE; ^{123}I-MIBG; restaging

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Neuroblastoma is the most common extracranial malignant solid tumor in children, accounting for 8%–10% of all pediatric malignancies (*1,2*). It usually develops in a paraspinal location in the chest or abdomen, originating from embryonal neural crest cells (*3*). It has a wide spectrum of presentation that depends on the biologic characteristics of the tumor. On one end of the spectrum is stage 4S disease, which is primarily a disease of infants that either resolves spontaneously or is exquisitely sensitive to minimal treatment. On the other end of the spectrum is highly aggressive neuroblastoma, which involves many organ systems, is often resistant to multimodality treatment, and is associated with poor outcomes. Diversity of clinical presentation and behavior reflects the biologic characteristics of the tumor. Insights into the biologic features of the tumor have led to improved understanding of its clinical behavior. These include amplification of the MYCN (v-myc avian myelocytomatosis virus–related oncogene, neuroblastoma-derived), deletion of chromosome 1p, or other segmental or numeric chromosomal abnormalities.

The first neuroblastoma staging system, the International Neuroblastoma Staging System, was developed in the late 1980s and was later modified as risk groups were defined. The International Neuroblastoma Risk Group Task Force developed the International Neuroblastoma Risk Group Staging System for presurgical staging. This system relies on clinical criteria and image-defined risk factors (*4,5*).

Anatomic imaging modalities such as CT and MRI are essential for evaluating abdominal neuroblastoma masses. Nuclear medicine imaging modalities, such as ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) planar whole-body scintigraphy, are used to characterize primary tumors and detect distant metastatic sites including lymph nodes, bones, bone marrow, and soft tissues. Historically, ^{123}I-MIBG has been used with 2-dimensional planar imaging for initial staging and follow-up. Somatostatin receptor imaging with SPECT octreotide scanning was later introduced to evaluate about 10% of non–^{123}I-MIBG-avid neuroblastoma cases (*6–8*). In the early 21st century, hybrid 3-dimensional SPECT/CT scanners have come into routine use in clinical practice for the evaluation and staging of neuroblastoma patients, compared with 2-dimensional planar imaging.

In the late 1990s, ^{18}F-FDG PET was shown to be a valuable tool to demonstrate the heterogeneity of disease in neuroblastoma patients and non–^{123}I-MIBG-avid disease and proved to be a good prognostic indicator (*9*). Over the last 25–30 years, new radiotracers compatible with PET scanners

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have been introduced in neuroblastoma imaging, including ^{18}F-L-dihydroxyphenylalanine, ^{124}I-MIBG, and ^{68}Ga-labeled DOTA-peptides. ^{18}F-L-dihydroxyphenylalanine and ^{68}Ga-DOTATATE PET/CT techniques have shown superiority over ^{123}I-MIBG in sensitivity and specificity (*10–13*).

With the Food and Drug Administration approval of ^{68}Ga-DOTATATE for the evaluation of neuroendocrine tumors, its clinical use has been contemplated in neuroblastoma. Here, we present our findings on the value of ^{68}Ga-DOTATATE PET/CT in restaging and evaluation of response to therapy and provide an expert opinion on clinical use.

MATERIALS AND METHODS

This was a retrospective review of data for patients evaluated for neuroblastoma staging or restaging with ^{68}Ga-DOTATATE PET/CT from May 2019 to October 2021. Medical records were reviewed, and disease characteristics, indications for PET imaging, and findings were analyzed. The results were retrospectively analyzed for feasibility, logistics, radiation exposure, and utility in answering the clinical question.

Evaluations were also based on consensus at multidisciplinary conference reviews and multimodality reviews, including biopsy results combined with clinical follow-up.

Five ^{123}I-MIBG scans were also performed on these patients at various time points. These scans were used for comparison regarding the spatial and contrast resolution of neuroblastoma lesions. ^{68}Ga-DOTATATE PET was used when the ^{123}I-MIBG supply was disrupted during the coronavirus disease 2019 pandemic.

All patients gave regular clinical written informed consent for imaging with ionizing radiation. The study was done after institutional review board approval.

Definitions

Complete metabolic response was assigned when no metabolically active lesions were seen on the ^{68}Ga-DOTATATE scan. Incomplete metabolic response was assigned when previously documented lesions were still present on the scan, albeit fewer or with significantly reduced metabolic activity, using visual interpretation aided by semiquantitative interpretation (>50% reduction in uptake).

Patients

Fifteen ^{68}Ga-DOTATATE scans were performed on 8 patients with neuroblastoma who either were receiving active treatment or were seen during follow-up. Indications for ^{68}Ga-DOTATATE PET included response evaluation or restaging at the time of relapse.

There were 5 female and 3 male patients, with a median age of 30 mo (range, 4–60 mo). The diagnosis of neuroblastoma was confirmed histologically and biochemically (elevated levels of urinary catecholamines) in all patients. Staging and risk stratification were performed according to the International Neuroblastoma Staging System. All patients had baseline MRI scans for primary tumor evaluation. The tumor showed a poorly differentiated histology in all patients. Adverse cytogenetic features were seen in only 1 patient. On the basis of the above information, 4 patients were classified in the high-risk group and 4 in the intermediate-risk group. Their characteristics are summarized in Table 1.

TABLE 1
Baseline Patient Characteristics

Characteristic	Data
Sex	
Male	3
Female	5
Age (mo)	
Median	30
Range	4–60
Histopathology	
High risk	7
Not available	1
Catecholamines	
Normal	0
Elevated	8
Cytogenetics	
Adverse	1
Not adverse	6
Not available	1
Baseline imaging	
MRI	8
^{123}I-MIBG	4
PET	3
Baseline disease involvement	
Soft tissue/lymph node involvement	8
Bony metastatic lesions	5
Bone marrow involvement	3
Stage	
II	3
III	1
IV	4
Risk group	
Intermediate	4
High	4

Data are number unless otherwise indicated.

Staging and Risk Stratification Protocols

The International Neuroblastoma Staging System was used. Patients were treated according to stage and risk group, provided by Children's Oncology Group protocols (ANBL0531, ANBL1531, and ANBL1232). Response evaluation was performed according to the protocol based on international recommendations (*14*).

^{68}Ga-DOTATATE PET/CT

DOTATATE radiolabeled with ^{68}Ga was produced locally. After quality control tests, patients were injected according to the weight-based activities of the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine. After an uptake phase of 45–60 min, the patients were scanned on a GE Healthcare Discovery 690 PET/CT device as previously described (*15*).

RESULTS

Fifteen ^{68}Ga-DOTATATE PET/CT scans were performed during this period. Three of these scans were at baseline for staging evaluation, 10 for response evaluation, and the remaining 2 at the time of relapse (or suspected relapse) for restaging. All patients were simultaneously evaluated with anatomic imaging (MRI) and PET/CT.

All 8 patients had ^{68}Ga-DOTATATE–avid disease. ^{68}Ga-DOTATATE PET/CT accurately staged patients in all 3

compartments (primary tumor, soft tissue/lymph nodes, bony metastasis and bone marrow).

Baseline Staging

Of the 3 ^{68}Ga-DOTATATE PET scans performed at baseline for initial staging, the primary mass and the metastatic lesions in soft tissue and in the bony skeleton were identified. Two of the scans also correctly identified the presence of bone marrow disease, which was confirmed on bone marrow biopsy.

Response Evaluation

Ten ^{68}Ga-DOTATATE PET scans were performed to evaluate the response of patients undergoing active therapy. Two of these showed a complete metabolic response, 6 showed an incomplete metabolic response, 1 showed a mixed response, and 1 showed progressive disease. All findings were crucial in therapeutic decision making.

Restaging

The remaining 2 scans were performed for restaging in patients who had a proven or suspected relapse. Although the primary lesion and the suspected metastatic lesions were identified on the first scan (scan 2) correctly, the suspected lesion for the second patient (scan 13) was not ^{68}Ga-DOTATATE–avid. The patient remained under observation, with subsequent resolution of the suspected lesion on anatomic imaging.

Table 2 summarizes the indications and the findings seen on all 15 scans.

DISCUSSION

Anatomic imaging using MRI or CT is essential in delineating the characteristics of the primary mass, including vascular invasion and locoregional extension, especially at initial staging, and therefore is beneficial in determining image-defined risk factors. Similarly, disease response at the primary site can frequently but not always be determined by these modalities. However, response is at times better evaluated through nuclear medicine imaging techniques. ^{68}Ga-DOTATATE Pet also has a clinical advantage over ^{123}I-MIBG SPECT/CT and morphologic imaging in several respects, as will be discussed below.

Logistics and Preparation

^{68}Ga-DOTATATE PET offers a more favorable logistical and supply profile than ^{123}I-MIBG. Scans can be completed within 90 min (injection, uptake phase, and image acquisition), including about 15–20 min of scanning time. In contrast, ^{123}I-MIBG SPECT or SPECT/CT requires at least 18–24 h and up to 72 h to complete from injection, including about 90 min of scanning time on day 2. Therefore, ^{68}Ga-DOTATATE Pet allows not only for shorter scanning time but also potentially less sedation to pediatric patients (*16,17*). Additionally, whereas ^{68}Ga-DOTATATE can be produced on site, ^{123}I- or ^{131}I-MIBG cannot be produced locally and has to be procured from distant vendors, necessitating a long time-lag from scan order to scan scheduling and completion.

TABLE 2
Summary of ^{68}Ga-DOTATATE PET/CT Scans

Patient no.	Indication	GA	RT dose (mCi/MBq)	Concurrent anatomic imaging	Soft-tissue lesions	Bony lesions	Bone marrow involvement	Conclusion	Concordance
1	Restaging	Yes	2.16/80	MRI	Yes	No	No	Metastatic disease	Yes
2	Response	Yes	2/74	MRI	Yes	No	No	mIR	Yes
3	Staging	Yes	2.3/85.5	Radiography, ultrasound, MRI	Yes	Yes	Yes	Metastatic disease	Yes
4	Response	Yes	1.24/46	MRI	Yes	Yes	Yes	mIR	Yes
5	Response	Yes	1.2/44.6	MRI	Yes	Yes	Yes	mIR	Yes
6	Response	No	1.74/64.4	MRI	Yes	Yes	Yes	PD	Yes
7	Response	No	2/73.7	MRI	Yes	Yes	No	mMR	Yes
8	Response	No	1.75/65	MRI	Yes	Yes	No	mIR	Yes
9	Response	Yes	2.65/98	MRI	Yes	No	No	mCR	Yes
10	Response	Yes	1.3/47	MRI	Yes	No	No	mIR	Yes
11	Staging	No	2.75/102	Radiography, ultrasound, MRI	Yes	Yes	Yes	Metastatic disease	Yes
12	Response	Yes	1.48/55	MRI	Yes	No	No	mIR	Yes
13	Restaging	Yes	1/37	MRI	No	Yes	No	Lesion on MRI not ^{68}Ga-DOTATATE–avid	More accurate response on PET
14	Staging	Yes	2/74	CT, MRI	Yes	Yes	No	Numerous soft-tissue and bony lesions	PET identified additional lesions
15	Response	No	1.4/51.6	MRI	No	No	No	mCR	Yes

GA = general anesthesia; RT = radiopharmaceutical dose; mIR = metabolic incomplete response; PD = progressive disease; mMR = mixed metabolic response; mCR = complete metabolic response.

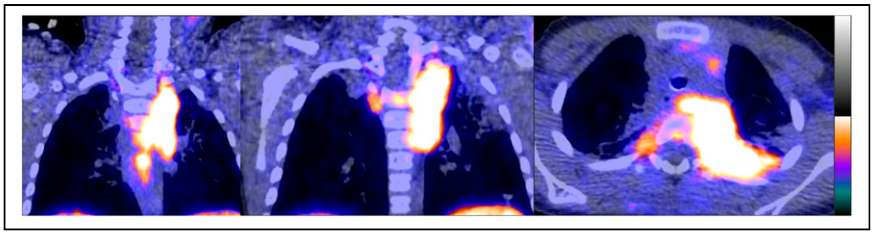

FIGURE 1. Increased sensitivity noted, with additional T3 vertebral body ^{68}Ga-DOTATATE–positive lesion seen on coronal and axial images (left to right) not appreciated on patient's morphologic MRI.

An additional layer of complexity is added by the requirement that the guardian pick up the thyroid blockade medication from the hospital or department, potentially adding to the length of the process or the degree of inconvenience for the patient or guardian. In preparation for ^{123}I-MIBG scans, close attention to any medications interfering with uptake of the radiotracer is necessary, including some over-the-counter medications. The innocuous presence of interfering medications can potentially alter ^{123}I-MIBG uptake in different lesions, reducing the sensitivity of the test and mimicking a response on follow-up studies. On the other hand, ^{68}Ga-DOTATATE PET scans do not require any special preparation or have any innocuous medication interference.

Radiation Exposure and Sensitivity

Compared with SPECT radiotracers, PET radiotracers are needed at lower activities because of the greater sensitivity of the scanner, which also means a lower cumulative radiation exposure as reported by our group (*15*) and others (*9*). Alexander et al. (*18*) concluded that ^{68}Ga-DOTATATE has a reduced clearance and administration time, a reduced radiation exposure, and limited toxicity in comparison to ^{123}I-MIBG. Newer total-body scanners will completely change this paradigm, offering the potential for a dose exposure equivalent to a few chest radiographs or a transatlantic flight. This advantage will allow frequent monitoring of these patients and the response to treatment.

The superior sensitivity of ^{68}Ga-DOTATATE PET over conventional functional and morphologic imaging in several neuroendocrine tumor pathologies has also been demonstrated. Janssen et al. demonstrated this in head and neck paragangliomas (*19*) and suggested that ^{68}Ga-DOTATATE PET is more sensitive than triple-phase MRI or CT in detecting metastatic liver lesions within a variety of gastroenteropancreatic neuroendocrine tumors (*20*). Shahrokhi et al. (*21*) noted similar findings. ^{68}Ga-DOTATATE PET/CT showed greater sensitivity (100%) on a per-patient basis than ^{131}I-MIBG SPECT/CT (77.8%). On a per-lesion basis, ^{68}Ga-DOTATATE PET/CT identified 52 lesions, whereas ^{131}I-MIBG SPECT/CT identified only 30. Fallahi et al. also found that ^{68}Ga-DOTATATE PET/CT revealed more lesions in 36% of their cohort and changed management in 20% of instances compared with CT or MRI (*22*). Goel et al. also showed the superiority of ^{68}Ga-DOTATATE PET in evaluating bone lesions in a cohort of 30 pediatric neuroendocrine tumor patients compared with CT (*23*). This experience is similar to ours.

During follow-up, it is critical not to miss a lesion because of scanning technique limitations when distinguishing between old lesions and disease progression. Given the higher sensitivity of PET than of ^{123}I-MIBG SPECT/CT, CT, or even MRI, more lesions are likely to be detected at diagnosis, as well as during response evaluation. At diagnosis, missing of lesions that are below the sensitivity threshold for ^{123}I-MIBG SPECT/CT or even MRI may lead to a patient's being undertreated, resulting in a poorer outcome. Similarly, at response evaluation, lack of recognition of metastatic lesions can lead to inappropriate treatment decisions, as illustrated in Figures 1 and 2.

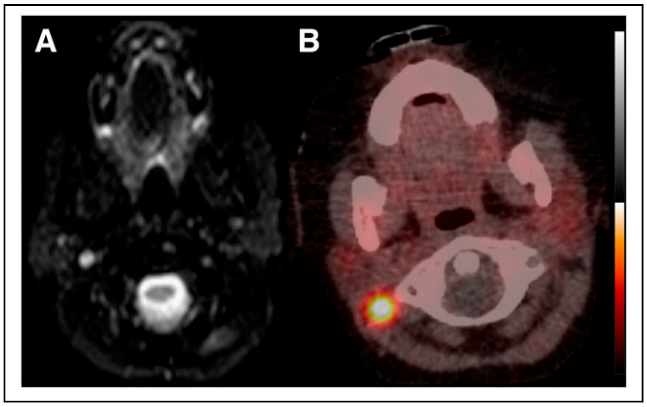

FIGURE 2. Persistent right-neck lymph node uptake on ^{68}Ga-DOTATATE PET/CT (B) that has normal size and other morphologic criteria on correlative short-tau inversion recovery MRI (A).

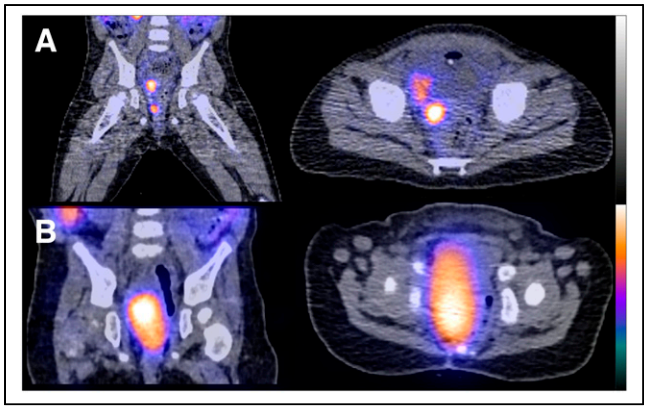

FIGURE 3. Improved spatial and contrast resolution of pelvic lesions on coronal (left) and axial (right) ^{68}Ga-DOTATATE PET/CT (A) compared with MIBG SPECT/CT (B).

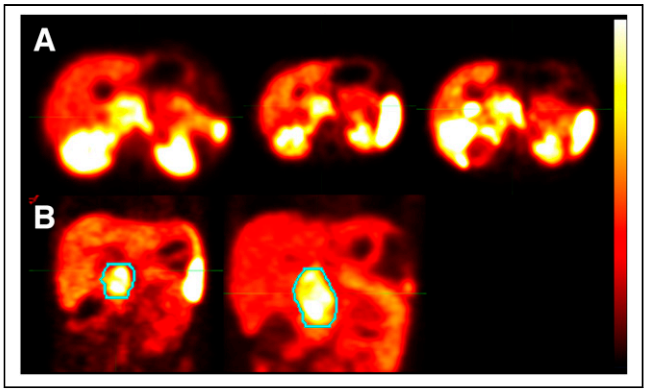

FIGURE 4. Early progression in primary mass detected on ^{68}Ga-DOTATATE PET/CT, with increase in volume not apparent on correlative MRI because of associated variable signal changes, edema, and necrosis. PET tumor thresholding allows accurate assessment of viable tumor volumes on axial PET images at, from left to right, initial staging, 2 mo, and 6 mo (A) and on coronal PET images at, from left to right, 2 and 6 mo (B).

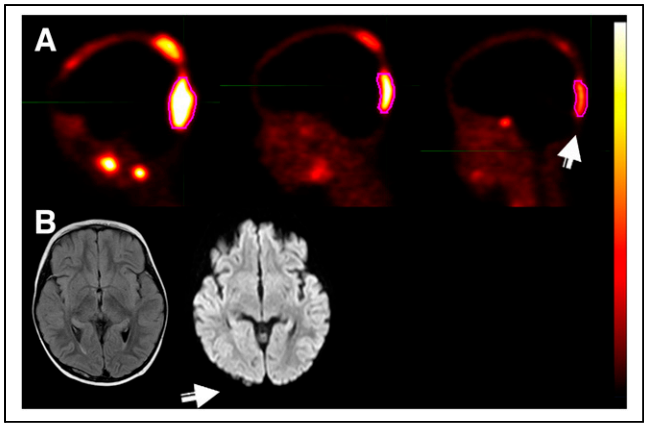

FIGURE 6. (A) Improved but persistent bony skull lesions (arrow) at, from left to right, initial staging, 2 mo, and 6 mo on ^{68}Ga-DOTATATE PET. (B) These changes (arrow) are not well visualized, however, on correlative T1-weighted and fluid-attenuated inversion recovery MRI performed on same day at 6 mo.

Resolution in Evaluating Early Response to Therapy and Disease Progression

^{68}Ga-DOTATATE PET has shown better spatial, temporal, and contrast resolution than SPECT/CT. This is important at the time of staging and even more so at the time of restaging; a difference in the degree of response by 2 closely situated lesions is better delineated by PET than by SPECT/CT. Also, improved delineation of the volume of individual lesions gains further significance at the time of radiotherapy planning, as illustrated by Figure 3. McElroy et al. (*24*) also reported that ^{68}Ga-DOTATATE PET better delineates tumor volume for more accurate external-beam radiotherapy and proton-beam therapies.

Additionally, ^{68}Ga-DOTATATE PET/CT, as well as other functional imaging techniques, were found to detect progression or a response to therapeutic changes earlier than morphologic imaging (*11,25*), especially if the boundaries of the viable tumor are difficult to assess on morphologic imaging, as seen in Figure 4.

Similarly, evaluation of response in the bone marrow and cortical bony disease can be challenging with CT and MRI compared with PET-based imaging, as illustrated in Figures 5 and 6. Figure 5 shows that, at 6 mo, although bone marrow disease has resolved on the PET scan, changes persist on the correlative MRI scan. Figure 6 shows that improvement of persistent bony disease of the skull is difficult to see on follow-up MRI but is clearly appreciated on serial ^{68}Ga-DOTATATE PET/CT scans.

Quantification and Lesion Characterization

Although quantitative assessment during treatment monitoring is possible and has improved with the latest SPECT/CT scanners, PET quantification methods are more established and more accurate (*26*). Absolute quantification and multiparametric assessments will also be possible with newer total-body scanners.

Regarding posttreatment evaluations, improved lesion characterization with ^{68}Ga-DOTATATE PET/CT has been evident. Such evaluations with CT and MRI can be challenging because of the presence of necrosis, inconsistent diffusion-weighted imaging changes, and inconsistent contrast enhancement patterns before and after treatment. Imaging with ^{68}Ga-DOTATATE PET/CT avoids these challenges with better lesion characterization, better thresholding, and better tumor volume measurements than for SPECT or MRI, as illustrated by Figure 7 and Supplemental Figure 1

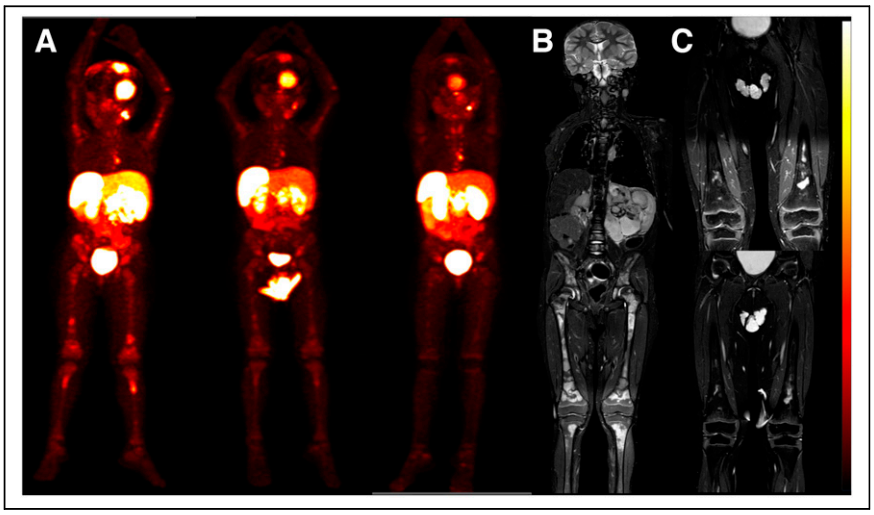

FIGURE 5. (A) Resolution of bone marrow disease on ^{68}Ga-DOTATATE PET/CT (from left to right: initial staging, 2 mo, and 6 mo). (B and C) Short-tau inversion recovery MRI still showing changes at 6 mo (false-positive MRI) (initial staging [B], 2 mo [C top], and 6 mo [C bottom]).

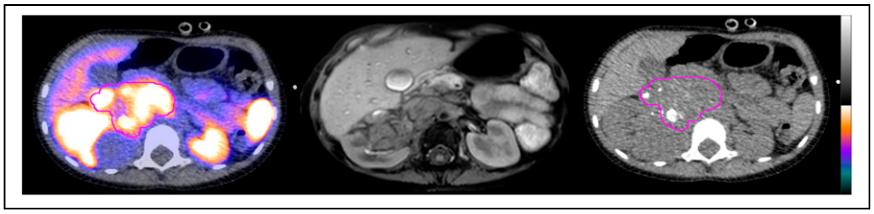

FIGURE 7. Viable tumor volume delineation using thresholding techniques is more accurate and established on ^{68}Ga-DOTATATE PET/CT (left) than on T1-weighted MRI (middle) or CT (right).

(supplemental materials are available at http://jnmt.snmjournals.org).

Metastatic Disease Detection

^{68}Ga-DOTATATE PET has been described to show extensive metastatic disease in cases completely ^{123}I-MIBG-negative or weakly positive. This poses the clinical conundrum of potentially missing significant disease or significantly downstaging certain patients with ^{123}I-MIBG imaging, whether it be at initial staging, restaging, or assessment of response to therapy (*25,27,28*). On the other hand, low ^{68}Ga-DOTATATE uptake has been seen in poorly differentiated tumors and has correlated with a poor prognosis (*29–32*).

In case reports by Torun et al. (*28*) and Telli et al. (*27*), ^{123}I-MIBG scans failed to reveal bone and bone marrow involvement. Kong et al. (*11*) found additional disease in 38% of their cohort of pediatric neuroblastoma patients with ^{68}Ga-DOTATATE PET/CT compared with ^{123}I-MIBG imaging, and 1 patient was upstaged through detection of bone marrow involvement.

Additionally, various studies (*24,33,34*) have reported distinct advantages—including higher detection efficiency and a greater target-to-background ratio—for ^{68}Ga-DOTATATE PET/CT in the evaluation of pediatric and adult neuroendocrine tumors.

Regarding studies on pediatric patients, Gains et al. (*12*) examined the use of ^{68}Ga-DOTATATE PET/CT in 8 children with relapsed or refractory high-risk neuroblastoma. Six patients showed abnormal PET/CT uptake high enough to make them suitable to receive molecular peptide receptor radionuclide therapy. This was a preliminary indicator of the promising potential of ^{68}Ga-DOTATATE PET as an imaging technique for pediatric neuroblastoma patients. Gains et al. also more recently compared ^{68}Ga-DOTATATE PET maximum-intensity projections with ^{123}I-MIBG planar scintigrams in 42 high-risk neuroblastoma patients. ^{68}Ga-DOTATATE was positive in all patients, whereas ^{123}I-MIBG was positive in 40 patients. ^{68}Ga-DOTATATE identified bone lesions in 97% (35/36) of the patients, versus 81% (29/36) for ^{123}I-MIBG, and identified soft-tissue lesions in 100% (33/33) versus 88% (29/33), respectively (*35*).

Other advantages of ^{68}Ga-DOTA peptide imaging include high tumor-to-background contrast (high SUVs) even for small lesions, no need for a cyclotron, and the possibility of peptide receptor radionuclide therapy in a theranostic paradigm (*26*).

In essence it seems as if ^{123}I-MIBG has been used for more than 30 years with some success; however, recent data are uncovering its limitations even when using advanced hybrid SPECT/CT techniques (*10–13*). Octreotide scans have been replaced with ^{68}Ga-DOTATATE PET because of its superiority. The time may have come to use better tools such as ^{68}Ga-DOTATATE PET, when and where available, in initial staging, restaging, and assessment of response to therapy in neuroblastoma patients.

CONCLUSION

^{68}Ga-DOTATATE PET/CT offers added value and a superior edge to other imaging modalities in restaging and response assessment in neuroblastoma patients. Further multicenter evaluations in larger cohorts are needed.

DISCLOSURE

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

KEY POINTS

QUESTION: What is the value of ^{68}Ga-DOTATATE PET/CT for clinical use in restaging and assessment of response to therapy in neuroblastoma patients?

PERTINENT FINDINGS: In our cohort of 8 pediatric neuroblastoma patients, ^{68}Ga-DOTATATE PET/CT was superior to other imaging modalities. Some advantages of ^{68}Ga-DOTATATE PET/CT scans include ease of preparation and improved sensitivity, resolution, quantification, and lesion characterization.

IMPLICATIONS FOR PATIENT CARE: We hope our findings will encourage the use of ^{68}Ga-DOTATATE PET more widely for initial staging, restaging, and assessment of response to therapy in neuroblastoma patients.

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