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Original Article

Safety and accuracy of ^{68}Ga-DOTATOC PET/CT in children and young adults with solid tumors

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Abstract: ^{68}Ga-DOTA-tyr3-Octreotide (^{68}Ga-DOTATOC) PET/CT has been shown to have high accuracy in adults with neuroendocrine tumors, however has not been studied in pediatric patients. This study evaluated the safety and accuracy of ^{68}Ga-DOTATOC PET/CT in children and young adults with solid tumors that express somatostatin receptor type 2. A series of three prospective, IRB approved, clinical trials evaluating safety and efficacy of ^{68}Ga-DOTATOC PET/CT were conducted for subjects aged 6 months to 90 years. This study reports the results for the 26 children and young adults, aged 16 months to 29 years who participated in these trials. The administered activity of ^{68}Ga-DOTATOC was 1.59 MBq/kg with an upper limit of 111 MBq for subjects < 18 years and 148 MBq for young adults. Safety was assessed with laboratory studies and patient/parent report of symptoms before and after the scan. Scans were interpreted in consensus by two board-certified nuclear medicine physicians. Each scan was categorized on a patient basis as true positive, true negative, false negative or false positive against a reference standard that included a combination of histopathology, other imaging modalities and clinical follow-up. Nine Grade I adverse events (AEs) occurred among 26 subjects, none of which were attributable to ^{68}Ga-DOTATOC. Sensitivity of ^{68}Ga-DOTATOC PET/CT was 88% (14 true positive, 2 false negative) and specificity was 100% (10 true negative, 0 false positive). ^{68}Ga-DOTATOC PET/CT is safe and accurate in children and young adults with solid tumors expressing somatostatin receptor type 2.

Keywords: ^{68}Ga-DOTATOC, children, somatostatin, solid tumor

Introduction

Somatostatin receptor expression has been demonstrated in pediatric tumors arising from neuroectodermal, neural crest, and diffuse neuroendocrine tissues. These tumors include medulloblastoma, supratentorial primitive neuroectodermal tumors, and meningioma in the central nervous system; neuroblastoma and pheochromocytoma/paraganglioma in the peripheral nervous system; and neuroendocrine tumors (NETs) arising in the diffuse neuroendocrine system throughout the body [1-6]. Collectively, more than 90% of these rare pediatric tumors express somatostatin receptors and can be visualized with somatostatin receptor imaging techniques [7-11].

Early pediatric studies investigated the use of ^{111}In-DTPA-Octreotide single photon emission tomography (SPECT) imaging in children with solid tumors and demonstrated its potential applications in the diagnosis and posttherapy follow up of children with brain tumors [9, 12]. More recently ^{68}Ga labeled DOTA conjugated peptides have been developed for somatostatin receptor positron emission tomography (PET) imaging. The most commonly used ^{68}Ga labeled DOTA-peptides are ^{68}Ga-DOTA-D-Phe^{1}-Try^{3}-Octreotide (^{68}Ga-DOTATOC), ^{68}Ga-DOTA-Tyr^{3}-Thr^{8}-octreotide (^{68}Ga-DOTATATE), and ^{68}Ga-DOTA-1-Nal^{3}-octreotide (^{68}Ga-DOTANOC). ^{68}Ga-DOTATATE has been recently approved by the FDA for clinical use; ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC are investigational at this time. All of

these ^{68}Ga labeled DOTA-peptides have significantly higher affinity for somatostatin receptor subtype 2 compared to ^{111}In-DTPA-Octreotide [13, 14]. An intra-patient comparison of ^{68}Ga-DOTATOC and ^{111}In-DTPA-Octreotide in adult patients demonstrated significantly better sensitivity of ^{68}Ga-DOTATOC, particularly in detection of osseous and pulmonary lesions of NETs [15]. In a meta-analysis of adult studies, the sensitivity and specificity of ^{68}Ga-DOTATOC in diagnosis of neuroendocrine tumor lesions were reported at 95% and 85% respectively [16]. The radiation dose is also significantly lower from ^{68}Ga labeled DOTA-peptides compared to ^{111}In-DTPA-Octreotide, with an adult dose of 4.3 mSV for 185 MBq of ^{68}Ga-DOTATOC versus 17.7 mSv for a typical 222 MBq administration of ^{111}In-DTPA-Octreotide [17, 18].

While somatostatin receptor imaging with PET/CT using ^{68}Ga-DOTA peptides is becoming standard of care for detection and staging of neuroendocrine tumors in adults [5], its safety and efficacy have not yet been demonstrated in children and young adults. This study examined two hypotheses, namely: 1. ^{68}Ga-DOTATOC PET/CT will be safe in children, with no Grade 3 or greater adverse events; and 2. ^{68}Ga-DOTATOC PET/CT will demonstrate high accuracy in children and young adults with neuroendocrine or other somatostatin receptor expressing solid tumors.

Materials and methods

Patients

This report includes the safety and accuracy results of ^{68}Ga-DOTATOC PET/CT in children and young adults enrolled in 3 prospective clinical trials between 11/15/2012 and 6/11/2016. Although these three clinical trials had different end-points, including safety and efficacy and impact of ^{68}Ga-DOTATOC PET/CT on patient management and its comparison to conventional imaging, the same safety and accuracy measures were obtained in each study allowing combination of the data for 3 studies in children and young adults. Subjects or their parents signed written, informed consent to enroll in one of three consecutive, prospective trials, each consistent with the Health Insurance Portability and Accountability Act and approved by the University of Iowa Institutional Review Board (IRB) as well as the United States Food and Drug Administration (FDA). Each trial was registered on clinicaltrials.gov. Patients were evaluated for potential adverse events prior to discharge from the PET Center and with a follow-up phone call at 24 hours. Laboratory parameters were obtained within 24 hours prior to and within one week following PET/CT and included hematologic (CBC with differential), renal (BUN, Cr) and liver function (bilirubin, AST, ALT) tests. Adverse events were scored according to the CTEP-AERS.

Imaging protocol

^{68}Ga-DOTATOC was produced in the University of Iowa PET center using an automated ^{68}Ge/^{68}Ga generator coupled with a ModularLab Pharm Tracer fluid handling system (Eckert-Ziegler, Germany) under an investigational new drug approval (IND# 114,398). GMP grade DOTATOC was obtained from ITG-Garching, Germany. Quality control of the radiopharmaceutical was determined by measurement of radiochemical purity, product sterility, and chemical purity as required by the FDA under IND# 114,398. PET/CT scans were obtained 50-70 minutes after the IV administration of 1.59 MBq/kg (0.043 mCi/kg) ^{68}Ga-DOTATOC with a maximum dose of 111 MBq (3 mCi) in subjects < 18 years, or 148 MBq (4 mCi) in young adults; a low-dose non-contrast CT was performed for localization and attenuation correction. Images were interpreted qualitatively with focal ^{68}Ga-DOTATOC activity above normal background considered positive for somatostatin receptor uptake. Each scan was interpreted in consensus by two board certified nuclear medicine physicians who were blinded to other imaging studies and clinical history.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and adverse events. To assess the effects of ^{68}Ga-DOTATOC on pre- to post-scan changes in laboratory values, linear mixed effects models with an exchangeable correlation structure among the repeated measures were applied. Each scan was reviewed for the presence of abnormal uptake in the head, neck, chest, abdomen and pelvis to determine disease sites in the brain, in lymph nodes (cervical, thoracic and abdomen-pelvis), bowel, liver, adrenals, spleen, pancreas, and bones. A patient-based analysis of the imaging findings was performed. A positive scan was classified as *true positive (TP)* if a DOTATOC positive

Table 1. Subject Characteristics

Variable		N=26	%
Gender	Female	16	61.5
	Male	10	38.5
Race	Asian	2	7.7
	Black or African American	1	3.8
	Unknown	6	23.1
	White	17	65.4
Ethnicity	Hispanic or Latino	1	3.8
	Non-Hispanic	18	69.2
	Unknown	7	26.9
Trial	*Comparator	6	23.1
	**Impact	7	26.9
	***Safety	13	50.0
Disease	Neuroendocrine Tumor	16	61.5
	Suspected NET based on symptoms and elevated serum markers	4	15.3
	Pheochromocytoma/paraganglioma	2	7.7
	Medulloblastoma	1	3.8
	Supratentorial primitive neuroectodermal tumor	1	3.8
	Meningioma	1	3.8
	Neuroblastoma	1	3.8

*Comparator Study of ^{68}Ga-DOTATOC PET/CT with Octreoscan + high-resolution, contrast-enhanced CT for diagnosis and staging in neuroendocrine tumors and other somatostatin receptor positive tumors NCT01869725. Impact of 68Ga-DOTATOC PET-CT Imaging in Management of Neuroendocrine Tumors NCT02441062. ***Safety and Efficacy of ^{68}Ga-DOTA-tyr3-Octreotide PET/CT in Diagnosis, Staging, and Measurement of Response to Treatment in Patients with Somatostatin Receptor Positive Tumors NCT01619865.

lesion was confirmed by histopathology and/or conventional imaging studies (contrast-enhanced CT, MRI or ^{111}In-Octreotide scan) obtained within 12 months of the ^{68}Ga-DOTATOC PET/CT scan. The scan was considered *false positive (FP)* if a ^{68}Ga-DOTATOC positive site was found to be benign by histopathology or disappeared without interval intervention (other than octreotide therapy) on follow-up ^{68}Ga-DOTATOC scan. A negative scan was considered *true negative (TN)* if no disease was found at clinical follow-up including all available conventional imaging and *false negative* (*FN*) if tumor was found on clinical and imaging follow-up within 12 months. Sensitivity, specificity, positive predictive and negative predictive values were calculated based on these results and used to describe the performance of the imaging modality.

Results

Subjects

Twenty-six eligible children and young adults were included in this analysis. All subjects had known, recently resected, or suspected solid tumor; known diagnoses included neuroendocrine tumor, pheochromocytoma, paraganglioma, meningioma, medulloblastoma, supratentorial primitive neuroectodermal tumor, and neuroblastoma. Characteristics of the 26 subjects are described in **Table 1**; the youngest subject was 16 months and the eldest was 29 years (median age: 16); 18 patients were 18 years or younger and 8 patients were between 19-29. Race was primarily white and ethnicity primarily non-hispanic; 61.5% were female. The median post-scan clinical follow-up period was 19 months (range: 2-45 months); for the subgroup with a true-negative scan the median follow-up was 24 months (range: 6-45 months). At last follow-up 3 patients have died of disease, 10 patients are alive with disease and 13 patients have no evidence of disease.

Adverse events (AEs)

All AEs reported for each of 26 subjects are summarized in **Table 2**. Of nine reported AEs, none were greater than Grade 1 and none were

Table 2. Adverse Events associated with ^{68}Ga-DOTATOC PET/CT

Adverse Event	Grade
Elevated AST	1
Diarrhea	1
Decrease in hemoglobin	1
Nausea	1
Sensory neuropathy	1
Pain	1
Pain-Abdomen	1
Pain-Neck	1
Vomiting	1

Table 3. Performance Characteristics of ^{68}Ga-DOTATOC PET/CT

Sensitivity	88%
Specificity	100%
Positive Predictive Value	100%
Negative Predictive Value	83%

attributable to ^{68}Ga-DOTATOC. Pre- and post-scan laboratory values, including complete blood count and differential, blood urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), and bilirubin were obtained in 20 subjects. A single decrease in hemoglobin and a single increase in AST were observed; no treatment was required and neither was considered clinically significant or related to ^{68}Ga-DOTATOC.

Imaging results

^{68}Ga-DOTATOC PET/CT was positive for tumor in 14 patients and negative in 12 patients. All 14 positive scans were true positive. In 4/14 patients, tumor was confirmed on histopathology, including a pulmonary neuroendocrine tumor (n=1), metastatic neuroendocrine tumor in the liver and abdominal lymph nodes (n=1), meningioma (n=1) and a differentiating neuronal neoplasm (n=1). In 10/14 patients, presence of tumor was confirmed by imaging. There were 2 false negative scans; one in a patient with medulloblastoma and the second in a young adult with Grade 2 metastatic neuroendocrine tumor (Ki-67 of 20%) in the liver and lung with unknown primary. In 10 patients with a true negative scan, no tumor was found after a median follow-up of 24 months (range: 11-45 months). The 10 true negative scans included 6 subjects with appendiceal neuroendocrine tumors with a history of perineural invasion or greater than 12-month history of elevated chromogranin A and/or serotonin following surgery and negative conventional imaging. The other 4 patients with true negative scans were patients with suspected but not previously documented neuroendocrine tumors with symptoms of carcinoid syndrome and at least one NET biomarker elevated consistently when repeated three times (gastrin, serotonin, chromogranin A) and also with negative conventional imaging. The performance of ^{68}Ga-DOTATOC PET/CT scan in all patients are summarized in **Table 3**. **Figure 1** shows ^{123}I-MIBG scan and ^{68}Ga-DOTATOC PET/CT scan of a patient with neuroblastoma. **Figure 2** shows the ^{111}In-Octreotide scan and ^{68}Ga-DOTATOC PET/CT scan of a patient with small bowel NET.

Discussion

To our knowledge, the present report represents the first safety and efficacy analysis of ^{68}Ga-DOTATOC in a pediatric patient population. In 26 children and young adults imaged with ^{68}Ga-DOTATOC; there were only nine Grade I, reversible adverse events, none attributable to ^{68}Ga-DOTATOC. Sensitivity and specificity of ^{68}Ga-DOTATOC PET/CT were extremely high, at 88% and 100% respectively in our study in a variety of pediatric solid tumors, with positive predictive value of 100% and negative predictive value of 83%. Only few studies have investigated potential toxicity ^{68}Ga labeled DOTA-octreotide analogues (DOTATOC, DOTATATE, and DOTANOC) in adults. Esfahani et al. found no adverse events in 12 adult patients imaged with ^{68}Ga-DOTATOC PET/MRI [19]. Deppen et al. also reported no significant adverse events in 78 patients imaged with ^{68}Ga-DOTATATE [20]. ^{68}Ga labeled DOTA-octreotide analogues also have a significantly lower radiation exposure compared to either ^{111}In-DTPA-Octreotide or ^{123}I-MIBG and are more convenient for patients as they require a single visit rather than several visits over two-three days.

Neuroendocrine tumors are considered rare in children, however a recent analysis of the data between 1975 to 2006 from Surveillance, Epidemiology, and End Results (SEER) Program shows that the prevalence of neuroen-

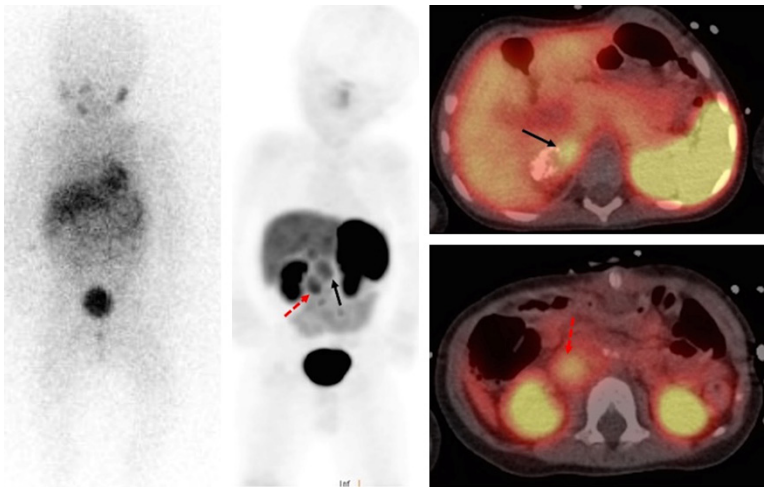

Figure 1. ^{123}I-MIBG and ^{68}Ga-DOTATOC PET/CT of a 17-month old patient with neuroblastoma with MYCN amplification after initial chemotherapy. A CT scan showed interval increase in soft tissue component of the calcified right adrenal lesion suggestive of progression. The MIBG scan (whole body images in the left column, SPECT/CT not shown) obtained 5 days prior to ^{68}Ga-DOTATOC PET/CT is negative. The ^{68}Ga-DOTATOC PET/CT scan (whole body maximum intensity projection images in the center and fused PET/CT in the right column) shows abnormal uptake in the partially calcified right adrenal lesion (black solid arrows) and in a paracaval node (red dashed arrows), confirming recurrent disease. Patient subsequently received second-line chemotherapy according to Children's Oncology Group (COG) ANBL1221 protocol, however, died from progressive disease 2 months later.

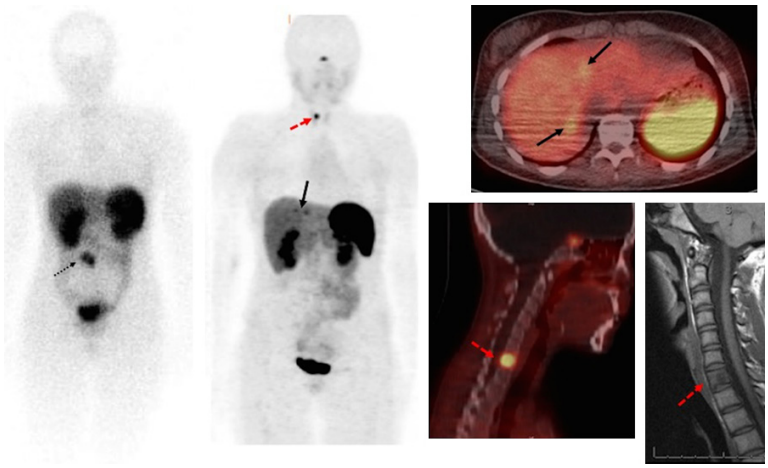

Figure 2. ^{111}In-DTPA-Octreotide and ^{68}Ga-DOTATOC scans of a 16-year old patient with small bowel NET. The preoperative ^{111}In-DTPA-Octreotide whole body (left column) and SPECT/CT images (not shown) showed the primary small bowel NET in the mid abdomen (dashed black arrow) and no metastatic site. Patient had resection of the primary tumor and underwent a ^{68}Ga-DOTATOC PET/CT scan 2 months after the ^{111}In-DTPA-Octreotide scan. The ^{68}Ga-DOTATOC PET/CT scan (whole body maximum intensity projection images in the center and fused PET/CT in the right column) demonstrates previously unknown metastases in the liver (solid black arrows) and at C7 vertebra (dashed red arrows). Subsequent MRI confirmed the lesions; low signal C7 lesion on T1 weighted MRI is shown (dashed red arrow).

docrine tumors is comparable to neuroblastoma [21]. Because over 90% of Grade I and II neuroendocrine tumors are somatostatin receptor positive [22, 23], PET/CT with ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC is an excellent whole body imaging technique that complements site directed MRI or CT in the diagnosis and staging of neuroendocrine tumors, particularly in situations in which the findings of conventional imaging are equivocal or when the primary tumor is not known [5, 24]. PET/CT with ^{68}Ga labeled DOTA-peptides also has a role in diagnosis and follow-up of neuroblastoma and paraganglioma, particularly in patients with MIBG-negative tumors [25, 26]. This is especially important to identify patients with aggressive tumors that have lost their ability to concentrate MIBG such as seen with neuroblastomas with MYCN amplification and paragangliomas with SDHB mutation and to identify patients who are candidates for peptide receptor radionuclide therapy (PRRT) [26-28]. Finally, these radiopharmaceuticals may also have potential applications in children with brain tumors, specifically in medulloblastoma or supratentorial primitive neuroectodermal tumors, to evaluate for tumor relapse versus posttreatment changes. In this regard, earlier studies using ^{111}In-DTPA-Octreotide SPECT/CT demonstrated that the combination of anatomical and functional imaging is helpful in differentiating postsurgical and radiation changes from recurrent disease [9].

Our study has limitations. The study includes 26 children and young adults with a variety of tumors and is necessarily limited in number for each of the various pediatric solid tumors; yet, the safety of ^{68}Ga-DOTATOC PET/CT in this age

group is clear. Conduct of a prospective efficacy trial on each pediatric solid tumor that expresses somatostatin receptors would be extremely difficult in that each tumor type included in this study is classified as an orphan tumor. This relative efficacy study however should help generate hypotheses for subsequent clinical trials on the use of ^{68}Ga-DOTATOC PET/CT for staging and treatment response assessment in children and young adults with solid tumors. This pilot pediatric study was also not designed to show the added value of ^{68}Ga-DOTATOC PET/CT over conventional imaging, although in several patients ^{68}Ga-DOTATOC was clearly superior over In-111 Octreotide or I-123 MIBG as seen in **Figures 1-2**. Most importantly, the demonstration of DOTATOC avidity of a variety of pediatric tumors opens a new therapeutic option for children with peptide receptor radiotherapy (PRRT) for refractory solid tumors that express somatostatin receptor type 2. These results add to the growing evidence that PRRT with ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE as a potential effective therapy in neuroblastoma, especially in ^{123}I-MIBG negative disease [8, 29]. Similarly, for neuroendocrine tumors that progress following surgery, octreotide or lanreotide, everolimus, sunitinib, or chemotherapy, a positive ^{68}Ga-DOTATOC PET/CT opens the possibility of PRRT.

Conclusion

^{68}Ga-DOTATOC PET/CT is safe in children and young adults with high accuracy for detection of somatostatin receptor type 2 positive tumors.

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