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^{68}Ga-DOTATATE PET/CT for Neuroblastoma staging. Utility for clinical use.

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Running Title: ^{68}Ga-DOTATATE and neuroblastoma

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MIBG imaging has been the standard for neuroblastoma staging for many decades. Novel agents such as ^{18}F DOPA and ^{68}Ga DOTATATE are being used nowadays in academic centers. During the COVID-19 pandemic, procurement of MIBG has proved particularly challenging, necessitating the use of ^{68}Ga DOTATATE positron emission tomography.

Methods: ^{68}Ga DOTATATE PET/CT imaging was carried out for staging of three pediatric patients with Neuroblastoma at our institution. A review of the literature was also completed.

Results: ^{68}Ga-DOTATATE is FDA approved for imaging of somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumors. ^{68}Ga DOTATATE PET/CT scans were successfully carried out in all patients. All patients showed DOTATATE avid disease. PET scans showed excellent spatial resolution and demonstrated high accuracy in concordance with current EANM guidelines.

Conclusion: We have presented ^{68}Ga-DOTATATE PET/CT imaging believe it can be reliably used as an alternative to MIBG for staging of neuroblastoma. Its advantages include 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; ^{68}Ga DOTATATE; COVID 19

Introduction:

Neuroblastoma the most common extracranial solid tumor in pediatric age group accounts for about 10% of all solid tumors. It varies in presentation from self-resolving stage 4S disease to the highly malignant variant associated with extremely poor prognosis. Staging evaluation of neuroblastoma requires anatomical as well as nuclear medicine imaging to look for skeletal metastatic deposits[1,2]. ^{123}I metaiodobenzylguanadine (MIBG) can be used for localization of neural crest tumors such as neuroblastoma, pheochromocytoma and other neuroendocrine tumors. MIBG with ^{131}I and more recently ^{123}I has been the standard for neuroblastoma staging since its utility was first reported by Geatti et al in 1985 [3,4].

Reported sensitivity and specificity of ^{123}I MIBG is ~90%[2,5]. However, as 10% of neuroblastomas are MIBG non-avid, alternate imaging techniques have been investigated including positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F FDG) and L-3,4-Dihydroxy-6-[18F]fluorophenylalanine (^{18}F DOPA) and 1,4,7,10-tetraazacyclotetradecane-*N,N',N'',N'''*-tetraacetic acid (DOTA)-conjugated peptides including ^{68}Ga-DOTATATE PET/CT. 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 (SSTR) are variably expressed in neuroblastoma [10,11]. Somatostatin analogues such as DOTATATE have been in clinical use for nearly a decade. Their role is most established in imaging and treatment of adult neuroendocrine tumors (NET) and pheochromocytoma, but also studied in neuroblastoma in limited settings[7,8]. 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].

As MIBG production is limited globally, the SARS-CoV-2 (COVID-19) pandemic has resulted in unacceptable delays in carrying out MIBG scans due to interruption in international air traffic. Its availability became particularly challenging at our institution, we therefore decided to perform DOTATATE PET scans for three newly diagnosed patients with neuroblastoma. This PET agent is locally produced in a nearby center obviating the delivery logistics. Here we report our results with a review of the literature.

Methods:

At the beginning of COVID 19 pandemic, three patients were diagnosed with neuroblastoma at Sidra Medicine. MIBG scintigraphy had to be cancelled for patient 1 due to radiopharmaceutical not arriving on the scheduled date due to the cancellation of flights. In discussion with the clinical team, we decided to carry out DOTATATE PET/CT imaging instead. For subsequent patients, DOTATATE PET was done electively to avoid delay and hazard during the pandemic.

A ^{68}Germanium/^{68}Gallium generator was used to produce ^{68}Ga locally, which was radiolabeled with DOTATATE. Required quality control tests were performed prior to injecting the patient in accordance with good manufacturing practices (GMP). Following radiopharmaceutical injection an uptake phase of 45-60 minutes took place prior to scanning the patient. All 3 patients were scanned on a GE 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, ASIR, 0.5 s rotation time, 40-mm collimation), was performed for attenuation correction and anatomical localization followed by a whole body PET at 4 min per bed position with an 11 slice overlap. Images were reconstructed with time of flight iterative reconstruction algorithm with a correction for point spread function (VPFX - 2 iterations, 28 subsets), and a 3.4 mm post reconstruction Gaussian filter. The final pixel sizes were 1.56 x 1.56 mm with a slice thickness of 3.27 mm. All 3 patients were scanned under general anesthesia (GA). The need for sedation was independent of the type of study, as they would have required GA for MIBG as well. SNMMI/EANM weight-based activities were administered (2 mCi; 2.75 mCi and 1.24 mCi respectively).

Clinical Summary:

Patient 1: A 23-month old toddler presented with lower back pain, ataxia and leg weakness for 5 days. 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 T2-T4 vertebrae, causing spinal cord compression and edema. He underwent emergency laminotomy and laminoplasty by the neurosurgeons and a de-bulking procedure resulting in return of lower limb function over the next 48 hours.

Patient 2: A 6-year old girl presented with intermittent limp over 2 months. There were no other symptoms. On physical examination, she was unable to stand straight due to left leg pain and had mild tenderness on the left side of abdomen. MRI scan of her abdomen and pelvis demonstrated a large left supra-renal mass and numerous bony metastatic lesions.

Patient 3: A 3.5-year old girl presented with weight loss, left eye swelling, body aches and constitutional symptoms over several months. She was severely malnourished and had left sided proptosis. MRI scan showed a right sided adrenal mass as well as numerous liver metastases and multiple vertebral lesions.

Clinical and imaging findings are summarized in Table 1 and supplemental Table 1 and Figures 1-4.

Discussion:

COVID-19 pandemic has posed many unanticipated and unprecedented healthcare challenges worldwide, including care of cancer patients[13]. Prior to the pandemic, establishing cancer diagnosis and carrying out the standard staging investigation was 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 light of limited but compelling evidence of its utility for initial staging of neuroblastoma. Our results will add to the evidence base for future studies.

^{68}Ga-DOTATATE scans in our patients showed a high spatial resolution and high accuracy in concordance with reports in 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 lengthy acquisition process, protracted imaging schedule requiring repeated visits to the nuclear medicine department and occasional need for inpatient admission for younger patients. Another disadvantage is the need for thyroid blockade with Lugol's 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 by using a generator and the patient is injected and imaged on the same day. No special preparation is required other than avoiding SST analogues.

Role of DOTATATE PET has previously 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 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 where MIBG was negative, whereas 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 out of 12 lesions, vs. 5 shown by MIBG[20]. Krois et al compared the sensitivity and specificity of ^{68}Ga-DOTATATE to MIBG and morphological imaging in their series of 11 patients (mixed pediatric and adult cohort). Although, only 5 of 11 patients had a diagnosis of neuroblastoma, DOTATATE sensitivity was 97% vs 90% for MIBG[5]. In a case report, Agarwal et al reported the utility of ^{68}Ga-DOTATATE PET/CT in diagnosis and response evaluation in a 12 year old child with neuroblastoma[12].

All lesions evaluable on MR 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 EANM weight-based activity calculator, (62 MBq/1.7 mCi for ^{68}Ga DOTATATE and 136 MBq/3.7 mCi for ^{123}I MIBG) an approximate 25% radiation dose saving can be made with the use of ^{68}Ga

DOTATATE[14, 21,22]. Reduction in 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 compared to SPECT. Practical advantages also include more rapid imaging requiring less sedation as well as no specific patient preparation requirements. Considering ^{68}Ga DOTATATE has been FDA approved for use with PET for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in pediatric patients and the relative ease to acquire for clinical use, it should be considered for routine use in staging of neuroblastoma patients.

Conclusions:

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

Figures:

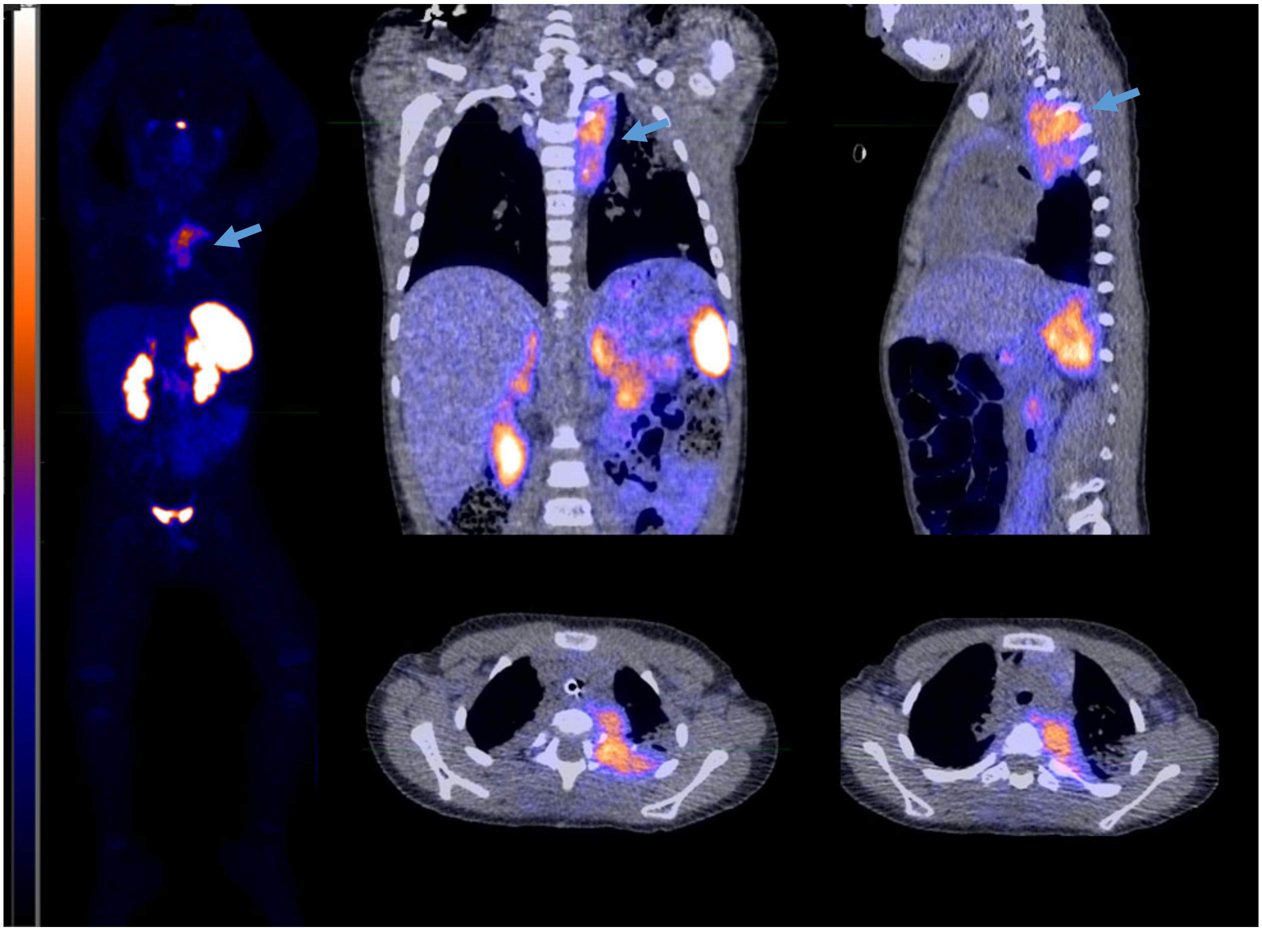

Figure 1. Increased uptake in a left sided paravertebral mass and invading the spinal canal and adjacent vertebral body of T3 (blue arrow).

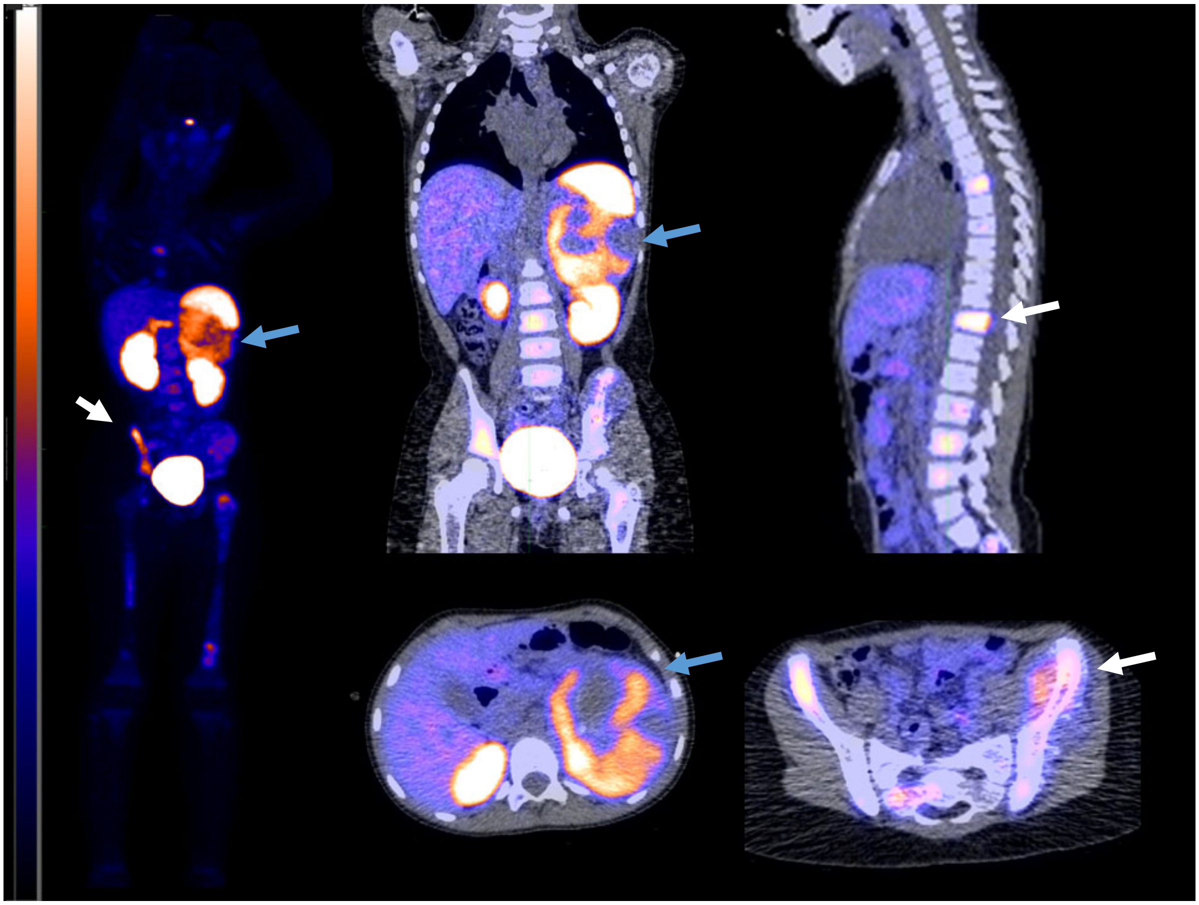

Figure 2. Uptake in left suprarenal mass with areas of necrosis (blue arrow) and evidence of skeletal metastasis (white arrows) and bone marrow infiltration.

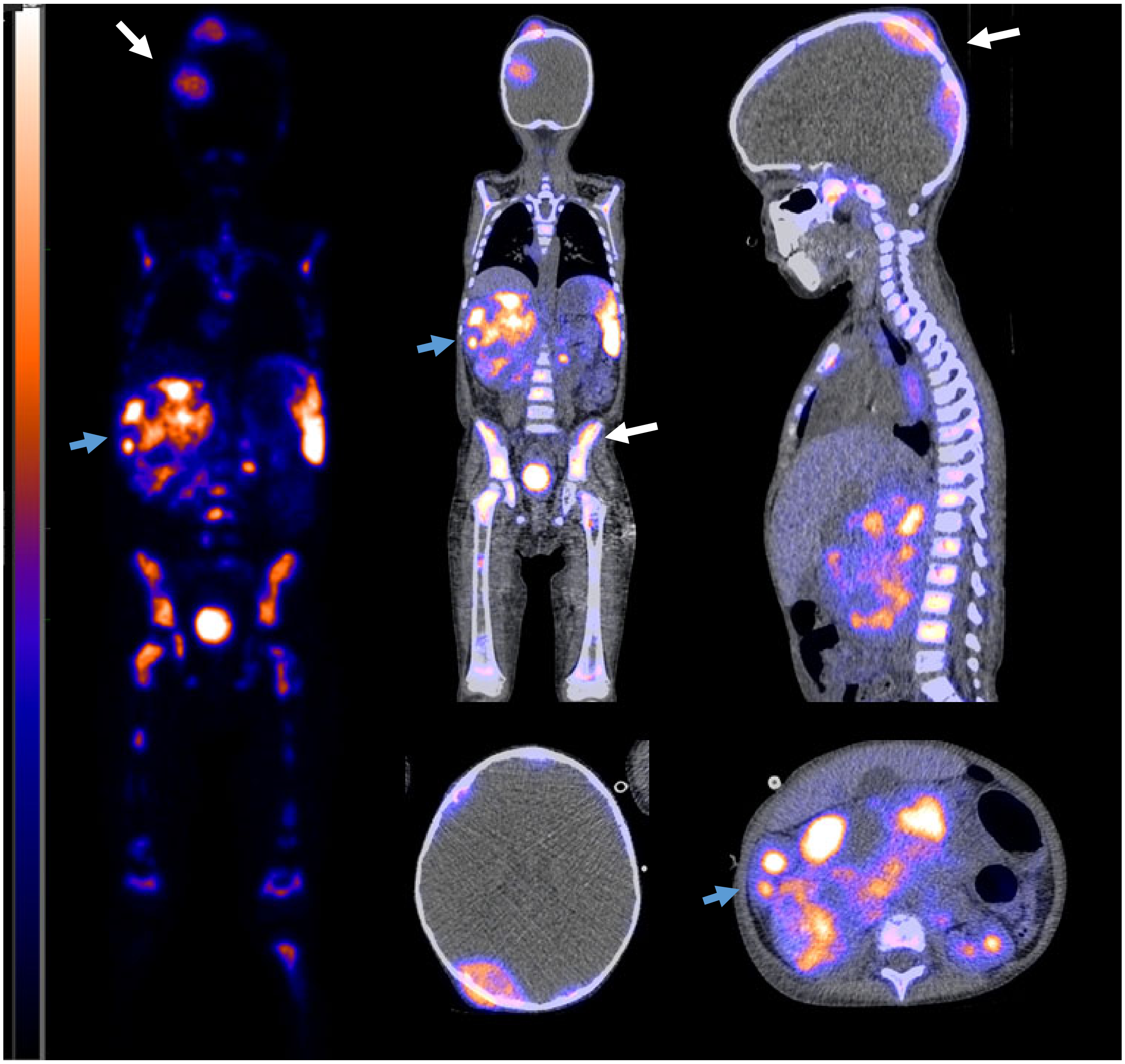

Figure 3. Heterogeneous uptake in a lobulated right suprarenal mass (blue arrow) with diffuse skeletal metastasis including in the skull (white arrows) and diffuse bone marrow infiltration.

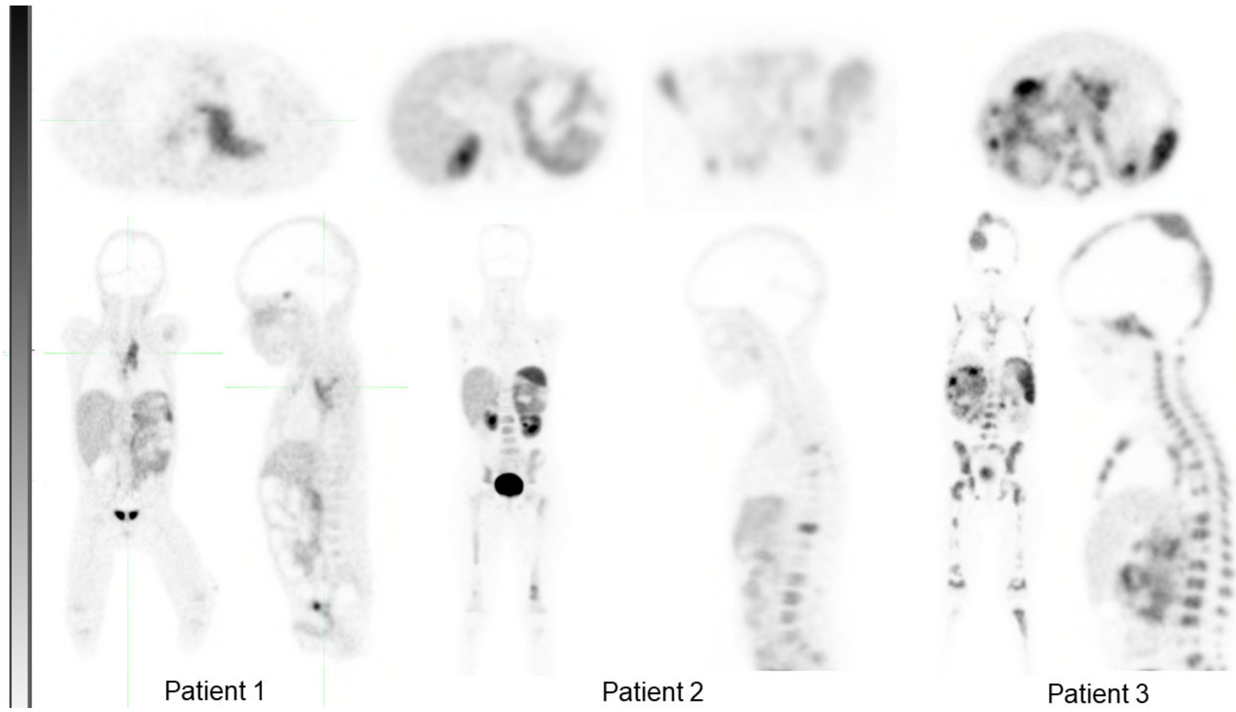

Figure 4. Summary of PET images for patients 1-3.

Table 1. Patient Characteristics

	Patient 1	**Patient 2**	**Patient 3**
Age	23 months	6 years	3.5 years
Gender	Male	Female	Female
Clinical presentation	Ataxia, irritability, progressing to paraparesis	Limp, discomfort on left side of abdomen	Body pains, swelling of left eye, weight loss, cachexia
Histopathology	Poorly differentiated Neuroblastoma	Poorly differentiated Neuroblastoma	Not done
Cytogenetics **N-Myc** **[1]SCA ($1p^-$, $11q^+$, any other, [2]LOH)** **Alk** **[3]NCA**	 Not amplified Not seen No rearrangement Not seen	 Not amplified $1q^+$, $11q^-$, $17q^+$, X^-, No LOH No rearrangement Not seen	 Not done
Bone Marrow	No evidence of infiltration	Infiltrated by non-hematopoietic tumor, neuroblastoma	Infiltrated by non-hematopoietic tumor, neuroblastoma
Urinary catecholamines: **VMA/Creatinine Ratio** **HVA/ Creatinine Ratio**	 14.1(0-6.3) 9.9 (0-13.6)	 90.7 (0-4.7) 95.6 (0-9.4)	 209.8 (0-6.3) 191.0 (0-13.6)

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