

Comparative evaluation of iodine-131 metaiodobenzylguanidine and 18-fluorodeoxyglucose positron emission tomography in assessing neural crest tumors: Will they play a complementary role?

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Abstract

Background: 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) has established a role in the evaluation of several malignancies. However, its precise clinical role in the neural crest cell tumors continues to evolve. **Purpose:** The purpose of this study was to compare iodine-131 metaiodobenzylguanidine (¹³¹I-MIBG) and FDG-PET of head to head in patients with neural crest tumors both qualitatively and semiquantitatively and to determine their clinical utility in disease status evaluation and further management. **Materials and Methods:** A total of 32 patients who had undergone ¹³¹I-MIBG and FDG-PET prospectively were evaluated and clinicopathologically grouped into three categories: neuroblastoma, pheochromocytoma, and medullary carcinoma thyroid. **Results:** In 18 patients of neuroblastoma, FDG PET and ¹³¹I-MIBG showed patient-specific sensitivity of 84% and 72%, respectively. The mean maximum standardized uptake value (SUV_{max}) of primary lesions in patients with unfavorable histology was found to be relatively higher than those with favorable histology (5.18 ± 2.38 vs. 3.21 ± 1.69). The mean SUV_{max} of two common sites (posterior superior iliac spine [PSIS] and greater trochanter) was higher in patients with involved marrow than those with uninvolved one (2.36 and 2.75 vs. 1.26 and 1.34, respectively). The ratio of SUV_{max} of the involved/contralateral normal sites was 2.16 ± 1.9. In equivocal bone marrow results, the uptake pattern with SUV estimation can depict metastatic involvement and help in redirecting the biopsy site. Among seven patients of pheochromocytoma, FDG-PET revealed 100% patient-specific sensitivity. FDG-PET detected more metastatic foci than ¹³¹I-MIBG (18 vs. 13 sites). In seven patients of medullary carcinoma thyroid, FDG-PET localized residual, recurrent, or metastatic disease with much higher sensitivity (32 metastatic foci with 72% patient specific sensitivity) than ¹³¹I-MIBG, trending along the higher serum calcitonin levels. **Conclusions:** FDG-PET is not only a good complementary modality in the management of neural crest cell tumors but also it can even be superior, especially in cases of ¹³¹I-MIBG nonavid tumors.

Key words: 18-Fluorodeoxyglucose positron emission tomography, metaiodobenzylguanidine, neural crest cell tumor

Introduction

The neural crest cell-derived tumors originate from the primitive pluripotent stem cells and during early fetal development these cells invaginate and migrate along the neural axis and finally differentiate to form the various sympathoadrenergic systems of the body.^[1-3] These functionally and metabolically active amine precursor uptake and decarboxylation cell-derived tumors form a large heterogeneous group of malignancies and demonstrate increased circulating and urinary levels of the secreted hormones and their metabolites.^[1-3] Conventional anatomic imaging modalities (such as ultrasonography, computed tomography [CT], and magnetic resonance imaging [MRI]) are the initial investigational method commonly employed, on early clinicobiochemical suspicion, though they may fail to detect these small tumors with micrometastasis and especially cannot depict their unique functionality.^[1,3,4]

These tumors are usually further evaluated by the metaiodobenzylguanidine (MIBG; ¹³¹I/123-I labeled metaiodobenzylguanidine) scintigraphy, which utilizes the sympathoadrenergic pathways for lesion detectability and may serve as a preamble to targeted radionuclide therapy in appropriate settings.^[1,2] The reported sensitivity and specificity of iodine-131 MIBG (¹³¹I-MIBG) are quite high (≥90%) for pheochromocytoma and neuroblastoma while that for medullary carcinoma of the thyroid (MCT) are much lower about 30%.^[3,4] The ¹³¹I-MIBG avidity does vary due to some *de novo* factors or disease course-related causes.^[3-5] In recent times, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) has been investigated for potential

roles in these relatively rare groups of tumors in tissue characterization, metastatic potential evaluation, and predicting prognosis.^[4,5]

Materials and Methods

This was a 2-year prospective study conducted at a tertiary center. All the referred patients with proven/suspected neuroblastoma, pheochromocytoma, and medullary carcinoma of thyroid were included irrespective of age and sex. Pregnant/lactating women, patients with uncontrolled diabetes mellitus, and patients taking any drug that can interfere with the tumoral uptake of MIBG were excluded from this study.

The patients underwent whole-body FDG-PET (using dedicated GE Advance PET scanner, USA) and ¹³¹I-MIBG diagnostic studies (using a dual-head large field of view Gamma Camera-Siemens E-Cam, Germany) sequentially; both were performed following standard preparatory requisites and accepted protocols.

Two experienced nuclear medicine physicians reviewed all the scans, and data were analyzed by the following criteria: (a) Qualitative: The number, visual intensity, and pattern of uptake in FDG and ¹³¹I-MIBG. The visual intensity of tumoral FDG and ¹³¹I-MIBG concentrations was further graded as low/I, moderate/II, and intense/III as per uptake was less, equal, or more than the normal physiological uptake of the liver. (b) Semiquantitative: The standardized uptake values (SUVs) were used for the lesions detected in FDG PET. The mean maximum standardized uptake value (SUV_{max}) values were calculated in the form of mean ± standard deviation.

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Results

A total of 32 patients were evaluated during the study [Table 1].

Neuroblastoma

Among the 18 referred patients, most had eventually diagnosed metastatic disease (International Neuroblastoma Staging System) at the time of initial study (Stage III [$n = 3$]/IV [$n = 13$]/IVs [$n = 1$]), except one who had Stage I (cervical primary) disease ($n = 1$). FDG-PET and ¹³¹I-MIBG studies were positive in 13 and 11 primary sites, respectively. This was as compared to 17 depicted by prior CT scans out of the total 18 patients. However, in four patients with CT/FDG discrepancy, the CT scans were actually done before therapy, and no recent CT scan was available for direct comparison (i.e. true-negative FDG-PET). According to the Shimada classification^[5] of histopathological prognostic subgroups of neuroblastoma, the mean SUV_{max} of the primary lesion in 11 patients with unfavorable histology was 5.18 ± 2.38 , whereas the mean SUV_{max} in 7 patients with favorable histology was 3.21 ± 1.69 . The mean vanillylmandelic acid (VMA) levels (mg/24 h) of the patients were found to be 127.16 ± 227.17 , suggesting a wide variation of this biomarker, not correlated much with tumoral tracer uptake.

In detecting metastatic involvement, ¹³¹I-MIBG depicted 4 skull and 1 orbito-mandibular, 3 neck, 2 chest, and 2 axillary sites and in one patient with Stage IVs disease, multiple soft-tissue involvement of both extremities and lumbar region, altogether in 9 patients, whereas FDG PET showed one lesion in the orbito-mandibular region of skull, 2 neck, 5 chest, 5 axillary sites, and multiple soft-tissue involvement in the Stage IVs patient, altogether in 12 patients. Retroperitoneal lymph nodes were visualized distinctly from the primary lesion in 12 patients; among them, 3 were posttherapy patients, showing no uptake at the known primary site.

For evaluating the bone marrow, 9 had biopsy-proven marrow metastasis while other 9 had none. Of the involved cases, MIBG showed marrow uptake in 5 and FDG showed uptake in 6 patients, with a typical asymmetric, patchy pattern with skip lesions. In all the biopsy-proven uninvolved marrows, MIBG showed no uptake while FDG showed a diffuse pattern of uptake in 4 of them, all of whom were posttherapy patients. SUV_{max} of PSIS and greater trochanter of the femur of patients with biopsy-proven involved marrow was 2.36 ± 1.50 and 2.75 ± 1.93 while that of uninvolved marrow was 1.26 ± 0.47 and 1.34 ± 0.35 , respectively. Furthermore, SUV_{max} of the skip marrow lesions was 3.41 ± 1.85 and that of contralateral marrow sites was 2.10 ± 1.59 , with a ratio of SUV of the involved/contralateral sites being 2.16 ± 1.9 [Table 2a].

Pheochromocytoma

The results of the seven pheochromocytoma patients are depicted as follows: FDG-PET could detect lesions in all of them (100% patient-specific sensitivity). In 1 patient, FDG detected primary lesion only, and in 4 others, both primary and metastasis were shown. There were 2 more patients where FDG uptake was noted in the metastatic lesions only. The mean value of the SUV_{max} of the primary lesions was found to be 19.68 ± 13.21 . The mean SUV_{max} of the metastatic lesions was

Table 1: Salient characteristics of the recruited patients

	Number of Patients
Total number of patients studied	32
Histological tumor types	3
Neuroblastoma	18
Prognostic subtypes: Shimada classification ^[6]	3
Unfavorable	11
Favorable	4
Ganglioneuroblastoma	3
Pheochromocytoma	7
Medullary carcinoma of thyroid	7

Table 2a: Uptake characteristics of the primary lesions of neuroblastoma

Patient number	¹³¹ I-MIBG (grades)	FDG-PET (grades)	SUV _{max} (g/ml)
1	III	III	5.2
2	III	III	2.5
3	III	III	3.4
4	No uptake	No uptake	Not detectable
5	III	III	6.2
6	III	III	3.5
7	III	III	7.1
8a	III	III	5.2
8b	No uptake	No uptake	1.4
9	III	III	10.1
10	No uptake	No uptake	Not detectable
11	I	No uptake	Not detectable
12	No uptake	III	2.6
13	II	III	5.4
14	I	III	5.5
15	III	III	2.8
16a	No uptake	No uptake	Not detectable
16b	No uptake	No uptake	Not detectable
17	No uptake	No uptake	Not detectable
18	II	II	2.3

SUV: Standardized uptake values, PET: Positron emission tomography, FDG: Fluorodeoxyglucose, ¹³¹I-MIBG: Iodine-131 metaiodobenzylguanidine

16.15 ± 14.81 . For metastatic evaluation, ¹³¹I-MIBG showed 13 sites while FDG detected 18 sites [Table 2b].

Medullary carcinoma of thyroid

All the seven patients had prior total thyroidectomy with bilateral modified neck dissection. They had been mainly referred for the detection of metastatic sites and disease recurrence with raised serum calcitonin level. The ¹³¹I-MIBG was negative for all but one patient, where bilateral cervical nodal uptake was seen. FDG-PET could demonstrate metastatic foci in 5 out of the 7 patients (72% patient-specific sensitivity) with the mean SUV_{max} of 8.23 ± 4.31 , in altogether 32 sites. The mean serum calcitonin level was 1965.6 ± 1515.6 pg/ml (range of 1570–17,604). In 2 cases, where FDG-PET was negative, the serum calcitonin level was 2 pg/ml in one and no recent biochemical report was available in the other patient.

Discussions

The conventional approach of assessing neural crest tumors is morphological imaging, followed by ¹³¹I-MIBG/somatostatin receptor imaging for the functional

Table 2b: Uptake characteristics of the primary lesions of pheochromocytoma

Patient number	¹³¹ I-MIBG (sites/grades)	PET (sites/grades)	SUV _{max}
1	B/L ADR (III)	B/L ADR (III)	Right/left ADR - 15.56/12.89
2	RP LN (III)	RP LN (III)	RP LN - 35.54
3	Left upper abdominal focus (I)	Right ADR (III)	Right ADR - 5.02
4	Left ADR (III)	Left ADR (III)	Left ADR - 10.89
5	No uptake	No uptake	Not detectable
6a	No uptake	No uptake	Not detectable
6b	No uptake	No uptake	Not detectable
7	UB (III)	UB (III)	UB - 31.41

RP: Retroperitoneal, LN: Lymph node, PET: Positron emission tomography, ¹³¹I-MIBG=Iodine-131 metaiodobenzylguanidine, SUV: Standardized uptake values, ADR: Adrenal, UB: Urinary bladder, B/L: Bilateral

components.^[1-3] We endeavored to evaluate the disease status using FDG-PET and to assess its impact on further management. Papaioannou and McHugh^[7] in their review concluded that FDG-PET could emerge as a promising modality for revealing childhood neuroblastoma, whereas Shulkin *et al.*^[4] studied the pattern of FDG uptake in 17 neuroblastoma patients and found it to be more intense before therapy while variable patterns after therapy. In our study, FDG-PET and ¹³¹I-MIBG detected 13 and 11 primary sites, respectively. In all the patients where the primary site was not detected by FDG-PET were of postchemotherapy status, which might reflect therapeutic response but cannot be conclusively commented as baseline/pretherapy scintigraphy or recent CT was not available for vis-à-vis comparison. The noted wide variation of the biomarker urinary VMA, not correlating much with the qualitative and semiquantitative parameters of the tumoral tracer uptake, suggested that neither secretor status nor biochemical therapeutic response can be commented on reliably.

The FDG uptake pattern was usually heterogeneous with intense foci with/without areas of central necrosis. While ¹³¹I-MIBG uptake appeared as an area of increased tracer concentration compared to the background activity, details of the lesion in ¹³¹I-MIBG were limited due to poor spatial resolution of the gamma camera, planar imaging, and nonoptimal imaging characteristics of I-131 as compared to those of FDG-PET. Thus, the results were congruent in these regards with the published studies. However, of note is the relatively higher mean SUV_{max} of the primary lesion in patients with unfavorable histology as compared to those with favorable Shimada classification subgroup (5.18 vs. 3.21)-likely providing additional tumoral characterization, implicating aggressive tumor with a higher metastatic potential.

The study by DuBois *et al.*^[8] demonstrated that treatment response and overall event-free survival were decreased in patients with bone marrow, central nervous system, intracranial/orbital, lung, and pleural metastases, whereas relatively improved in those with liver and skin metastases. We observed that uptake foci were more distinctly visualized in FDG-PET as compared to the MIBG scan. However, although the patient-specific detectability was found to be slightly higher for FDG than ¹³¹I-MIBG (in 12 vs. 9 patients), the overall region-wise detection of metastatic lesions was found to be similar in both the scans.

The bone marrow metastasis needs special mentioning as the predilection is quite high due to the congenial ambience

of metastatic spread, especially in children due to wider red marrow distribution and increased blood flow to the growing skeleton. Tanabe *et al.*,^[6] in their analysis of bone marrow by MRI, demonstrated metastases in 45 femurs of 23 patients. They also observed that the rate of disappearance of marrow metastases after chemotherapy was significantly higher for nodular lesions as compared to diffuse involvement (100% vs. 26% patients). It tended to persist after therapy in patients with associated bone involvement. This suggests that powerful systematic chemotherapy and additional targeted therapy to lesions remaining after chemotherapy are needed to improve the cure rate and survival of patients with advanced neuroblastoma. We found bone marrow uptake in 5 and 6 out of 9 patients with biopsy-proven involved marrow in ¹³¹I-MIBG and FDG-PET, respectively. In patients with involved marrow, the FDG uptake pattern was patchy, asymmetric with skip lesions. The ¹³¹I-MIBG also showed the patchy uptake. The tiny focal skip lesions detected by the FDG could not be distinctly visualized by the MIBG due to poor resolution of the planar gamma imaging compared to the tomographic nature of the PET scan.

Sampling error in bone marrow examination is a contentious issue, which might lead to interpretation dilemma, improper staging, and treatment protocol selection. The mean SUV_{max} of two common sites was found to be higher in cases with involved marrow than that of uninvolved one (2.36 and 2.75 vs. 1.26 and 1.34, respectively). Furthermore, the ratio of SUV_{max} of the skip lesions of the involved/contralateral sites was 2.16 ± 1.9. Thus, although the marrow ¹³¹I-MIBG uptake is considered scintigraphic gold standard due to its high specificity for detecting disease involvement, our study showed that uptake pattern coupled with SUV estimation in the FDG-PET study is also quite distinctive for marrow involvement. In cases with equivocal bone marrow biopsy results, these findings can help redirect the biopsy site selection with a probability of better diagnostic yield.

Shulkin *et al.*^[9] showed that most (22 out of 29 patients) pheochromocytomas accumulate FDG. It is especially useful in defining those pheochromocytomas that fail to concentrate MIBG, in about 10–15% of cases. These observations lead to more extensive evaluation of FDG PET in these tumors, regardless of their ¹³¹I-MIBG avidity. In our study, FDG-PET could detect lesions in all of them (100% patient-specific sensitivity). The uptake pattern of FDG in the primary lesions was intense with areas of central necrosis with mean SUV_{max} of 19.68 ± 13.21. The ¹³¹I-MIBG showed similar detectability

for the primary. However, in case of localizing the metastatic foci, FDG-PET showed much more intense, spherical foci of increased tracer concentration than ¹³¹I-MIBG. The mean SUV_{max} of the metastatic lesions was 16.15 ± 14.81 . In two patients (about 29% of patients), dramatically increased number of metastatic foci was detected in FDG-PET than ¹³¹I-MIBG, which leads to change in the further management.

The overall reported sensitivity of ¹³¹I-MIBG in MCT is about 30% while the specificity is quite high (>90%).^[1,2] Moreover, Brandt-Mainz *et al.*^[10] reported that FDG-PET can detect MTC with a reasonable sensitivity of 78% when the calcitonin level is above 1000 pg/ml but appears to be of limited use if the calcitonin level is below 500 pg/ml. Ong *et al.*^[11] found no such definitive cutoff value, but there seems to be a general trend of more likelihood of positive FDG-PET scans with higher serum calcitonin levels. Our study results were congruent to those of the published data. While ¹³¹I-MIBG were negative for all the patients except one, FDG-PET scans demonstrated metastatic foci in 5 out of the 7 patients (about 72% patient-specific sensitivity with mean SUV_{max} of 8.23 ± 4.31) in a total 32 sites, trending along with the higher serum calcitonin levels. The lower detection rate in patients with low serum calcitonin could be probably due to the slow growth rate of these tumors, smaller lesion size of the micrometastatic foci, and overall lesser tumor burden.

Conclusions

From our study results, it could be concluded that FDG-PET can have a potentially useful complementary role to ¹³¹I-MIBG and at times can perform better in certain patients, especially in those with poor MIBG avid lesions. It may help in redirecting the proper biopsy site for improved diagnostic yield for bone marrow involvement.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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