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18F-FDG PET/CT Versus I-131 MIBG Scan in Diagnosis of Neuroblastoma Osseous Infiltrates; Comparative Study

Amr, M[1]. Kotb, M[1], Moustafa, H[2]. Fathy, H[1] and Omar, W[1]

[1] *Nuclear Medicine unit National Cancer Institute, Cairo University,* [2] *Nuclear Medicine & Radiation oncology center, Cairo University, Egypt*

ABSTRACT:

Purpose: To compare diagnostic performance of 18F-FDG PET/CT & I-131 MIBG in neuroblastoma osseous lesions. **Materials and method:** cross sectional study with 63 pathologically proved NB patients with dominating high risk category (~65.1 %) who underwent paired F-18 FDG PET/CT and MIBG scans (with maximum 2 weeks interval) using standard techniques for purpose of initial , post-therapy or follow up assessment. Clinico-pathological, radiological and follow up data were also collected. **Results**: On lesion based analysis of neuroblastoma bone metastases, though non-optimum sensitivity was noted with both modalities yet statistically significant higher sensitivity was seen with 18F-FDG PET/CT (73.1%) as compared to that of I-131 MIBG (55.2 %) (***p- Value=0.03)***. Higher (non-statistically significant) specificity of 100% was seen with I-131 MIBG compared to 92.5% for FDG PET/CT (p-value=0.95). **Conclusion:** FDG PET/CT scanning may have an added value in detection of NB osseous lesions compared to I-131 MIBG, which may help to guide BMB (Bone Marrow Biopsy) in patients with either (I-131 MIBG or 18F-FDG PET/CT) positive scans.

Keywords: FDG PET/CT, MIBG, Neuroblastoma osseous infiltrates

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Corresponding Author: Amr, M**.**   **E mail:** Mai_4a@yahoo.com

INTRODUCTION:

Neuroblastoma (NB) stands out among paediatric solid tumours because of its relative frequency, intriguing natural history, prognostic biologic features, and therapeutic challenges. This embryonal neoplasm often encases vascular structures and, unlike most solid cancers, usually presents with substantial metastatic disease *(1).*Adverse clinical prognostic factors include osseous metastases, substantial involvement of bone marrow in infants, and any degree of distant bone marrow invasion in older patients*(2).*Functional imaging plays an important role in the assessmentof neuroblastoma, from the initial diagnosis and stagingto the evaluation of treatment response and detection ofrecurrent disease. Scan findings not only aid in initial staging but also often guide therapeutic decisions at points during treatment. In recent years, iodinated-meta-iodo-benzyl-guanidine (123/131 I-MIBG) and 99mTc-methylene diphosphonate have been the radiopharmaceuticals used for neuroblastoma assessment.

 18F-FDG 18-Fluorine Fluro-deoxyglucose: is a positron-emitting glucose analog concentratedwithin cells using the glucose transporter. Becausemost tumor cells preferentially use glucose forenergy, 18F- FDG uptake is seen within most tumors.The use of 18F-FDG PET/CT is increasing,

although its roleremains less clear. Questions remain regarding when and inwhich patient's 18F-FDG PET/CT is most useful*(3).*The aim of this work was to evaluate the diagnostic performance of 18FFDG PET/CTversus I-131 MIBG in detection of bone/bone marrow infiltrates in neuroblastoma patients.

PATIENTS AND METHODS:

This comparative (mixed retro- & prospective) study was conducted on 63 patients They were referred to Nuclear Medicine department in different clinical phases of disease (initial, post-therapy or follow up) from Oct., 2009 till Jan. 2014.. Each patient underwent whole body I-131 MIBG scan and 18F-FDG PET- CT with maximum two weeks time interval in between.

.I-31 MIBG scintigraphy protocol: Prior to I-131 MIBG scan, all patients were prepared by oral administration of Lugol's iodine as thyroid-blocking agent for 7 days starting 1 day before I-131-MIBGinjection. The I-131 MIBG dose ranged from 0.5-1.5 mCi (Weight dependent), was given slowly intravenously. Images were acquired at 24, 48 &may be 72 hours post injection using the same ADAC gamma camera system but mounted to a high energy collimator. Whole body sweeps were

taken for anterior and posterior projections at speed 5-8 cm/min. Additional static images for the trunk were taken when needed for more anatomical delineation for average acquisition of 300 K-counts/view.

18F-FDG PET/CT protocol: After fasting for 4-6 hours and ensuring blood glucose level below 150 mg/dl, injection of 3MBq /kg body weight 18F-FDG was done. Scanning started 60-90 min after tracer injection, 5–7 bed positions; acquisition time, 2-3 min/bed position using a dedicated PET-CT scanner. Patients were examined in the supine position with arms elevated, and CT scanning was started from the vault of skull with the following parameters: 40 mAs; 130 kV; slice thickness,

2.5 mm; pitch, 1.5. The CT scans reached caudally to feet or mid tibiae. PET over the same region was performed immediately after acquisition of the CT images (2-3min/bed position). The CT-data were used for attenuation correction, and images were reconstructed as 5-mm slices applying a standard iterative algorithm (ordered-subset expectation maximization).

When necessary, sedation was used in accordance with guidelines before 18F-FDG PET/CT or 131 I-MIBG imaging to ensure patient immobilization and adequate image quality.

Image interpretation: All studies were reviewed by 2 nuclear medicine physicians in

Consensus. Patchy inhomogeneous 18F-FDG uptake in the bone marrow, especially in the absence of recent chemotherapy or hematopoietic stimulating factors, was interpreted as positive for bone marrow infiltration.ForI-131 MIBG scans no physiological osseous uptake therefore any uptake above the background activity in bone considered suspicious for a NB tumour or metastatic localizations. Results of both modalities were compared to those of bone marrow biopsy.

Statistical analysis: Data was analysed using SPSS win statistical package version 20 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate.The sensitivity, specificity, predictive values and accuracy were calculated for I-131 MIBG &18F-FDG PET/CT. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. A *p-* value < 0.05 was considered significant.

RESULTS:

The age of our group ranged from 2 to 156 months with a median and mean of 24 and 35.2 months respectively. There was a predominance of disease in males with male to female ratio 1.4:1.The majority of our group were of high risk category (65.1 %) and

stage IV represented 63.5%.On lesion based analysis of neuroblastoma bone metastases (n= 107), diagnostic performance of bothimaging modalities (I-131 MIBG& 18F- FDG PET/CT) was assessed and correlated to BMB results. *Figure (1)* revealed MIBG avid suprarenal mass with multiple osseous infiltrates, while PET MIP revealed the FDG avid left suprarenal mass with multiple osseous lesions with better delineation of the disease burden and higher No: of lesions could be detected with superior resolution.

statistically significant difference in sensitivity was seen, that was 55.2% for I-131 MIBG compared to 73.1 % for FDG *(P-value=0.04)*. On the other hand no statistically significant difference was noted at the rest of parameters including specificity, total accuracy, & PPV yet with a trend for difference at NPV (p- value =0.07)), *(Table 1). Figure (2)* illustrates the diagnostic performance of I-131 MIBG versus 18F-FDG PET/CT in detection of osteo-medullary NB lesions.
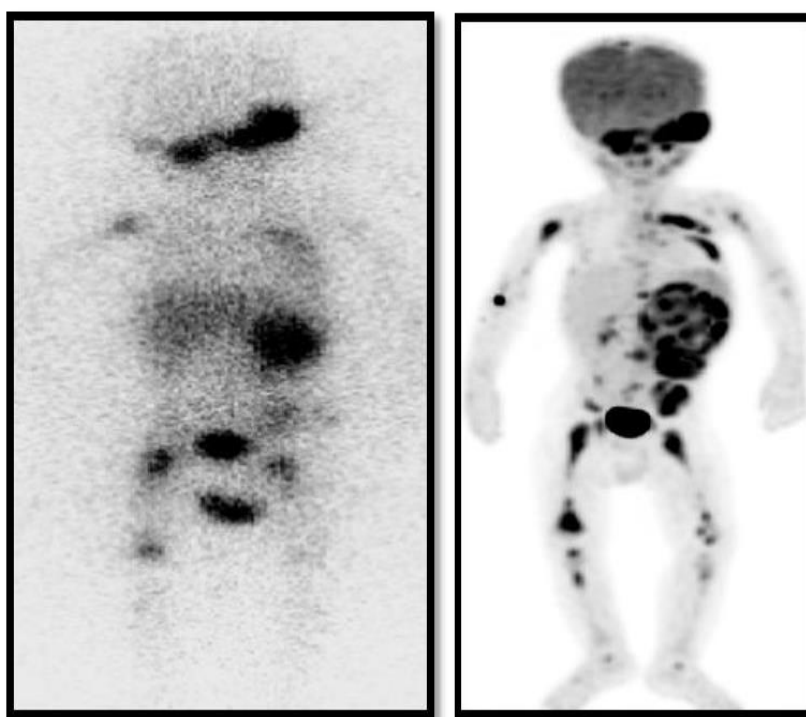

Fig. (1): **I**-131 MIBG WB scan revealed the left MIBG avid suprarenal mass with multiple osseous infiltrates (left). PET MIP (right) revealed the FDG avid left suprarenal mass and the multiple osseous lesions with better delineation of the disease burden and more No. of lesions could be detected with superior resolution.

Table (1): Comparative diagnostic performance of I-131 MIBG versus 18F-FDG PET/CT in Neuroblastoma bone/bone marrow metastases (no. of lesions=107).

Modality / Lesions	I-131 MIBG	FDG	P-value
Sensitivity	55.2 %	73.1 %	*0.04*
Specificity	100 %	92.5 %	*0.92*
Total accuracy	72 %	80.4 %	*0.77*
PPV*	100 %	94.2%	*0.96*
NPV*	57.1 %	67.3%	*0.07*

*PPV: Positive Predictive Value***NPV:** Negative Predictive Value**.**
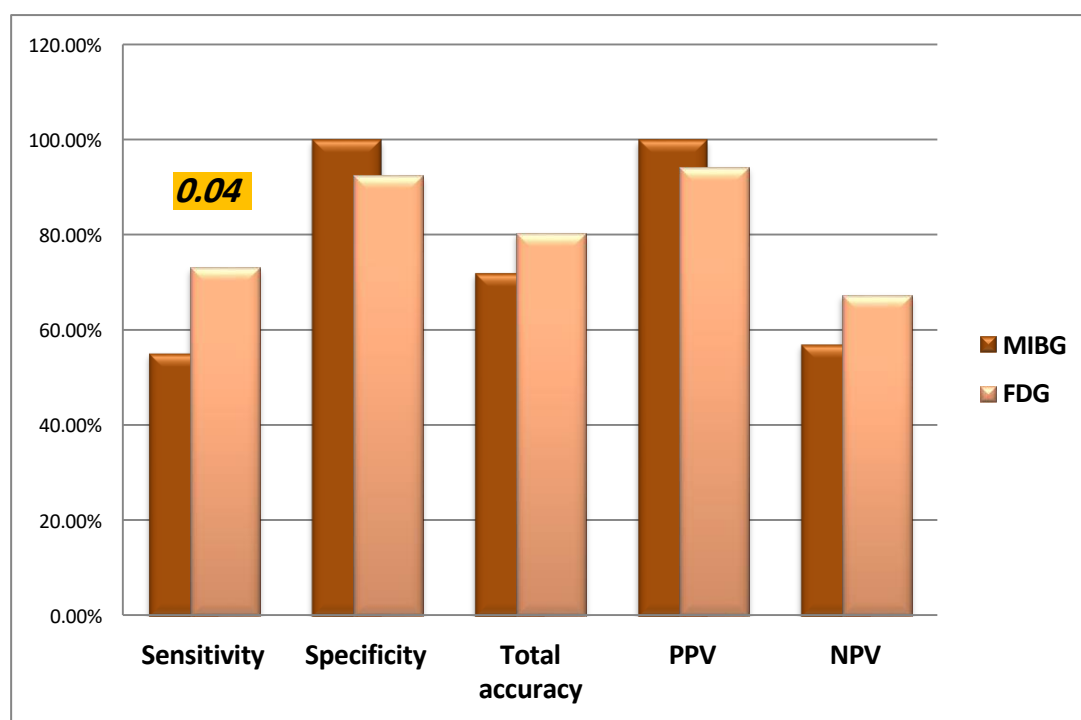
Fig. (2). I-131 MIBG versus 18F-FDG PET/CT in osteo-medullary NB lesions.

DISCUSSION:

Bone marrow metastasis of neuroblastoma is conventionally detected by cytological and histological examination of marrow issued of both posterior iliac crests *(4)*. However, in addition to its invasive nature this technique suffer from sample error as the area examined is limited& did not reflect actual tumour burden in bone marrow. This may influence risk stratification to therapy in neuroblastoma patients. For this reason sensitive techniques exploring larger territories of bone marrow are important, especially in the follow up, to allow a more accurate evaluation of response to treatment. The usefulness of I-131 MIBG scintigraphy has been widely demonstrated in the diagnosis, staging and follow-up of neuroblastoma*(5).*The main reported advantage of I-131 MIBG over 18F-FDG was its superiority in depicting clearly the bone/bone marrow component of the disease because uptake of I-131 MIBG was not confounded by bone marrow activation due to previously applied therapies *(6).* This was the case in our study with specificity of 100% noted with I-131 MIBG compared to 92.5 % with 18F-FDG PET/CT.Despite the specificity of the underlying mechanism for tumour localization, there are several limitations for the use of I-131 MIBG for the detection of skeletal involvement by neuroblastoma in our study. These include poor physical characteristics, low injected dose due to high radiation exposure, and low yield of photon flux as well as low detection efficiency of sodium-iodide (Tl) crystal for the 364 KeV gamma photon. All results in poor image quality and increase frequency of false negative results and consequently limit the sensitivity of MIBG in detection of NB bone marrow infiltrates *(7).*In contrast, the better physical characteristics of FDG, the high photon flux of positron emission, the better detection efficiency of PET/CT system as well as the reconstructed images enhances the detection efficiency of 18F-FDG PET/CT in exploration of NB marrow infiltrates compared to I-131 MIBG *(8).* Finally the biological factor that include the grade of de- differentiation of NB marrow infiltrates especially in advanced disease may enhance FDG efficiency & contrary limit the efficiency of I-131 MIBG scanning in detection of BM infiltrates. Accordingly in this study a significantly higher sensitivity for F18-FDG PET/CT in detection of bone marrow NB infiltrates compared to I-131 MIBG scanning*(9, 10)*. Though both modalities didn't show optimum bone detection yet higher sensitivity, NPV and accuracy were noted with 18F-FDG PET/CT (73.1%, 67.3%, 80.4%) compared to I-131 MIBG (55.2%, 57.1%, 72%) respectivelythat

was statistically significant as regards the sensitivity (P<0.05%).Similar results, of 51 high-risk subjects studied by *Kushner et al*. showed 18F-FDG PET to be better than MIBG for detection of both extra-cranial osteo-medullary and soft-tissue lesions and even more, suggested that PET, alone with bone marrow testing, is sufficient for extra- cranial disease detection *(10).*On the contrary, 123I-MIBG was more sensitive overall and for bone lesions than 18F-FDG PET as reported by the New Approaches to Neuroblastoma Therapy (NANT) trial that enrolled 21 patients with relapsed NB, assessed before MIBG therapy *(11).*Furthermore the noticed high comparable specificity indices of both modalities may raise a possibility of cancelling bone marrow biopsy in neuroblastoma patients with positive bone marrow infiltrates in either scans, however further study with larger population sample is needed to verify such finding.

CONCLUSIONS:

FDG PET/CT scanning seemed to have a superior yield in sensitivity indices in detection of NB osseous lesions compared to I-131 MIBG. Comparable high specificity noted with both modalities may highlight a new proposal for possible subsiding the need for BMB in patients with either(MIBG or18F- FDG PET/CT) positive scans yet further larger scale studies are needed.

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