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^{131}I-MIBG in Neuroblastoma, is Not Simply the Uptake in the Primary Mass

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ABSTRACT

Neuroblastoma is the third most common malignancy of childhood. Nowadays, MIBG has become a central procedure for staging and defining extent and location of neuroblastoma tumors. The recommendations of the International Neuroblastoma Staging System (INSS) indicate that MIBG scintigraphy must be performed in patients with neuroblastoma at the time of initial staging and as a follow-up tool during therapy.

Purpose: Of this study is to identify the role of ^{131}I-MIBG scintigraphy in neuroblastoma patients and to correlate it with other diagnostic modalities for staging and follow up of neuroblastoma.

Methods: The study was conducted on 26 patients provisionally diagnosed to have neuroblastoma. On histopathologic verification 5 of these 26 patients were rediagnosed as non-neuroblastoma. Since the study aims at assessing the diagnostic power of ^{131}I-MIBG scan, these 5 cases were not excluded. The 21 histopathologically diagnosed as neuroblastoma were 11 patients in stage IV, 7 in stage III and 1 patient in each of stages I, II and IV-S. Each, patient underwent a standard comprehensive diagnostic work up, Radiological imaging by conventional X-ray, ultrasound, CT and/or MRI was carried out. In all patients ^{131}I-MIBG scintigraphy was performed, among them 15 patients underwent additional ^{99m}Tc-MDP bone scan as well.

Results: The 21 neuroblastoma patients were studied according to the results obtained from CT, MRI and ^{131}I-MIBG scanning. The outcome demonstrated that CT and MRI were able to detect lesions in 19 out of 21 patients; while in 2 patients no lesions were detected. ^{131}I-MIBG scan showed actively functioning lesions in 16 out of the above 19 patients, while in 3 patients MIBG scan was negative. There was no false positive result by ^{131}I-MIBG scan. Accordingly, ^{131}I-MIBG is able to detect neuroblastoma lesions with an overall sensitivity of 84.2%, specificity of 100% and an accuracy of 85.7%. Detection of primary lesions by ^{131}I-MIBG was significantly better than ^{99m}Tc-MDP bone scanning (92.31% vs 61.54% respectively) ($p < 0.01$). For skeletal metastases, ^{131}I-MIBG scan has a higher ability to detect more lesions than ^{99m}Tc-MDP bone scan ($p = 0.023$).

Conclusions: ^{131}I-MIBG has excellent ability to discriminate between neuroblastoma and other small round cell pediatric tumors. ^{131}I-MIBG was found to be significantly superior to conventional bone scanning in revealing both primary and metastatic osseous lesions. It is recommended to perform ^{131}I-MIBG scanning at initial presentation to confirm the histopathologic diagnosis and to monitor subsequent response to therapy.

Key Words: *Iodine 131 - Neuroblastoma - Tc-99m MDP bone scan.*

INTRODUCTION

Neuroblastoma is the third most common malignancy of childhood, exceeded in frequency only by primary brain tumours and leukemia **[1,2]**. These highly malignant tumors arise from primitive neuro-ectodermal cells. Neuroblastomas compromise about 10% of pediatric tumors and account for about 15% of cancer deaths in children. Neuroblastoma is one of the small round cell neoplasms of childhood. These neoplasms of childhood include in addition, Ewing's sarcoma, Non-Hodgkin's lymphoma, Primitive neuroectodermal tumors (neuroepithiliomas) and undifferentiated soft tissue sarcomas as Rhabdomyosarcoma **[3,4]**. Neuroblastomas are neoplasms of young children with 75% occurring by age 4 or younger and 50% by age 2. They may originate wherever sympathetic nervous tissue is found. The location of the primary tumor at the time of diagnosis varies and changes with age. The most common site of origin for neuroblastoma is within the abdomen (65%), whereas thoracic and cervical primary tumors are seen in 34% and in about 1% of patients, a primary tumor cannot be found **[2,5]**. Neuroblastoma tends to present in advanced stage leading to poor prognosis, as despite the use of increas-

ingly aggressive treatment regimens, long-term survival is less than 15% [6].

Attempts to develop radiotracers that concentrate in adreno-medullary tissues began nearly 30 years ago. Initial efforts were centered on catecholamines and their precursors [7,8]. Subsequent work by Wieland [9] was conducted with the meta-isomer. Metaiodobenzylguandine (MIBG). Radioiodinated MIBG is an alkaylguanidine that bears structural similarity to the neurotransmitter and catecholamine hormone-norepinephrine. Initial and current scintigraphic experiences with MIBG were obtained using the ^{131}I-labeled compound. Iodine-131 has suboptimal physical imaging properties and dosimetery. Despite this, the sensitivity and specificity are quite high, being around 87% and 98%, respectively [10-16]. The use of ^{123}I for labelling takes advantage of better physical properties for imaging and favorable radiation dosimetery. In reality, however, a minor controversy about accuracy and specificity exists regarding the use of ^{123}I versus ^{131}I MIBG [17]. It may be preferred to use ^{123}I-MIBG for its image clarity; nevertheless, there should be no hesitation to use ^{131}I-MIBG for imaging if the former is unavailable.

Nowadays, MIBG has become a central procedure for staging and defining extent and location of neuroblastoma tumors [18]. Accordingly, the recommendations of the International Neuroblastoma Staging System (INSS) indicate that MIBG scintigraphy must be performed in patients with neuroblastoma at the time of initial staging and as a follow-up tool during therapy [19,20].

The aim of this study is to identify the role of ^{131}I-MIBG scintigraphy in neuroblastoma patients and to correlate it with other diagnostic modalities for staging and follow up of neuroblastoma.

PATIENTS AND METHODS

Patients: The study was conducted on 26 patients provisionally diagnosed to have neuroblastoma and referred to nuclear medicine unit in Kasr Al-Aini University Hospitals during the period from June 1999 to July 2000. On histopathologic verification 5 of these 26 patients were rediagnosed as non-neuroblastoma [Ewing's sarcoma; peripheral Primitive Neuroectodermal tumor (PNET), Schwannoma and 2 undifferentiated small round cell tumor]. Since the study aims at assessing the diagnostic power of ^{131}I-MIBG scan, these 5 cases were not excluded.

The 21 histopathologically diagnosed as neuroblastoma were 13 boys and 8 girls with a mean age (±SD) of 4.13±4.06 years (range 2 m-16 years). The baseline characteristics of all the patients are listed in Table (1).

According to Evans staging system [21,22], there were 11 patients in stage IV, 7 in stage III and 1 patient in each of stages I, II and IV-S.

Each, patient underwent a standard comprehensive diagnostic work up, including clinical and physical examination, laboratory investigations including, urea, serum creatinine, neurone specific enolase (NSE) and bone marrow aspiration Radiological imaging by conventional X-ray, ultrasound, CT and/or MRI was carried out in all patients. In all 21 patients whole body ^{131}I-MIBG scintigraphy was performed. In 15 patients additional ^{99m}Tc-MDP bone scanning for skeletal survey were acquired.

^{99m}Tc-MDP bone scan and ^{131}I-MIBG scintigraphy protocols:

Bone scanning was performed 2-3 hours after I.V. dose of 185-370 MBq (5-10 mCi) according to predetermined weight dependent pediatric dose. A large field of view dual head (ADAC, vertex) Gamma Camera equipped with a low energy high resolution collimator was used to obtain anterior and posterior whole body images at a speed of 10-12 cm/min and/or regional spot views of 500 Kcounts/view.

Prior to ^{131}I-MIBG scintigraphy, all patients were prepared by oral administration of Lugol's iodine as a thyroid-blocking agent for 7 days, starting 1 day before ^{131}I-MIBG injection. The ^{131}I-MIBG dose ranged from 0.5-1.5 mCi (weight dependent), was given slowly intravenously, followed by 10 ml of saline. Images were acquired at 24, 48 and 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 a speed of 5-8 cm/min. Additional static images for the trunk were taken - when needed for more anatomical delineation - for an average acquisition of 300 kcounts/view.

Image interpretation:

The interpretation of ^{131}I-MIBG was done mainly qualitatively. For each MIBG or bone scan a visual score was calculated to assess the extent of bone metastases. The skeleton was divided into 10 zones: 1- Calvarium; 2- Base of the skull and face; 3- Cervico-thoracic spine; 4- Lumbo-sacral spine; 5- Ribs, sternum and scapulae; 6- Pelvis; 7- Upper arms; 8- Forearms and hands; 9- thighs; 10- Legs and feet. All zones were scored using a 4-point scale: 0 = no uptake; 1 = single focal uptake; 2 = multiple abnormalities, less than 50% of the zone involved; 3 = multiple abnormalities equal to or more than 50% of the skeletal zone. Intensity of uptake was not taken into account in this analysis. This zone scheme was adopted from Perel et al. [23].

A total score was then calculated by adding the individual scores of the 10 zones.

Statistical methods:

Results were expressed as the mean ± SD or frequency when appropriate. Comparisons between ^{131}I-MIBG, CT and MRI were done using the Pearson's Bivariate correlation and Student's *t*-test. The sensitivity, Specificity, predictive values and accuracy were calculated using standard statistical tests to measure the validity of ^{131}I-MIBG scintigraphy. Differences among different imaging modalities were evaluated by non-parametric significance tests. A probability value less than 0.05 was considered statistically significant.

RESULTS

The study was conducted on 26 patients diagnosed provisionally as having Neuroblastoma. The male to female ratio was 1.6:1. Sixteen patients had a positive ^{131}I-MIBG scan, while 10 patients had a negative scan. On histopathologic verification 5 of them were rediagnosed as non-neuroblastoma [Ewing's sarcoma; peripheral primitive neuroectodermal tumor (PNET), Schwannoma and 2 undifferentiated small round cell tumor] and were considered as true negative MIBG scans. The detectability of lesions by CT and/or MRI was referred to as an adjuvant standard test besides the histopathological diagnosis against which statistical judgment of MIBG scintigraphy was made. Accordingly, the other 5 ^{131}I-MIBG negative patients, although histopathologically diagnosed as neuroblastoma, two of them were free in CT scan (true negative), while the other 3 patients were considered false negative as they had small lesions < 1.5 cm seen in CT and/or MRI scanning (Fig. 1).

The clinical data for the 21 patients histopathologically diagnosed as neuroblastoma are listed in Table (1). The neuroblastoma primary sites were abdominal in 18 patients and extra-abdominal in 3 (mediastinal, intra-spinal and in the brain). The ^{131}I-MIBG scan was positive in 16 of the 18 patients with abdominal primary. The other two patients had a negative ^{131}I-MIBG; one had performed incomplete surgical excision leaving a residual retro-peritoneal tumor evident in the post-operative CT scan (false -ve), while the other 2 patients with abdominal and mediastinal neuroblastoma had complete surgical excision with free CT (true negative). All the 3 patients with extra-abdominal primary tumor had a false negative ^{131}I-MIBG scan (Fig. 1).

The mean age for the 21 patients histopathologically diagnosed as neuroblastoma (16 MIBG +ve and 5 -ve MIBG) was 4.13±4.06 years, that was significantly lower than the 5 non-neuroblastoma patients whom had a mean age of 8.16±3.95 ($p < 0.05$).

Diagnostic ability of ^{131}I-MIBG scintigraphy for neuroblastoma compared to anatomical imaging modalities:

The 21 neuroblastoma patients were analyzed according to the results obtained from CT, MRI and ^{131}I-MIBG scanning. The outcome demonstrated that CT and MRI were able to detect lesions in 19 out of 21 patients; while in 2 patients no lesions were detected. ^{131}I-MIBG scan showed actively functioning lesions in 16 out of the above 19 patients, while in 3 patients MIBG scan was negative. There was no false positive result by ^{131}I-MIBG scan. Accordingly, ^{131}I-MIBG is able to detect neuroblastoma lesions with an overall sensitivity of 84.2%, specificity of 100% and an accuracy of 85.7%.

Lymph node detection by ^{131}I-MIBG:

Out of the 16 patients with positive ^{131}I-MIBG scan, there was 9 patients with abdominal lymph nodes as detected by CT and MRI. ^{131}I-MIBG scan was positive for lymph node detection in 6 of them, while it was negative in the remaining 3 patients. The bulky abdominal pri-

mary lesions may have obscured the lymph nodes in these 3 patients. All CT, MRI and ^{131}I-MIBG imaging modalities were negative in remaining 7 patients. Hence, sensitivity of ^{131}I-MIBG scan to detect lymph node involvement was estimated to be 66.6%, while the specificity, positive and negative predictive values (PPV, NPV) were 100%, 100% and 70%, respectively. The total agreement for L.N. detection between ^{131}I-MIBG scan and other anatomical imaging modalities (CT and MRI) were in 13 out of 16 patients that equals to 81.25% ($p < 0.05$).

^{99m}Tc-MDP bone scintigraphy versus ^{131}I-MIBG:

The primary masses in neuroblastoma are characterized by high incidence of tumor calcification; therefore exhibit soft tissue uptake in ^{99m}Tc-MDP bone scintigraphy. In the present study, 15 neuroblastoma patients performed both ^{131}I-MIBG scan and bone scanning. Of those 15 patients, two showed no residuals on CT scanning after complete surgical excision and hence were excluded from the comparison. In the remaining 13 patients, ^{131}I-MIBG whole body scan was able to detect primary lesions in 12 patients (92.31%), while in ^{99m}Tc-MDP bone scanning, only 8 patients (61.54%) showed positive uptake in the primary abdominal masses. The statistical difference was significant and highly in favor of the ^{131}I-MIBG scan ($p < 0.01$) (Table 2).

Eight out of the 15 patients who performed bone scanning had evidence of skeletal metastases detected by ^{131}I-MIBG and/or bone scanning. In 7 patients; ^{131}I-MIBG scan had a higher score denoting ability to detect more lesions, while in one patient the score was equal in both techniques (Fig. 2). The mean ^{131}I-MIBG score for these patients was significantly higher than the mean ^{99m}Tc-MDP bone scan score (10.25±6.79 versus 7.75±6.96; $p = 0.023$) (Table 2).

Bone marrow involvement by ^{131}I-MIBG scanning:

Amongst the 16 patients with positive ^{131}I-MIBG, 11 had bone marrow involvement documented by bone marrow aspiration. Nine of the 11 patients had evidence of bone marrow disease in the ^{131}I-MIBG scan, giving a sensitivity, specificity, PPV and NPV of 81.8%, 100%, 100% and 71.4%, respectively with an overall agreement with bone marrow aspiration biopsy of 87.5% (Fig. 3).

Table (1): Clinical characteristics of the 21 neuroblastoma patients.

Characteristic	Value/ number	Percentage
Age at diagnosis in years:		
Mean ± S.D.	4.13±4.06	
Range	(0.2-15.5)	
Sex:		
Male	13	62
Female	8	38
Primary tumor site:		
Adrenal	12	57.1
Retroperitoneal	6	28.6
Mediastinum	1	4.8
Spinal	1	4.8
Brain	1	4.8
Metastatic tumor sites:		
Bone	10	47.6
Bone marrow	11	52.4
Lymph nodes	8	38.1
Liver	2	9.5
Stages:		
I	1	4.8
II	1	4.8
III	7	33.3
IV	11	52.4
IV-S	1	4.8
MIBG scan:		
Positive cases	16	76.2
Negative cases	5	23.8
True -ve	3	
False -ve	2	
Elevated NSE level	16/20	80

Table (2): Comparison between MDP bone scan and MIBG scintigraphy for detection of primary and metastatic lesions in neuroblastoma (n = 13 patients).

	Bone scan	MIBG scan	*p* value
	No. (%)	No. (%)	
Primary lesions:			
Positive	8 (61.54%)	12 (92.31%)	< 0.01
Negative	5 (38.48%)	1 (7.6%)	< 0.01
Metastatic lesions:			
Mean score	7.75	10.25	0.023
(SD)	(6.9)	(6.79)	

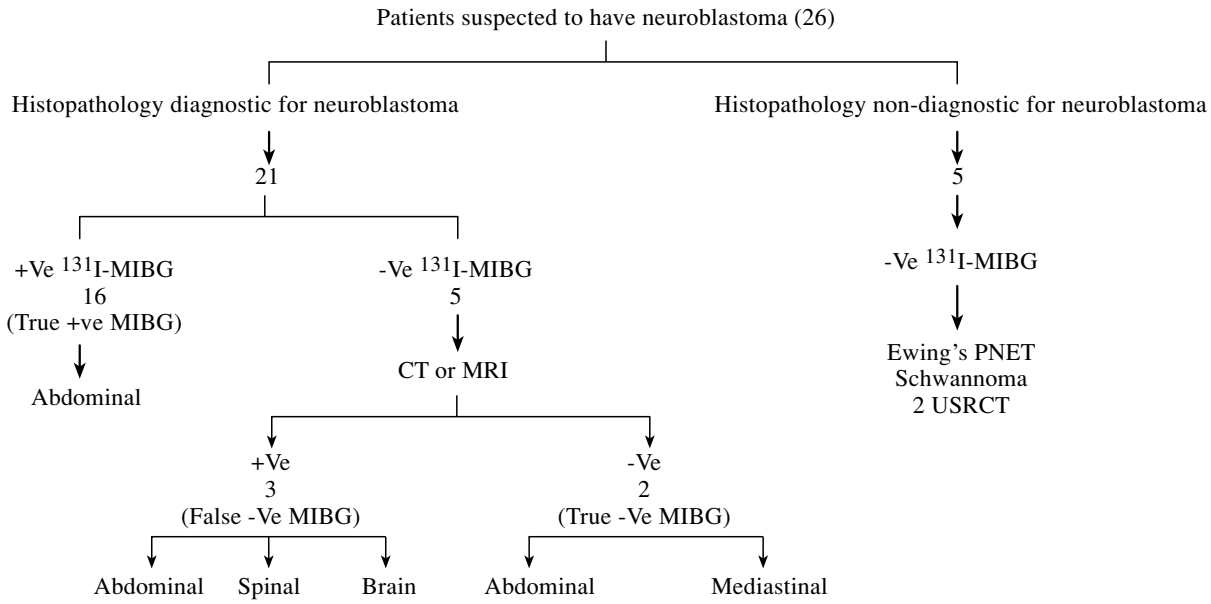


Fig. (1): Scheme showing the outcome of 26 patients with suspected neuroblastoma.
-Ve; Negative uptake; +ve; Positive uptake, PNET; Primitive neuroectodermal tumour and USRCT; Undifferentiated small round cell tumour.

Fig. (2-A)

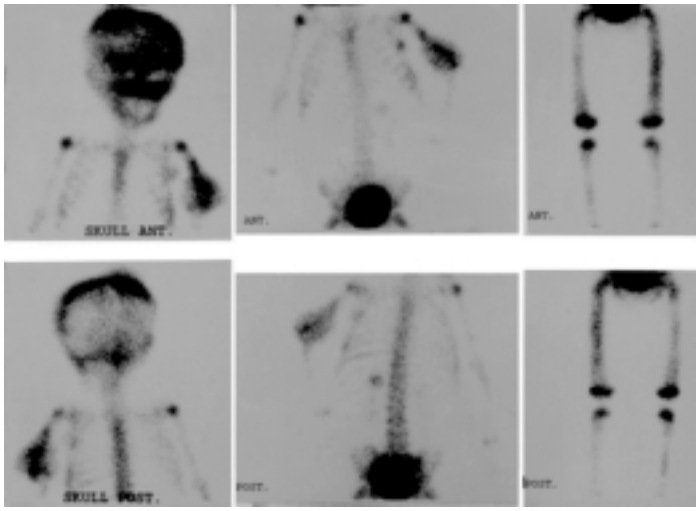


Fig. (2-B)

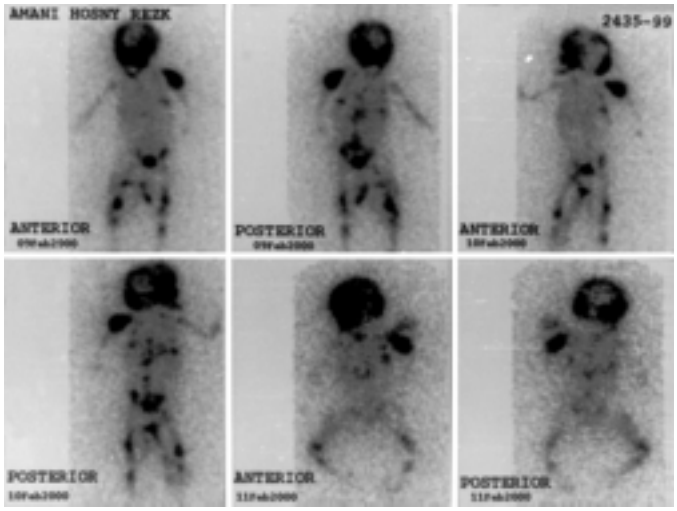
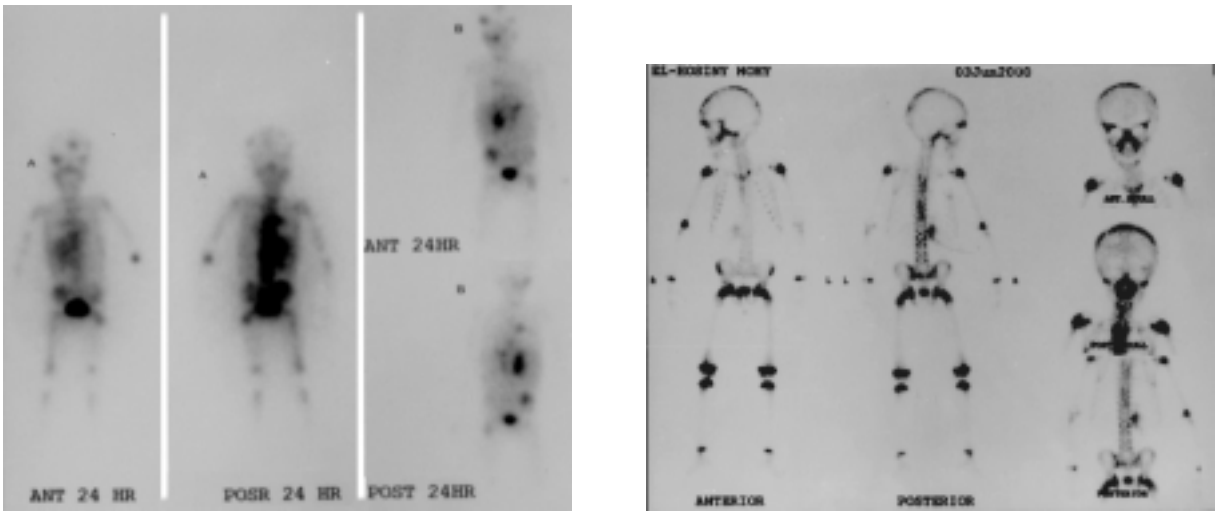


Fig. (2): A- ^{99m}Tc-MDP bone scanning and B- ^{131}I-MIBG scintigraphy in a 2.5 years old child. MIBG demonstrates more extensive involvement and is able to detect more metastatic sites than those seen in the bone scanning.



(A) (B)

Fig. (3): A- ^{131}I-MIBG showing uptake by the right supra-renal mass, multiple osseous metastases and evident bone marrow involvement in multiple areas. B- ^{99m}Tc-MDP bone scanning for the same child showing calcified abdominal primary and few osseous lesions with no ability to assess bone marrow affection.

DISCUSSION

Radio-labelled MIBG scintigraphy is a well-established examination in the diagnosis and follow-up of neuroblastoma patients. It is the scintigraphic standard, although attempts to develop other tracers continue. MIBG remains the simple best agent for imaging neuroblastoma and as a prerequisite for MIBG therapy. It is to be noted that most tracers evaluated in neuroblastoma had been compared to MIBG **[24-29]**.

The ability to screen the entire patient in a single non-invasive ^{131}I-MIBG procedure is clearly advantageous with considerably good detection ability. Averaging eight different publications revealed a mean overall sensitivity; specificity; PPV and NPV of 87%, 94%, 98% and 70% respectively **[10-16,30]**.

In this work, ^{131}I-MIBG scan was performed for 26 patients of suspected neuroblastoma. Sixteen patients had a positive ^{131}I-MIBG scan confirming their clinical diagnosis of neuroblastoma, while the other 10 patients had a negative scan. Five patients were histopathologically verified and re-diagnosed as non-neuroblastoma (Ewing's sarcoma, PNET, Schwannoma and undifferentiated small round cell tumor). This was consistent with findings of Shimada et al. **[31]**, who stated that distinguishing Neuroblastoma from other small round blue cell tumors of childhood often requires techniques beyond haematoxylin-eosin staining and light microscopy. Immunohistochemistry (e.g. Immunoperoxidase techniques) and electron microscopy are helpful adjuncts. It is well established that uptake of MIBG by a mass in the appropriate clinical circumstances indicates a lesion of neuroendocrine origin and helps in distinguishing neuroblastoma from other small round cell tumours of childhood **[30,32]**. This reflects the utmost importance of ^{131}I-MIBG scintigraphy in supporting the equivocal histopathologic diagnosis, especially in the absence of immunohistochemistry, electron microscopy, tumor karyotyping or even verifying the cause of increased serum catecholamines or its metabolites. The value of ^{131}I-MIBG scintigraphy is emphasized when knowing that it is positive not only in patients with high levels of urinary catecholamines and metabolites but also in those with normal levels **[33,34]**.

The other 5 negative ^{131}I-MIBG patients were histopathologically diagnosed as neuroblastoma. Two of them were free in CT scan, while the other 3 patients had small detectable lesions in CT or MRI (11.5%). This is consistent with the cumulative results of prior studies reporting ~ 10% false negative rate for ^{131}I-MIBG scans due to either an intrinsic lack of the tumor's ability to concentrate ^{131}I-MIBG or to a minimal disease beyond the resolution of Gamma cameras **[35]**.

Relation between patients' age and ^{131}I-MIBG scintigraphic findings:

In the present study, the mean ages at diagnosis were compared in different subgroups. The mean age in years (±SD) was higher in the 5 non-neuroblastoma patients (8.16±3.95) when compared with the 21 patients histopathologically diagnosed as neuroblastoma (4.13±4.06) regardless of the ^{131}I-MIBG scan results ($p = 0.043$). On the other hand, the difference between the mean age of the 5 negative ^{131}I-MIBG neuroblastoma patients (5.4±5.09) and that for the 16 positive ^{131}I-MIBG group (3.74±3.78) failed to reach statistical significance ($p > 0.05$). This was not unexpected, since both sub-groups are histopathologically diagnosed as neuroblastoma and it suggests that both samples are likely coming from the same underlying population. Review of 668 neuroblastoma cases by Pediatric Oncology Group (POG) **[2]** revealed that the median age at diagnosis for neuroblastoma is 22 months and that 75% are less than 4 years in age. This comes into close agreement with our results.

In the same group of neuroblastoma patients studied by POG, it was found that 68% had disseminated disease at presentation **[2]**. It was also reported that more than 50% of children with neuroblastoma have bone marrow involvement, even in the absence of Roentgengraphic changes in bone **[36,37]**. These features had been met in our study, where the 16 ^{131}I-MIBG positive patients included 11 (68.75%) with disseminated disease. This was on the contrary to the negative ^{131}I-MIBG group, in whom none had evidence of bone metastases or bone marrow involvement.

Association between ^{131}I-MIBG scintigraphy and other diagnostic modalities:

Findings of ^{131}I-MIBG scintigraphy in this study were compared to other diagnostic modalities including histopathology, CT/MRI, ^{99m}Tc-MDP bone scan and bone marrow aspiration. There is a high degree of accuracy (85.7%) for ^{131}I-MIBG scans in identifying neuroblastoma when compared with the combined results of histopathology and CT or MRI. This value is very close to the literature reported accuracy, 84%-90% **[15,19,35,38,39]**. It is worth to realize that no false positive results were detected in these studies nor in our work.

^{131}I-MIBG scintigraphy and abdominal lymph nodes:

Among the 21-neuroblastoma patients, 9 had abdominal lymph nodes as detected by CT and MRI. ^{131}I-MIBG scan was positive for lymph node detection in 6 patients only, with sensitivity, specificity and accuracy of 66.6%, 100% and 81.25%, respectively. Although such diagnostic terms are derived from small groups, they are fairly consistent with the reported 60-70% sensitivity of ^{131}I-MIBG scintigraphy in disclosing lymph nodes and soft tissue metastases **[30,35,40]**. The false negative results for the detection of the primary mass (3 cases) or lymph nodes can be attributed to several factors, including: tumor heterogeneity, inadequate tumor uptake, lesions smaller than the resolving power of the camera (e.g. lymph nodes), sites of physiological ^{131}I-MIBG uptake (e.g. masking liver metastases) and the presence of voluminous neuroblastoma masses which surround or hide other lesions. In addition, uptake may be reduced during or immediately after chemotherapy or external radiation therapy **[11,30,41,42]**.

^{99m}Tc-MDP Bone scintigraphy in neuroblastoma:

^{99m}Tc-MDP bone scan was used primarily in the current work to detect osseous lesions. Occasional uptake by some primary neuroblastoma lesions was noted. This may provide additional information, however, it lacks acceptable sensitivity (61.5%) when compared to ^{131}I-MIBG scanning (92.3%). Moreover, for the extent of metastatic osseous involvement, ^{131}I-MIBG detected more metastatic lesions than ^{99m}Tc-MDP bone scan. The mean ^{131}I-MIBG score for 8 patients with stage IV was higher than bone scanning score (10.25 versus 7.75 respectively, $p = 0.0234$). These results were consistent with previous studies addressing that ^{131}I-MIBG revealed 10-40% more lesions than ^{99m}Tc-MDP bone scanning **[12,34,43-46]**. In addition, ^{131}I-MIBG has the advantage of differentiating active tumor lesions from healing or other unrelated lesions, which is a disadvantage of bone scan **[47]**. However, in tumors showing no uptake of ^{131}I-MIBG, the bone scan remains the method of choice for screening metastatic bone involvement **[30,48]**.

In conclusion, ^{131}I-MIBG is highly effective in the diagnosis of neuroblastoma with excellent ability to discriminate between neuroblastoma and other small round cell pediatric tumors. ^{131}I-MIBG was found to be significantly superior to

conventional bone scanning in revealing metastatic osseous lesions in neuroblastoma patients. It is recommended to perform ^{131}I-MIBG scanning at the time of initial presentation to confirm the histopathologic diagnosis and to monitor subsequent response to therapy.

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