I-MIBG in the diagnosis of primary and metastatic neuroblastoma

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Abstract

Objective

Neuroblastoma is the third most common malignancy of childhood. ¹³¹I-MIBG scintigraphy must be performed in patients with neuroblastoma at the time of staging. The aim of this study is to identify the role of ¹³¹I-MIBG scintigraphy in neuroblastoma patients in correlation with other diagnostic modalities for staging of the disease.

Methods

Twenty six patients provisionally diagnosed by clinical and imaging criteria to have neuroblastoma were included. On histopathologic verification 5 of these 26 patients were rediagnosed as non-neuroblastoma. Each patient had imaging by ultrasound, CT and/or MRI. In all cases, ¹³¹I-MIBG scintigraphy was performed, among them 15 patients had additional ⁹⁹ᵐTc-MDP bone scan.

Results

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. ¹³¹I-MIBG showed active lesions in 16 out of the above 19 patients, while in 3 patients ¹³¹I-MIBG was negative. There were no false positive result by ¹³¹I-MIBG scan. Accordingly, ¹³¹I-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 ¹³¹I-MIBG was significantly better than ⁹⁹ᵐTc-MDP bone scanning (92.31% vs. 61.54% respectively) (P < 0.05). For skeletal metastases, ¹³¹I-MIBG scan has a higher ability to detect more lesions than ⁹⁹ᵐTc-MDP bone scan (P=0.023).

Conclusions

¹³¹I-MIBG scintigraphy has an excellent ability to discriminate between neuroblastoma and other small round cell paediatric tumours. ¹³¹I-MIBG was found to be significantly superior to conventional bone scanning in revealing both primary and metastatic osseous lesions.

Key Words

Neuroblastoma, ¹³¹I-MIBG, Bone scanning, Skeletal metastases.

Introduction

Neuroblastoma is the third most common malignancy of childhood, exceeded in frequency only by primary brain tumours and leukaemias(¹). This highly malignant tumour arise from primitive neuro-ectodermal cells. Neuroblastoma comprise about 10% of paediatric tumours 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 tumours (neuroepitheliomas), and undifferentiated soft tissue sarcomas as Rhabdomyosarcoma (²). Neuroblastoma originate wherever sympathetic nervous tissue is found. The location of the primary tumour at the time of diagnosis varies and changes with age. The most common site of origin for neuroblastoma is within the abdomen (65%). Infants have more thoracic and cervical primary tumours and in about 1% of patients, a primary tumour cannot be found (¹). Neuroblastoma tend to present in an advanced
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Stage leading to poor prognosis. Despite the use of increasingly aggressive treatment regimens, long-term survival is less than 15% (3). Attempts to develop radiotracers that concentrate in adreno-medullary tissues began nearly 30 years ago. Initial efforts were centered on catecholamines and their precursors (4). Subsequent work by Wieland (5) was conducted with the meta-isomer, Metaiodobenzylguanidine (MIBG). Radiiodinated MIBG is an alkylguanidine that bears structural similarity to the neurotransmitter and catecholamine hormone norepinephrine. Initial and current scintigraphic experiences with MIBG were obtained using the 131I-labeled compound. 131I has suboptimal physical imaging properties and dosimetry. Despite this, the sensitivity and specificity are quite high, being around 87% and 98% respectively (6, 7). The use of 123I for labelling has the advantages of better physical properties for imaging and favourable radiation dosimetry. In reality, however, a minor controversy about accuracy and specificity exists regarding the use of 123I versus 131I MIBG (8). It may be preferred to use 123I-MIBG for its image clarity, nevertheless, there should be no hesitation to use 131I-MIBG for imaging if the former is unavailable.

Nowadays, 123I/131I-MIBG has become a standard procedure for staging and defining the extent and location of neuroblastoma tumours. Accordingly, the recommendations of the International Neuroblastoma Staging System (INSS) indicate that 123I/131I-MIBG scintigraphy must be performed in patients with neuroblastoma at the time of initial staging and as a follow-up tool during therapy (1, 9).

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

**Materials And Methods**

**Patients**

The study was conducted on 26 patients provisionally diagnosed by clinical and imaging criteria to have neuroblastoma. On histopathologic verification 5 of these 26 patients were re-diagnosed as non-neuroblastoma (Ewing’s sarcoma, Peripheral Primitive Neuroectodermal tumour (PNET), Schwannoma, and 2 undifferentiated small round cell tumour). Since the study aims at assessing the diagnostic power of 131I-MIBG scan, these 5 cases were not included.

The 21 histopathologically diagnosed cases 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 (10), there were 11 patients with stage IV, 7 with 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, neuron 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 131I-MIBG scintigraphy was performed. In 15 patients additional 99mTc-MDP bone scanning for skeletal survey were done.

**99mTc-MDP bone scan and 131I-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 paediatric dose. A large field of view dual head 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 131I-MIBG scintigraphy, all patients were prepared by oral administration of Lugol’s iodine as a thyroid-blocking agent for 7 days, starting one day before 131I-MIBG injection. The 131I-MIBG dose ranged from 0.5 – 1.5 mCi (weight dependent) and was given slowly intravenously, followed by 10 ml. of saline. Images were acquired at 24, 48 and 72 hours post-injection using the same gamma camera system but mounted to a high-energy collimator.
### Table 1: Clinical characteristics of the 21 neuroblastoma patients

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

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 and for an average acquisition of 300 kcounts/view.

**Image Interpretation**

The interpretation of $^{131}$I-MIBG was done mainly qualitatively. For each $^{131}$I-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 where: 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. (11).

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

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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 and 10 patients had a negative scan. On histopathologic verification 5 of these 10 patients were re-diagnosed as non-neuroblastoma (Ewing’s sarcoma, peripheral primitive neuro-ectodermal tumour (PNET), Schwannoma, and 2 undifferentiated small round cell tumour) and were considered as true negative $^{131}$I-MIBG scans. The detectability of the lesions by CT and/or MRI was referred to as an adjuvant standard test besides the histopathological diagnosis against which statistical judgment of $^{131}$I-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 lesions seen in CT and/or MRI scanning (Fig. 1).

### Results

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 large retro-peritoneal residual evident in the post-operative CT scan (false negative), while the other had complete surgical excision with free CT (true negative). (Fig. 1).

![Fig. 1: Scheme showing the outcome of 26 patients with suspected Neuroblastoma. PNET (Primitive Neuro-ectodermal Tumour), USRCT (Undifferentiated Small round Cell Tumour), (–Ve) Negative uptake), (+Ve) Positive uptake.](image-url)
The mean age for the 21 patients histopathologically diagnosed as neuroblastoma (16 +ve $^{131}$I-MIBG and 5 –ve $^{131}$I-MIBG) was 4.13 ± 4.06 years, that was significantly lower than the 5 non-neuroblastoma patients who 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 analysed 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 $^{131}$I-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 were 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 primary lesions may have obscured the lymph nodes in these 3 patients. All CT, MRI and $^{131}$I-MIBG imaging modalities were negative in the 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) was 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 tumour calcification. Therefore they show, 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 residues 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 favour of the $^{131}$I-MIBG scan (P < 0.05) [Table 2].

Skeletal Metastases detected by $^{131}$I-MIBG and/or bone scanning were present in 8 out of those 15 patients. In 7 patients, the $^{131}$I-MIBG scan has a higher score denoting ability to detect more lesions, while in 1 patient the score was equal in both techniques (Fig. 2 A & B ). The mean $^{131}$I-MIBG score for those 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>
<thead>
<tr>
<th></th>
<th>Bone Scan</th>
<th>$^{131}$I-MIBG Scan</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary lesions</strong></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>8 (61.54%)</td>
<td>12 (92.31%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Negative</td>
<td>5 (38.48%)</td>
<td>1 (7.6%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Metastatic lesions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score</td>
<td>7.75</td>
<td>10.25</td>
<td>0.023</td>
</tr>
<tr>
<td>(SD)</td>
<td>(6.9)</td>
<td>(6.79)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Comparison between $^{99m}$Tc-MDP bone scintigraphy and $^{131}$I-MIBG scintigraphy for detection of primary and metastatic lesions in Neuroblatoma (n=13 patients).
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Fig. 2 A: 99mTc-MDP bone scanning in neuroblastoma case.

Fig. 2 B: 131I-MIBG scintigraphy in a 2.5 years old child. 131I-MIBG demonstrates more extensive involvement and is able to detect more metastatic sites than those seen in the Bone scanning.

**Bone Marrow involvement by 131I-MIBG scanning**

Among the 16 patients with positive 131I-MIBG, 11 had bone marrow involvement documented by bone marrow aspiration. Nine of those 11 patients had evidence of bone marrow disease in the 131I-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 A & B).

**Discussion**

Radio-labelled MIBG scintigraphy is a well-established examination for the diagnosis and follow-up of neuroblastoma patients. It is the scintigraphic standard, and while attempts to develop other tracers continue, 123I/131I-MIBG remains the simple best agent for imaging neuroblastoma and as a prerequisite for 131I-MIBG therapy (12).

The ability to screen the entire patient in a single non-invasive 131I-MIBG procedure is clearly advantageous with considerably good detection ability. The literature data revealed a mean overall sensitivity, specificity, PPV and NPV of 87%, 94%, 98% and 70% respectively (13).

In this work, 131I-MIBG scan was performed for 26 patients of suspected neuroblastoma. Sixteen patients had a positive 131I-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 tumour). This was consistent with the findings of Shimada et al. \(^{(14)}\), who stated that distinguishing Neuroblastoma from other small round blue cell tumours 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 the uptake of \(^{131}\)I-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 \(^{(15)}\). This reflects the utmost importance of \(^{131}\)I-MIBG scintigraphy in supporting the equivocal histopathologic diagnosis, especially in absence of immunohistochemistry, electron microscopy, tumour 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 \(^{(16, 17)}\).

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 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 tumour’s ability to concentrate \(^{131}\)I-MIBG or to a minimal disease beyond the resolution of Gamma camera \(^{(18)}\).

**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) \(^{(1)}\) revealed that 68% had disseminated disease at presentation. 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 \(^{(1)}\). These features had been met in our study, where the 16 \(^{131}\)I-MIBG positive patients included 11 (68.75%) with disseminated disease.

**Association between \(^{131}\)I-MIBG scintigraphy and other diagnostic modalities**

The 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%. It should be noted that no false positive results were detected neither in their studies, nor in our work. The causes of false positive \(^{131}\)I-MIBG scintigraphy are uptake in hepatocellular carcinoma, adrenal medullary hyperplasia, diffuse renal uptake in cases of renal failure and in some cases of accessory spleens \(^{(1, 18)}\).

\(^{131}\)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 \(^{(18)}\).
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The false negative results for the detection of the primary mass (3 cases) or the lymph nodes can be attributed to several factors. These include, (1) tumour heterogeneity, (2) inadequate tumour uptake, (3) lesions smaller than the resolving power of the camera (e.g. lymph nodes), (4) sites of physiological 131I-MIBG uptake (e.g. masking liver metastases) and (5) 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. In addition, uptake may be reduced during or immediately after chemotherapy or external radiation therapy (13).

99mTc-MDP Bone scintigraphy in Neuroblastoma

99mTc-MDP bone scan was used primarily in the current work to detect osseous lesions. Occasional uptake by some primary neuroblastoma lesions was noted. Although this may provide additional information, it lacks acceptable sensitivity (61.5%) when compared to 131I-MIBG scanning (92.3%). Moreover, for the extent of metastatic osseous involvement, 131I-MIBG detected more metastatic bony lesions than 99mTc-MDP bone scan. The mean 131I-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 131I-MIBG reveals 10 – 40% more lesions than 99mTc-MDP bone scanning (17, 19). In addition, 131I-MIBG has the advantage of differentiating active tumour lesions from healing or other unrelated lesions, which is a disadvantage of bone scan, however, in tumours showing no uptake of 131I-MIBG, the bone scan remains the method of choice for screening metastatic bone involvement

Conclusion

In conclusion, 131I-MIBG is highly effective in the diagnosis of neuroblastoma with excellent ability to discriminate between neuroblastoma and other small round cell paediatric tumours. 131I-MIBG was found to be significantly superior to conventional bone scanning in revealing metastatic osseous lesions in neuroblastoma patients.

References


