Skeletal Assessment in Neuroblastoma—The Pitfalls of Iodine-123-MIBG Scans

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This study was carried out to compare iodine-123 metaiodobenzylguanidine ([^{123}I]MIBG) and technetium-99m-methylene diphosphonate bone scans (^{99m}Tc-MDP) in the detection of skeletal involvement by neuroblastoma. Forty-four children with neuroblastoma underwent both [^{123}I]MIBG and ^{99m}Tc-MDP scans within a 4-wk period; bone marrow examination also was performed; all these investigations were done both at diagnosis and at follow-up. At diagnosis, four children with Stage 4 disease had normal [^{123}I]MIBG scans but abnormal ^{99m}Tc-MDP scans, while at follow-up there were four children with negative [^{123}I]MIBG studies who later died from disseminated neuroblastoma. All eight scans are considered false-negative. In 24 children, the [^{123}I]MIBG revealed more extensive disease with 161 positive sites while the ^{99m}Tc-MDP scan showed only 100 positive sites; 34 of these sites were common to both studies. This study shows that underassessment of skeletal involvement by neuroblastoma occurred using [^{123}I]MIBG scans and that one cannot therefore substitute [^{123}I]MIBG for ^{99m}Tc-MDP bone scans in the staging of neuroblastoma.

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Neuroblastoma is the most common solid, extracranial malignancy of childhood and the most likely to metastasize to bone (*1*). The prognosis varies with age and clinical stage at diagnosis (*2*). Precise staging of disease at diagnosis and follow-up is essential to allow accurate assessment of treatment.

The greater detection rate of skeletal involvement by technetium-99m-methylene diphosphonate (^{99m}Tc-MDP) bone scanning has resulted in this technique replacing radiologic skeletal survey in the staging of neuroblastoma (*3,4*). Radiolabeled metaiodobenzylguanidine (MIBG), a specific marker for neural crest tumors including neuroblastoma (*5*), is in regular use in many centers. Moreover, it has been suggested that this agent should replace ^{99m}Tc-MDP (*6,7*). This study was designed to compare the value of ^{99m}Tc-MDP and [^{123}I]MIBG in the detection of skeletal metastasis in neuroblastoma.

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PATIENTS AND METHODS

A total of 44 unselected patients with a proven diagnosis of neuroblastoma by International Neuroblastoma Staging System (INSS) criteria (*8*) and examined with [^{123}I]MIBG scintigraphy between January 1986 and March 1988 were eligible for study. For inclusion, ^{99m}Tc-MDP and [^{123}I]MIBG scans must have been completed within 4 wk of each other, either at diagnosis or follow-up (90% were completed within the same week). Three patients were excluded due to incorrect timing of the studies and another five because the images were missing from the file. The 36 remaining children were aged between 1 wk and 11.5 yr of age (median age 3.0 yr) at diagnosis. There were 13 females. For staging data, see Table 1.

The [^{123}I]MIBG scans were performed according to the technique of Sisson (*9*). A list of drugs known to inhibit MIBG uptake was given to the parents with instructions that the children should avoid them for at least one week before the scan. Oral potassium iodide was administered for three days prior to the scan. The dose of [^{123}I]MIBG (120 MBq for children aged under 2 yr and 160 MBq for those over 2 yr) was administered intravenously over 1–2 min. The children were sedated, if necessary, for imaging. Whole-body images, performed 18–24 hr postinjection, were acquired for 5 min on a Scintronix gamma camera. Bone imaging was performed on the same camera 3 hr after intravenous administration of ^{99m}Tc-MDP at a dose of 260 MBq/M2.

For this study, the ^{99m}Tc-MDP scans were independently reviewed by one author (AMP), and the [^{123}I]MIBG scans by a second (IG). At that time, neither knew the results of the other's review. Individual lesions on ^{99m}Tc-MDP and [^{123}I]MIBG scans were marked on a body map.

Bone marrow was evaluated by bilateral aspirate and trephine biopsy in each case at diagnosis (*10*). These results and urinary catecholamine levels at the time of imaging, the final clinical stage (INSS criteria), treatment regime, and clinical progress were reviewed. Prior to restaging all Stage 3 and 4 patients received chemotherapy (OPEC regime, (*11*)); those with Stage 1 and 2 disease were treated with surgery with or without OPEC (maximum of four courses).

RESULTS

Twenty-eight patients were studied at diagnosis. (For Group A results, see Tables 1, 2, and 3). Six children were considered to have Stage 1–3 disease, and all had normal bone marrow examinations, ^{99m}Tc-MDP, and

TABLE 1
Staging of Patients*

Total Number	36
Stage 4	28
Stage 1–3	8
Group A at diagnosis	
Number	28
Stage 4	22
Stage 1–3	6
Group B at follow-up	
Number	22
Stage 4	18
Stage 1–3	4

* Eight children seen only at follow-up.

Note: INSS Criteria 1988 were used to prove diagnosis (see Ref. *8*).

TABLE 3
Correlation Between MDP Scanning (3A), MIBG Scanning (3B), and Marrow Examination at Diagnosis of Stage 4 Disease

		MDP	
3A		POS	NEG
Marrow	POS	19	0
Marrow	NEG	3	0
		MIBG	
3B		POS	NEG
Marrow	POS	15	4
Marrow	NEG	1	2

The proportion of positive bone scans, i.e., 19/19 is significantly higher ($p < 0.05$) (Chi-square test) than the proportion of positive MIBG scans, i.e., 15/19.

[^{123}I]MIBG scans; all were alive and well at a mean of 16 mo (range 9–24 mo) after diagnosis. All 19 children with Stage 4 disease, proven by positive bone marrow aspiration/trephine, had abnormal ^{99m}Tc-MDP scans but only 15 had positive [^{123}I]MIBG scans (Fig. 1). Three other children with positive ^{99m}Tc-MDP scans, suggestive of skeletal involvement, had normal marrow results; only one of these children had an abnormal [^{123}I]MIBG scan. If the three children with only bone scan evidence of Stage 4 disease are excluded, the false-negative rate for [^{123}I]MIBG was (4/19) (21%) (Figs. 2 and 3). All the children with positive ^{99m}Tc-MDP scans responded to chemotherapy and showed significant improvement on ^{99m}Tc-MDP scan at follow-up.

Follow-up (Group B). A total of 19 ^{99m}Tc-MDP and [^{123}I]MIBG scans were performed on 18 Stage 4 patients at follow-up and between 3 and 64 mo after diagnosis (mean = 9 mo) (Table 4). This group then received further therapy. There were six children with positive [^{123}I]MIBG scans and 12 with negative scans. Although 11 children had positive ^{99m}Tc-MDP bone scans, only three had new skeletal lesions. A persisting abnormality on ^{99m}Tc-MDP scan cannot be considered as evidence of active neuroblastoma (Branach P, *personal communication*, 1989); only ^{99m}Tc-MDP scans revealing new lesions can be considered as likely "true-positive." There were seven children with normal ^{99m}Tc-MDP scans, two of whom died from recurrent neuroblastoma, suggesting either a false-negative bone scan or no skeletal involvement at the time of relapse. Of the children who relapsed, there were as many with a positive as well as a negative [^{123}I]MIBG scan.

TABLE 2
Correlation between MDP and MIBG Scanning in Patients with Stage 4 Disease at Diagnosis

	MDP	
	POS	NEG
MIBG POS	17	0
MIBG NEG	5	0

Correlation between the number of positive sites demonstrated on the ^{99m}Tc-MDP and [^{123}I]MIBG scans at diagnosis and follow-up is shown in Table 5 and Figure 4. Five patients in Group A and two in Group B had ^{99m}Tc-MDP+/[^{123}I]MIBG+ abnormalities too numerous to count and were thus excluded from this analysis.

DISCUSSION

High quality ^{99m}Tc-MDP bone scans are required if the skeletal metastasis of neuroblastoma, which develop in the meta-physes of the long bones, are to be detected (Fig. 2). These abnormalities can be identified only with meticulous attention to technical detail and critical appraisal. Experience with ^{99m}Tc-MDP at this institution in over 150 children with neuroblastoma, and elsewhere (*12*), gives the authors confidence that certain abnormalities are diagnostic of Stage 4 disease.

It has been suggested that [^{123}I]MIBG may be a more sensitive tracer since it is specifically taken up by adrenal medulla and tumors arising from the medulla but not by normal bone (*13,14*). Iodine-123, a gamma emitter (159 KeV) provides a much better image than ^{131}I for diagnostic purposes. There is no accepted dose schedule for [^{123}I]MIBG in pediatrics, but the dose used in this study was approved by ARSAC and is the same as that used in most other centers. Initially, images were were obtained at 4 and 20 hr, but since the 4-hr image failed to provide any additional information this was discontinued (*15*). Using a preset scanning time of 5 min, we obtained images comparable in quality to our ^{99m}Tc-MDP bone scans.

In Group A, independent evidence of Stage 4 disease via bone marrow involvement was available; yet there were negative [^{123}I]MIBG scans giving a false-negative rate of 21%. Since INSS criteria include the results of

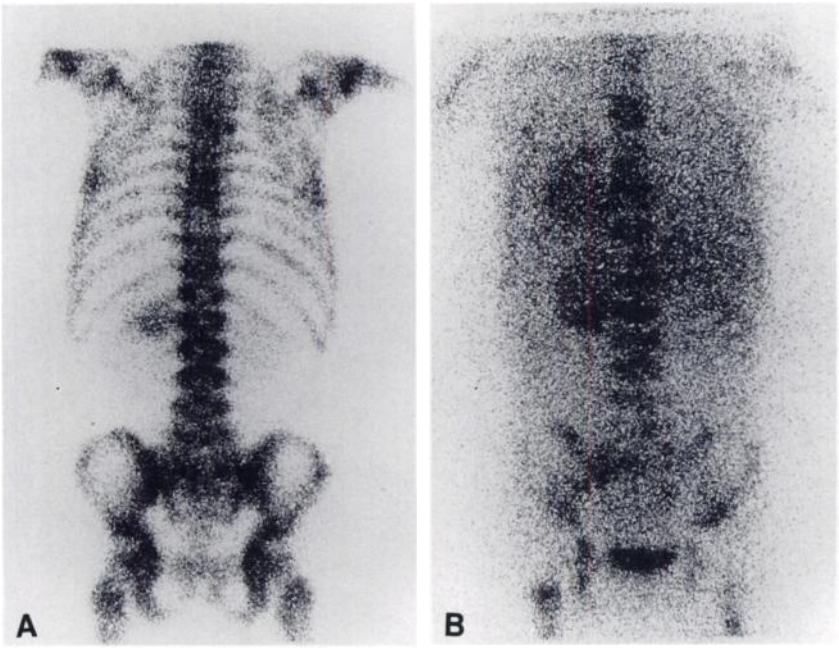

FIGURE 1
(A) Technetium-99m-MDP scan. The posterior view of the chest and abdomen shows abnormal increased uptake of isotope in the upper left femur and areas of decreased uptake in the vertebral bodies, mainly in the mid dorsal and upper lumbar area. (B) Iodine-123-MIBG scan. The posterior view of chest and abdomen shows abnormal accumulation of isotope in the vertebrae, pelvis, and femora. There is also accumulation of isotope in the left hemithorax and left suprarenal area corresponding to soft-tissue masses.

bone scanning, the false-negative rate for ^{99m}Tc-MDP in this series is indeterminate.

In Group B, the results are difficult to interpret since there is no "gold standard" for comparison with the two isotope studies. Neither isotope scan was helpful in predicting which children would relapse later on. Reversion of the bone scan to normal or a significant improvement following therapy suggests a response. Interpretation of the bone scan is problematic because bone scan abnormalities are nonspecific. Persistent lesions imply increased bone turnover but do not necessarily indicate the presence of viable tumor. At this

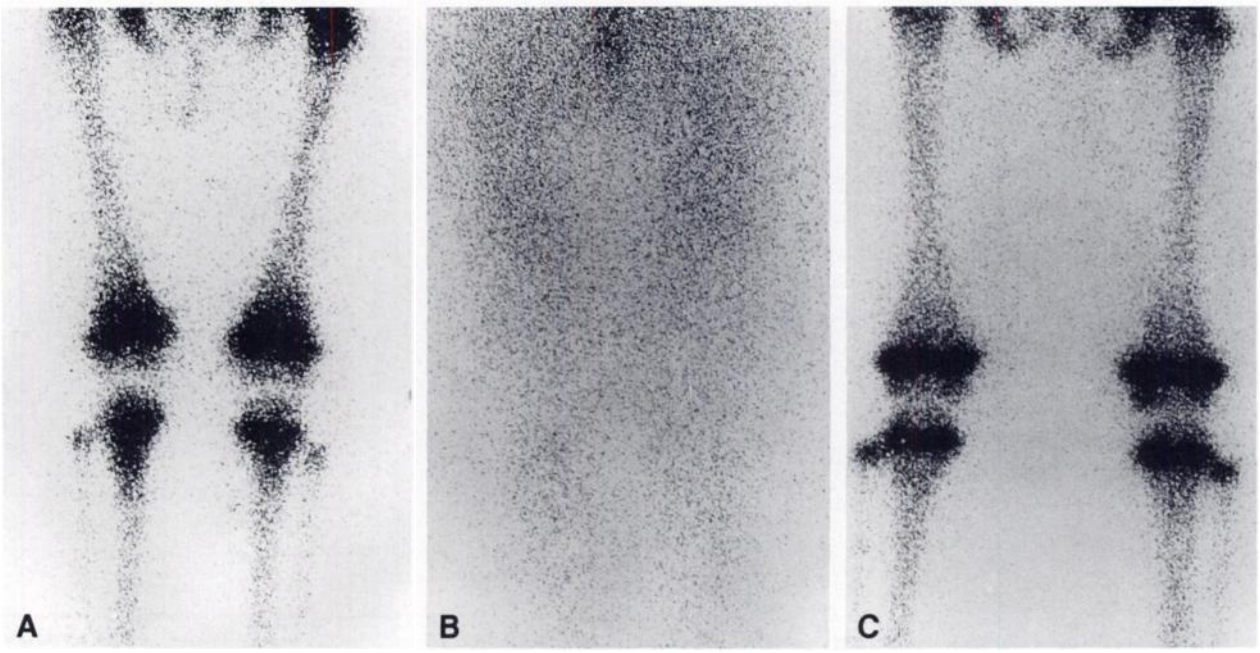

FIGURE 2
(A) Technetium-99m-MDP scan. The magnified view of the knees at diagnosis reveals loss of the normal clarity of the epiphyseal plate with abnormal uptake of isotope in the metaphysis of the lower femur and upper tibia. (B) Iodine-123-MIBG scan. The magnified view of the knees at diagnosis reveals no abnormal uptake of isotope in the skeleton. (C) Technetium-99m-MDP scan. The magnified view of the knees at follow-up, 3 mo after the first bone scan, shows normal appearances of the knees. The other skeletal lesions noted at presentation also had resolved. (Not demonstrated.)

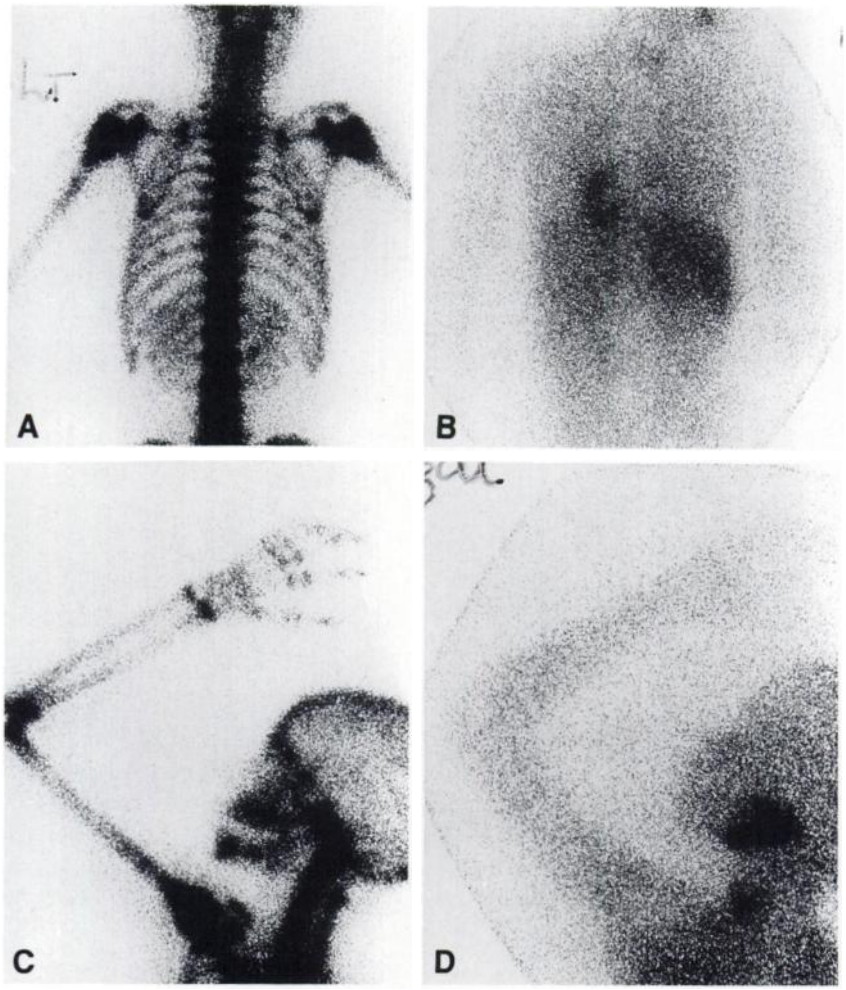

FIGURE 3
(A) Technetium-99m-MDP bone scan on a 4-yr-old boy at the time of diagnosis of neuroblastoma. The posterior view of the thorax and upper abdomen shows an abnormal increased uptake of isotope in the left proximal humeral diaphysis as well as in the posterior ribs on the right, below and medial to the scapula. The posterior upper ribs on the right show less marked abnormalities. Uptake by the tumor also is noted. (B) Iodine 123-MIBG scan. The posterior view of the thorax and abdomen reveals isotope in the heart, liver and thyroid gland. (The mother failed to give the child the full dose of potassium iodide.) No abnormal activity is seen in the ribs or left humerus. (C) Technetium-99m-MDP bone scan. Left lateral view of the skull and upper limb confirms the abnormal uptake in the proximal humeral diaphysis. (D) Iodine-123-MIBG scan. Left lateral skull and upper limb shows uptake of isotope in the salivary glands and thyroid but no abnormality is seen in the region of the humerus.

institution, new bone lesions are considered to be highly significant. Theoretically, [^{123}I]MIBG, as a more specific tracer, should have a role in detecting residual metastasis; however we have found that the status of either the [^{123}I]MIBG or ^{99m}Tc-MDP scan at follow-up was no help in predicting which children would relapse later on. One child in Table 4 deserves special mention since the ^{99m}Tc-MDP scan was positive with new lesions but with no other evidence of disease. He remains alive at 20 mo in clinical remission. Either his tumor has "turned" into a ganglioneuroblastoma or this may be a false-positive ^{99m}Tc-MDP scan.

Correlation of abnormal ^{99m}Tc-MDP and [^{123}I]MIBG uptake at individual sites in the skeleton (in 24 patients) revealed a significant number of discrepancies with an apparent greater sensitivity of the [^{123}I]MIBG (56%) compared to ^{99m}Tc-MDP (29%). Yet no child with an abnormal [^{123}I]MIBG scan had a normal ^{99m}Tc-MDP study. The majority of these lesions on [^{123}I]MIBG were in the axial skeleton, a pattern presumably reflecting bone marrow rather than bone metastasis, similar to that described by Gelfan and Harris (*16*). In contrast to other reports (*17*), the overall performance of [^{123}I]MIBG in initial staging and in the assessment of remis-

TABLE 4
Correlation Between MDP and MIBG Scanning in Patients with Stage 4 Disease at Follow-up

		MDP	
		POS	NEG
MIBG	POS	6	0
MIBG	NEG	5	7

TABLE 5
Number (%) of Sites Involved on ^{99m}Tc-MDP and/or [^{123}I]MIBG Scans in Both Groups of Children

	Group A	Group B	Total
MDP +ve/MIBG +ve	32 (19%)	2 (4%)	34 (15%)
MDP −ve/MIBG +ve	91 (54%)	36 (60%)	127 (56%)
MDP +ve/MIBG −ve	44 (26%)	22 (36%)	66 (29%)

n = 24 scans; seven patients were excluded due to excessive skeletal involvement.

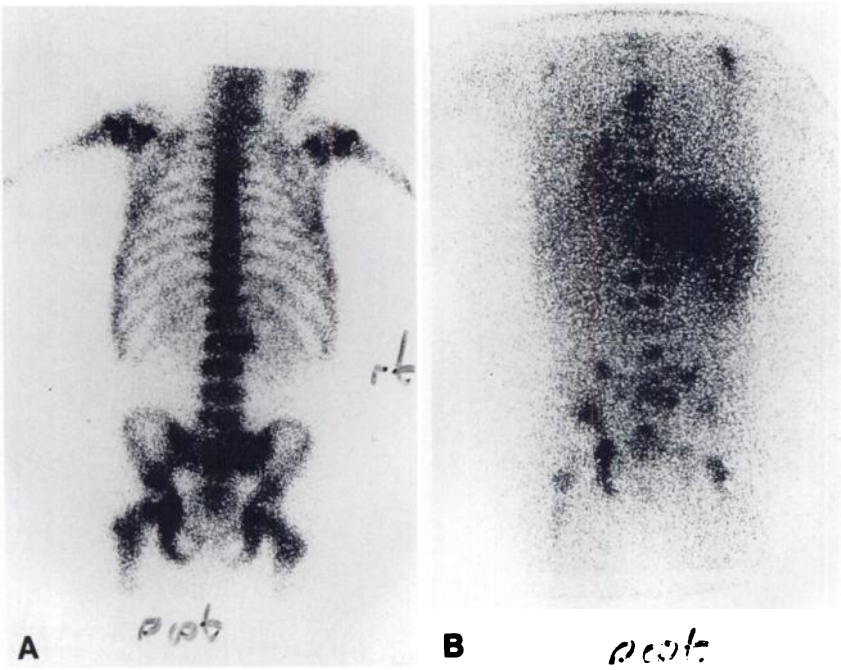

FIGURE 4
(A) Technetium-99m-MDP bone scan reveals abnormalities of L2, the right sacroiliac joint, the left acetabula roof, left ischium, left humeral metaphysis, and left hip/femoral neck. (B) Iodine-123-MIBG scan reveals abnormal uptake of isotope in multiple vertebrae, pelvis, upper left femur, and left shoulder. There is also uptake of the isotope by the tumor in the right adrenal area.

sion was disappointing, and this study raises serious doubts concerning proposals to replace ^{99m}Tc-MDP bone scans with [^{123}I]MIBG scans in patients with neuroblastoma (*6,7*). One possible reason for false-negative [^{123}I]MIBG scans is that, despite instructions to the contrary, these children took drugs that interfered with MIBG uptake. In Group B, a change in the metabolism of the malignant cells due to altered biology (*18*) or chemotherapy must be considered. Three centers have recorded negative [^{123}I]MIBG scans but positive [^{131}I]MIBG in the same children, which might provide an explanation for the false-negative scans (Hoefnagel CA, Ciofetta G, Piepsz A, *personal communications*, 1989). The false-positive rate for [^{123}I] MIBG at diagnosis is indeterminate as there was no patient with normal marrow and normal ^{99m}Tc-MDP scan with abnormal skeleton on [^{123}I]MIBG scan.

Other factors should be considered in deciding the role of [^{123}I]MIBG, i.e., the cost as well as poor availability to many centers and countries. Our findings suggest that the disease is accurately staged by ^{99m}Tc-MDP bone scanning, provided meticulous care is exercised in production and interpretation of the images.

The use of MIBG as a diagnostic agent cannot be precluded. There will always be a role for this agent in the patient in whom therapeutic [^{131}I]MIBG is being considered. However, close correlation with a recent bone scan is essential as there may be sites of skeletal metastasis which do not accumulate MIBG.

In summary, this study suggests that [^{123}I]MIBG scanning alone seriously underestimates the frequency and extent of bone secondaries. Technetium-99m-MDP bone scanning must, therefore, remain part of the routine assessment of patients with neuroblastoma.

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