Radioimmunodetection of Neuroblastoma with Iodine-131-3F8: Correlation with Biopsy, Iodine-131-Metaiodobenzylguanidine and Standard Diagnostic Modalities

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Iodine-131-3F8, a murine IgG_3 monoclonal antibody specific for ganglioside G_{D2} was evaluated by radioimmunoscintigraphy in 42 patients with neuroblastoma. Comparison was made with ^{131}I-metaiodobenzylguanidine (MIBG), ^{99m}Tc-methylene diphosphonate (MDP) bone scans, as well as computed axial tomography (CT) or magnetic resonance imaging (MRI). Iodine-131-3F8 detected more abnormal sites (283) than [^{131}I] MIBG (138) or ^{99m}Tc-MDP (69), especially in patients with extensive disease. In 20 patients with soft-tissue tumors demonstrated by CT/MRI, ^{131}I-3F8 detected the disease in 18. Upon surgical resection, two tumors interpreted as negative with ^{131}I-3F8 imaging revealed ganglioneuroma, one showing microscopic foci of neuroblastoma. In contrast, ^{131}I-3F8 imaging identified tumors that were confirmed histologically as neuroblastomas. In 26 patients with evidence of marrow disease by antibody scans, 14/26 had confirmation by iliac crest marrow aspirate/biopsy examinations. We conclude that ^{131}I-3F8 scintigraphy has clinical utility in the management of patients with neuroblastoma by improving the sensitivity of tumor detection.

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Neuroblastoma is the third most common solid tumor in childhood accounting for 7%–14% of the malignancy in this age group. It affects one in 10,000 children with a peak incidence at 2 yr of age. Most patients have extensive disease at diagnosis. Dose-intensive chemotherapy and radiotherapy have improved tumor response and patient survival (*1*). However, drug resistance invariably thwarts attempts to eradicate this disease. Curability of neuroblastoma depends on early and accurate detection. Radiographic methods currently available are inadequate in determining the full extent of metastatic disease. A more sensitive and specific imaging modality is [^{131}I] or [^{123}I]-metaiodobenzylguanidine (MIBG) (*2–4*). Iodine-131-MIBG has also been used in treating patients whose tumors were refractory to chemotherapy (*5–6*). Abnormalities demonstrated by [^{131}I]MIBG scintigraphy correlated well with clinical disease status, as well as assessments by means of other imaging modalities and tumor markers (*7–8*). As the number of patients studied by [^{131}I]MIBG increased, tumors were found that had escaped detection (*9–10*). Moreover, the percentage [^{131}I]MIBG injected dose per gram (%ID/g) in tumors was low (averaging 0.002%) (*11*). Tumor heterogeneity and inadequate tumor uptake could limit the clinical efficacy of [^{131}I]MIBG in neuroblastoma. Improved methods of tumor localization are needed. Radioimmunoscintigraphy offers this potential.

Several monoclonal antibodies against neuroblastoma have been tested for diagnosis and therapy (*12–14*) and early results appear promising. The antibody we have utilized is 3F8, a murine IgG_3 specific for disialoganglioside G_{D2} (*15*). Previous studies have shown that G_{D2} is present in high concentrations at about $5–10 \times 10^6$ molecules per cell in human neuroblastomas (*16*). 3F8 recognizes most neuroblastoma cell lines and reacts intensely with all fresh human neuroblastoma specimens by immunofluorescence; 3F8 does not react with most adult and fetal tissues (*15*). In nude mice xenografted with human neuroblastoma, ^{131}I or ^{125}I-labeled 3F8 localized in the tumors with high uptake (8%–50% ID/g) at 24 hr (*17*). Sufficient radiation dose could be delivered by i.v. ^{131}I-3F8 to eradicate xenografts completely (*18*). In preliminary patient studies (*19*), ^{131}I-3F8 localization ranged from 0.04% to 0.11% ID/g of tumor at 24 hr and was not affected by circulating serum G_{D2}. In addition, 3F8 could activate human complement to kill neuroblastoma cells and mediate tumor cytotoxicity in the presence of lymphocytes, neutrophils, and activated monocytes (*20–22*). 3F8 also has been used for purging tumor cells in bone marrow prior to cryopreservation and transplantation (*23*). When

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injected intravenously, it has induced prolonged remissions in some patients who failed conventional chemotherapy (*24*). The purpose of this study is to test whether ^{131}I-3F8 radioimmunoscintigraphy can provide superior sensitivity and specificity in the detection of metastatic neuroblastoma, when compared to [^{131}I]MIBG, technetium-labeled methylene diphosphonate bone scan (^{99m}Tc-MDP), computed axial tomography (CT), magnetic resonance imaging (MRI), tumor biopsies, as well as standard bone marrow examinations.

MATERIALS AND METHODS

Fifty-four radioimmunoscintigraphic studies using ^{131}I-3F8 were performed in 42 consecutive patients with either Stage III unresectable or Stage IV neuroblastoma. All of these patients had previous surgery and chemotherapy. They were referred to Memorial Sloan-Kettering Cancer Center for either bone marrow transplantation, continued chemotherapy, or other treatment modalities. Pathologic confirmation of the diagnosis was obtained in each patient. Clinical staging was carried out as part of this study. It included bilateral posterior iliac crest marrow biopsies and four aspirates (anterior and posterior left and right iliac crests), CT or MRI of previous or suspected sites of disease, bone scans, as well as 24-hr urine collections for catecholamines, vanillylmandelic acid (VMA), and serum LDH. Complete clinical remission (CR) is defined as no evidence of disease radiologically, biochemically, as well as by biopsy. In this group of CR patients, bone scans were normal except for four patients who had isolated areas of faint uptake that improved or normalized on follow-up bone scans. They also had repeatedly negative radiographic and marrow examinations. This study was approved by the Institutional Review Board and informed consents were signed by the patients or their parents. There were 21 males and 21 females with an age range from 1 to 24 yr [a majority of patients were between 2–8 yr (see Table 1)]. There were twelve patients older than 6, and two over 20 yr of age. Clinically, their disease status could be divided into four groups:

A. Progressive disease on chemotherapy with positive bone marrow examinations.
B. Progressive disease on chemotherapy with negative bone marrow examinations.
C. Active but stable disease on chemotherapy.
D. Complete clinical remission.

The monoclonal antibody 3F8 was manufactured under BB IND 2323 and radiolabeled under BB IND 2299 at Memorial Sloan-Kettering Cancer Center according to guidelines of the Office of Biologics Research and Review Center for Drugs and Biologics, Food and Drug Administration. For quality assurance, hybridoma 3F8 was found to be negative for adventitious agents by MAP, S^+L^-, and XC plaque assays, as well as negative for reverse transcriptase. MAP testing included screening for murine leukovirus, LCM virus isolation by intracerebral inoculation, murine saliva gland virus, mouse thymic virus, EDIM, and LDH virus isolations. Purified antibody 3F8 had to pass MAP and sterility testing (bacteria, mycoplasma, and fungal cultures), rabbit pyrogen testing, as well as safety testing in mice and guinea pigs. 3F8 was then conjugated to ^{131}I by the chloramine-T method (*19*). Specific activity of ^{131}I was 6–12 mCi/μg iodide. Radiolabeled antibody 3F8 must have >50% binding by in vitro antigen binding assay, >95% TCA precipitable and <3% free iodine by radio-thin layer chromatography. Periodic testing of radiolabeled antibodies was performed to ensure sterility as well as the absence of pyrogen.

Patients were given a saturated solution of potassium iodide (SSKI) orally for 7–10 days to block ^{131}I uptake by their thyroid glands. Following a negative skin test with intradermal injection of 1 μg of unlabeled 3F8, ^{131}I-labeled 3F8 (0.5 mg of protein with 2 mCi of ^{131}I) was given over a period of 20 min. Immediately upon the completion of the infusion, anterior and posterior total-body counts were measured using an uncollimated gamma camera with the window set for ^{131}I and positioned at a distance of 10 feet; this was similar to our routine dosimetric procedure for patients with thyroid cancer. Daily measurements were made. Serial blood samples were obtained 10 min, 24, 48, and 72 hr after injection to measure blood clearance. Anterior and posterior total-body images were obtained at 24, 48, and sometimes 120 hr on a Gemini 700 (General Electric, Milwaukee, WI) gamma camera with a high-energy collimator. Whenever necessary, lateral views as well as multiple spot views of special interest were also obtained. Total-body images were obtained at a scanning speed of 15–20 cpm for MDP and 6–8 cpm for antibody imaging, depending on the count rates at the sternum (bone scan) and liver (antibody and MIBG). Spot views were acquired at 10 min per view. Digital data were stored at 256 × 256 matrix size.

Iodine-131-MIBG was purchased from the Nuclear Pharmacy of the University of Michigan, Ann Arbor, MI. The thyroids of the patients imaged with [^{131}I]MIBG were protected by a saturated solution of potassium iodide administered orally (five drops daily) for 5 days. The [^{131}I]MIBG dose was 1 mCi/1.7 m^2. The first four patients, however, received a lower dose of 0.5 mCi/1.7 m^2 because of Internal Review Board protocol requirements. Total-body or multiple spot images of the entire body were obtained 24 and 48 hr after the administration of the tracer. Iodine-131-MIBG images were obtained within 1 wk prior to the antibody study in 19 patients and within 1 mo in 22 patients (mean 26 days, median 21 days).

Technetium-99m-MDP was used for bone scanning. The dose was 25 mCi/70 kg. Images were obtained on the Omega 500 (General Electric), Gemini 700 (General Electric), or Genesis (ADAC) 2–3 hr after injection. Spot views were obtained whenever necessary. Seventeen patients had bone scans performed less than 10 days prior to the antibody study (mean 4.6 days, median 5 days), and 25 patients had bone scans within 30 days (mean 10.4 days, median 8 days) of the study.

The number of abnormal sites of radionuclide uptake was estimated. Quantitative interpretation was sometimes difficult because of the contiguous nature of the lesions. The number of lesions should be considered as best estimates for comparison purposes.

RESULTS

Validation of ^{131}I-3F8 Scintigraphy by Histology

Surgical resection of the soft-tissue tumor(s) was carried out in nine patients after imaging with ^{131}I-3F8. Seven were antibody scan-positive and all were confirmed by the Department of Pathology as neuroblastomas. Two were ^{131}I-3F8 negative and were diagnosed as ganglioneuromas;

one of these tumors had microscopic foci of neuroblastoma. Iodine-131-3F8 imaging revealed hot spots suggestive of marrow involvement (corresponding sites were negative on bone scan or x-rays) in 26 patients. Iliac crest bone marrow aspirates and biopsies confirmed marrow disease in 14. Many of the abnormal marrow sites detected by 3F8 imaging were scattered and did not involve the iliac crest. Thus, random iliac crest marrow samplings might have missed these tumors.

Correlation between ^{131}I-3F8 Imaging and Other Imaging Modalities

The clinical status and imaging findings in the 42 patients were summarized in Table 1. Nineteen patients (Groups A and B) had progressive disease. Thirteen of them had bone marrow aspirates and/or biopsies showing involvement by neuroblastoma (Patients 1–13). Iodine-131-3F8 detected 177 sites of abnormal radionuclide uptake, [^{131}I]MIBG 92, and ^{99m}Tc-MDP 44. One patient (No. 13) with microscopic recurrence of marrow disease (a few scattered clumps in a high power field of the marrow smear) was antibody imaging-negative. Six patients had progressive disease on chemotherapy but without histologic evidence of marrow involvement (Patients 14–19). Five of these patients were imaged with all three modalities. The number of abnormal sites when compared totaled 54 (^{131}I-3F8), 20 ([^{131}I]MIBG) and 10 (^{99m}Tc-MDP), respectively. Seven patients had active but stable disease (Patients 20–26, Group C); one patient had positive bone marrow biopsy. Thirty-six abnormal sites were detected by ^{131}I-3F8, 22 by [^{131}I]MIBG, and 8 by ^{99m}Tc-MDP. Patient 26 had an isolated retroperitoneal ganglioneuroma with scattered foci of neuroblastoma. In 16 patients (Nos. 27–42, Group D) who were in clinical remission, five had abnormal radionuclide uptake by ^{131}I-3F8 scintigraphy, although fewer abnormal sites per patient were found, when compared to patients in Groups A–C. Even fewer hot spots were noted in [^{131}I]MIBG studies. Four patients in Group D had slightly abnormal bone scans. The iliac crest uptake of ^{99m}Tc-MDP in Patients 30 and 34 were attributable to postoperative changes related to bone marrow biopsies and harvests. Patient 33 had minimal increase in the left acetabulum without interval changes over a period of 1 yr and repeatedly had negative x-rays studies. Patient 32 had three faint areas of uptake in the thoracic spine and negative radiographic studies. After therapy, these patients (Nos. 30, 32, 33, 34) showed continuous improvement until all bone scans became normal after 2 yr.

Comparison of these imaging modalities among patients grouped by disease status is summarized in Table 2. Most of the abnormalities were seen in the bone or bone marrow. Although ^{131}I-3F8 detected more sites than [^{131}I]MIBG in individual subjects, the proportion of patients who were scan-positive (or -negative) showed excellent overall agreement (Table 3). Abnormalities of ^{131}I-3F8 images were seen in four patients who had negative MIBG studies. Two patients had obvious disease at the time of the study and both died within 6 mo. The other two patients developed recurrent marrow disease at 8 and 16 mo follow-up, respectively.

TABLE 1
Summary of Clinical Status and Comparison of Imaging Results

Pt. no.	Age	Sex	Number of abnormal radionuclide uptake sites			Bone marrow exam
			3F8	MIBG	MDP	
Group A: Progressive disease on chemotherapy with positive marrow						
1	9	M	30	10	2	+
2	24	F	28	7	12	+
3	4	M	20	8	6	+
4	15	F	19	10	5	+
5	6	F	15	21	0	+
6	14	M	15	10	2	+
7	5	M	13	10	10	+
8	4	M	11	12	4	+
9	4	M	11	3	2	+
10	2	F	6	1	0	+
11	2	M	5	0	1	+
12	4	M	4	0	0	+
13	7	M	0	0	0	+
Group B: Progressive disease on chemotherapy with negative marrow						
14	4	F	30	12	4	–
15	4	F	9	not done	4	–
16	5	M	8	3	3	–
17	3	F	7	2	0	–
18	7	F	5	2	3	–
19	7	M	4	1	0	–
Group C: Active but stable disease on chemotherapy						
20	4	F	11	8	3	+
21	5	M	8	6	0	–
22	24	F	6	1	2	–
23	5	F	4	2	1	–
24	5	F	4	2	0	–
25	3	F	3	3	2	–
26	8	M	0	0	0	–
Group D: Complete clinical remission						
27	2	M	6	1	0	–
28	2	F	7	2	0	–
29	6	M	1	1	0	–
30	4	M	1	0	1	–
31	5	F	1	0	0	–
32	15	M	0	0	3	–
33	3	M	0	0	2	–
34	3	M	0	0	1	–
35	5	M	0	0	0	–
36	3	F	0	0	0	–
37	6	M	0	0	0	–
38	2	F	0	0	0	–
39	6	F	0	0	0	–
40	3	F	0	0	0	–
41	3	F	0	0	0	–
42	2	M	0	0	0	–

TABLE 2
Comparison of Imaging Modalities

Clinical Status	Average number of lesions detected per patient		
	^{131}I-3F8	[^{131}I]MIBG	^{99m}Tc-MDP
A. Progressive disease with positive BM (1–13)†	13.6 ± 9.0* 177‡	7.1 ± 6.2 92	3.4 ± 3.9 44
B. Progressive disease with negative BM (14, 16–19)	10.8 ± 10.8 54	4.0 ± 4.5 20	2.0 ± 1.9 10
C. Active but stable disease (20–26)	5.1 ± 3.6 36	3.1 ± 2.9 22	1.1 ± 1.2 8
D. Complete remission (27–42)	1.0 ± 2.2 16	0.25 ± 0.58 4	0.44 ± 0.89§ 7

* Mean ± s.d.; BM = bone marrow test.

† Numbers in parentheses correspond to the patient numbers in Table 1.

‡ Total number of abnormal sites of uptake.

§ Abnormal ^{99m}Tc-MDP uptake disappeared in two patients without treatment. One patient had increased ^{99m}Tc-MDP uptake after iliac crest biopsy and another one at the surgical site after marrow harvesting.

Correlation between ^{131}I-3F8 and CT/MRI

Because of the extensive abnormalities noted in ^{131}I-3F8 and [^{131}I]MIBG scintigraphies, it was not feasible to obtain independent confirmation of all lesions. However, it was possible to correlate imaging information at soft-tissue sites in chest, abdomen and pelvis with conventional CT or MRI. As shown in Table 4, the likelihood of agreement was 93% ± 8%. Two patients had negative ^{131}I-3F8 scans despite the presence of tumor. When analyzed histologically, one showed ganglioneuroma and the other scattered foci of neuroblastoma.

Abnormal radionuclide uptake in the ^{131}I-3F8 images was clearly evident at 24–48 hr following injection of the labeled antibody. Since the target-to-non-target ratio was sufficiently high, no additional background subtraction was necessary to provide clear delineation of lesions. Rarely were liver and spleen imaged and the occurrence was only during the immediate postinjection period when blood radioactivity was high. Iodine-131-3F8 scans showed widespread bone and bone marrow involvement in Patient 3 (Fig. 1), illustrating the superiority of antibody over other imaging modalities. Figure 2 illustrates widespread bone or bone marrow disease, as well as right supraclavicular, infraclavicular, and axillary lymph node involvements in Patient 1. Intense uptake of ^{131}I-3F8 and [^{131}I]MIBG in the liver of Patient 7 corresponded to the region of the tumor defined by the abdominal CT (Fig. 3). Involvement of the lower portion of the liver and multiple areas of spine and right femur was found in Patient 10 (Fig. 4). The [^{131}I]MIBG localization in the liver tumor was poor. A large retrothoracic and retroperitoneal tumor was demonstrated in Patient 23 (Fig. 5).

TABLE 3
Correlation Between ^{131}I-3F8 and [^{131}I]MIBG* Imaging in 41 Patients

		[^{131}I]MIBG	
		+	−
^{131}I-3F8	+	24	4
	−	0	13

Likelihood of agreement = 90% ± 9% (95% confidence limits).

* Iodine-131-MIBG images were obtained within 1 wk prior to the antibody study in 19 patients and within 1 mo in 22 patients (mean 26 days, median 21 days).

TABLE 4
Evaluation of Chest/Abdomen/Pelvic Soft-Tissue Masses: Correlation Between ^{131}I-3F8 Imaging and CT/MRI in 42 Patients

		CT/MRI	
		+	−
^{131}I-3F8	+	18	1*
	−	2†	21

Likelihood of agreement = 93% ± 8% (95% confidence limits).

* This patient had a "hot spot" on [^{131}I]MIBG in the presacral soft tissue on repeated studies. Both ^{131}I-3F8, bone scan, and laparatomy failed to reveal any evidence of tumor.

† False-negative: first patient had abdominal ganglioneuroma and scattered foci of neuroblastoma. Second patient had ganglioneuroma.

The body retention, plasma radioactivity, and plasma half-lives of ^{131}I-3F8 in patients with either extensive disease (8 patients from Group A) or patients with minimal abnormalities (16 patients from Group D) were compared in Figure 6. Patients with more widespread abnormalities by antibody imaging had both faster body and blood clearance. No adverse side effects were observed.

Iodine-131-3F8 imaging was repeated in 12 patients, ranging from 2 wk to 1 yr after their first ^{131}I-3F8 exposure. None of them had neutralizing human antimouse antibodies (HAMA) or anaphylactoid antibodies. One patient developed a transitory episode of hypotension and transient loss of consciousness that responded to hydration without neurologic sequelae. Nine patients showed interim disease progression with excellent correlation of ^{131}I-3F8 imaging with known sites of disease. One patient had rapid clearance of ^{131}I-3F8 and no images could be obtained. Two patients continued to be free of metastatic disease by ^{131}I-3F8 scintigraphy and remained alive without evidence of tumor relapse.

DISCUSSION

Our study demonstrated that ^{131}I-3F8 could detect primary and metastatic neuroblastomas with excellent sensitivity and specificity. Histologic examination of ^{131}I-3F8-positive sites confirmed the presence of neuroblastoma. Iodine-131-3F8 was found to detect more abnormal primary and metastatic sites than either [^{131}I]MIBG or ^{99m}Tc-MDP bone scans. The correlation between ^{131}I-3F8 and

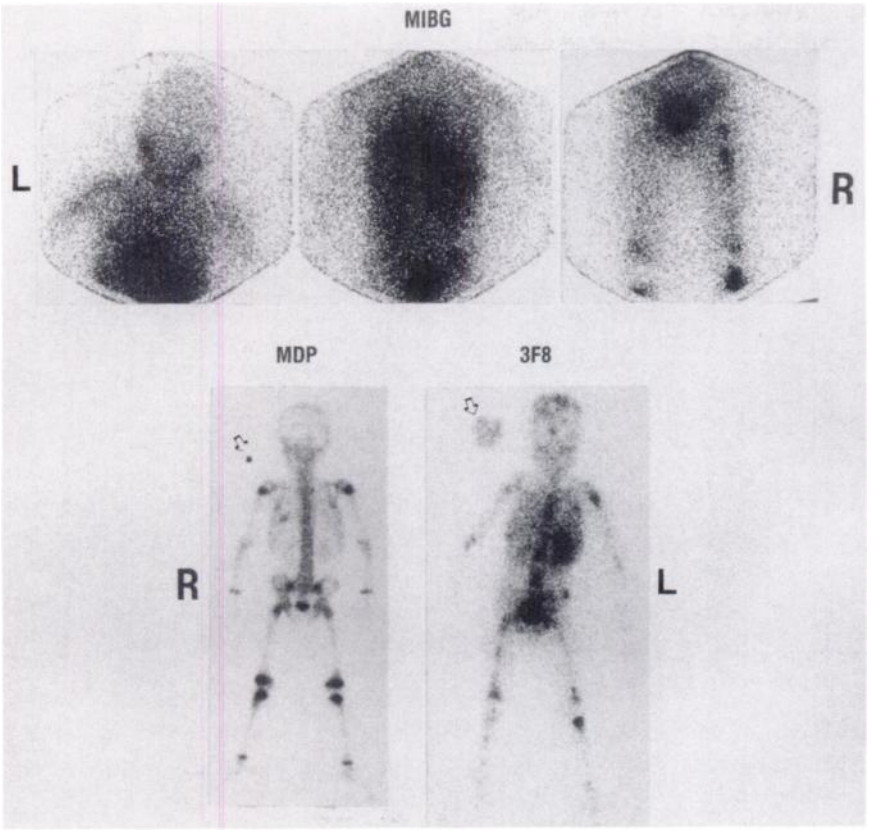

FIGURE 1. Posterior views of Patient 3: ^{131}I-3F8 imaging showed widespread abnormal uptake in the calvarium, spine, ribs, pelvis and all four extremities. Free iodine was trapped by the stomach and was also excreted in the urine (filling the bladder). MIBG localized in the same general areas. Parotid, cardiac, and hepatic uptake of [^{131}I]MIBG were seen. However, owing to the adjacent normal liver activity, spine abnormalities were not well delineated. The ^{99m}Tc-MDP bone scan showed increased uptake in the right hip, left shoulder, and right posterior 8th rib. Radioactive markers in the images (marked by arrows) were placed on the right side (R) of the patient. L = left side of the patient.

CT/MRI for soft-tissue abnormalities was excellent. Iodine-131-3F8 may provide a more sensitive diagnostic test for the detection of metastatic marrow disease than random marrow aspirates or biopsies.

Two other monoclonal antibodies against neuroblastoma have been used to define tumor deposits. Iodine-131-UJ13A was found to localize in 15 sites of primary and metastatic lesions from 9 patients with neuroblastoma.

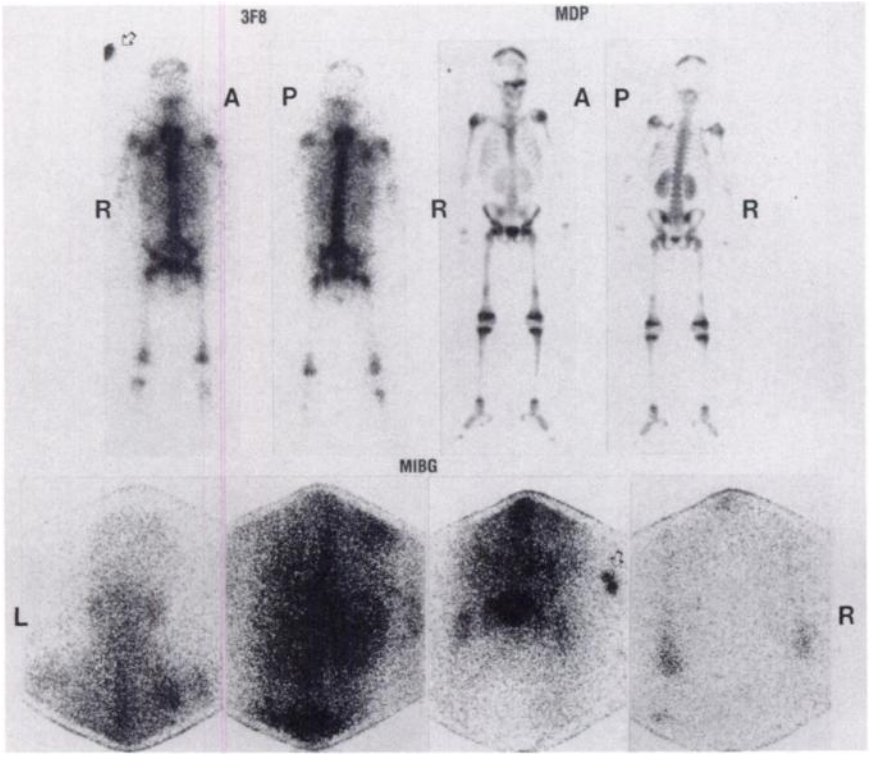

FIGURE 2. Patient 1: ^{131}I-3F8 uptake was evident in the calvarium, right axillary, both shoulders, spine, pelvis, and extremities. MIBG scan (posterior views) showed increased uptake in the right humerus, right clavicle, right axilla, spine and extremities, with less tumor versus normal tissue contrast. The ^{99m}Tc-MDP bone scan showed increased uptake in the shafts of both femurs. A = anterior view, P = posterior view, R = right side of patient, and L = left side of patient.

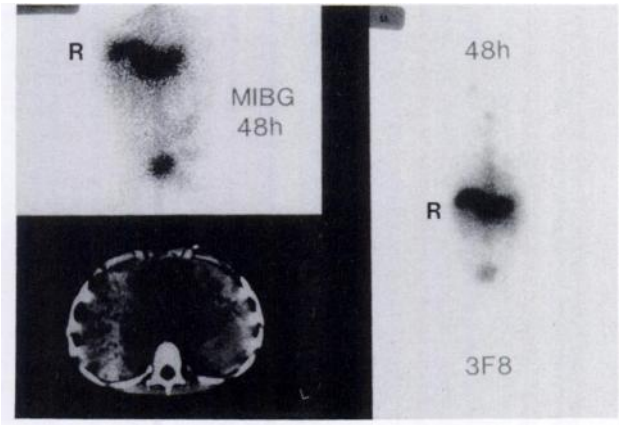

FIGURE 3. Posterior views of ^{131}I-3F8 and [^{131}I]MIBG scans of Patient 7 showed intense uptake in the superior posterior area of the liver. A large tumor mass was evident in the CT scan. Spine uptake in the vertebral column was seen in the ^{131}I-3F8 images but was less intense in the [^{131}I]MIBG scan.

One false-positive and two false-negative localizations were reported (*13*). This IgG_1 antibody was also used for targeting ^{131}I therapy in four patients who failed other conventional treatments (*25*). Liver uptake was seen in every patient, and bone marrow toxicity was noted when the therapy dose exceeded 2.8 mCi/kg. Objective responses were obtained in one of the four patients. The use of another IgG_1 monoclonal antibody BW 575/9 was recently reported. Good localization was seen in two out of three patients (*14*). Comparison of ^{99m}Tc-BW 575/9 and [^{123}I] MIBG was made in seven children with Stage IV neuroblastoma. The majority of tumor sites was detected by both modalities. However, 5 of 26 lesions were undetectable by [^{123}I]MIBG and 8 were not detected by immunoscintigraphy (*27*). It was concluded that there was a good correlation between these two modalities, and that their combined use could improve the detectability of metastatic disease (*26,27*).

Similar to our previous report of ^{131}I-3F8 imaging (*19*), this study was carried out in a group of patients who had been previously treated with chemotherapy, radiotherapy, and/or surgery. A great deal more bone marrow (or bone) disease was seen in this population than expected on clinical grounds. Since the bone marrow abnormalities were numerous, confirmation of the presence of tumor in all areas of increased uptake was not practical. Unless marrow disease was diffuse, negative iliac crest marrow examinations could be due to sampling error. Conversely, if marrow disease was scant, positive ^{131}I-3F8 images would be unlikely. Detection of minimal disease in bone marrow

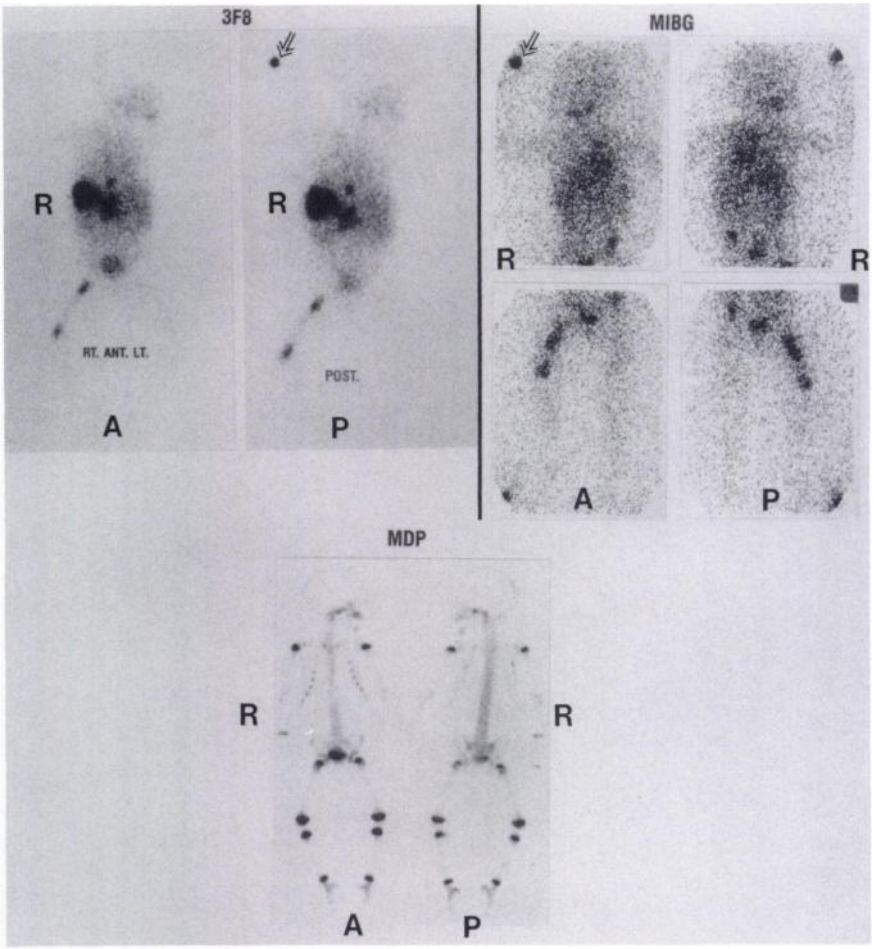

FIGURE 4. Patient 10: ^{131}I-3F8 imaging showed increased uptake in the lower portion of the right lobe of the liver, multiple areas in the mid- and lower thoracic spine, and right proximal and distal femurs. The large hepatic lesion was also found in CT, MRI, and ^{99m}Tc-sulfur colloid liver scan (data not shown). The [^{131}I]MIBG showed increased uptake in the right femur, left iliac bone, and right renal fossa but not the large tumor behind the liver. The MDP bone scan appeared normal. Anterior view (A) is on the left and posterior view (P) is on the right.

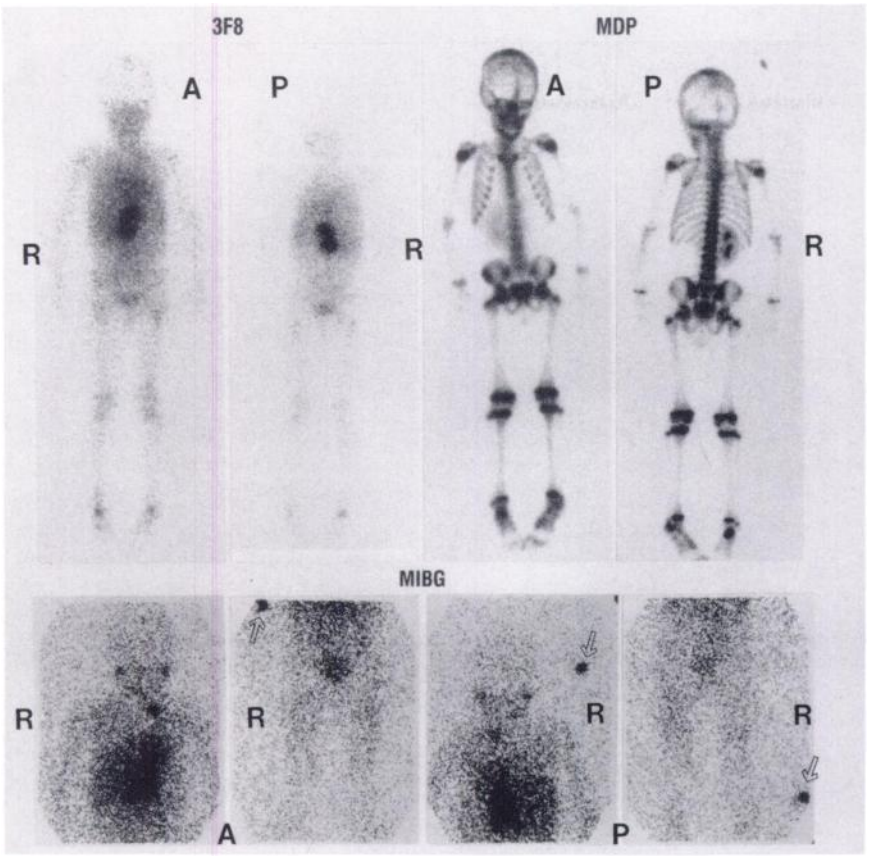

FIGURE 5. Patient 23: ^{131}I-3F8 imaging showed a tumor mass in the posterior thorax extending into the retroperitoneum. Irregular uptake in the spine and femurs was also noted. MIBG imaging showed left superior mediastinal, retrothoracic and retroperitoneal abnormalities. The ^{99m}Tc-MDP bone scan appeared normal in these areas. A = anterior view and P = posterior view.

that was histologically disease-free (by Wright-Giemsa and Hematoxylin-Eosin stains) has been previously reported using G_{D2} antibodies (i.e., 3F8) (*28*), as well as UJ13A (*29*) and BW 575/9 (*30*). Immunostaining of marrow specimens in patients with positive ^{131}I-3F8 scans have confirmed marrow disease in selected cases (unpublished data).

In order to compare the sensitivity of radiolabeled 3F8 and MIBG in the detection of metastatic neuroblastoma, we chose ^{131}I conjugates because they were the common conditions of usage. Although the likelihood of agreement between ^{131}I-3F8 and [^{131}I]MIBG was 90% when the unit of measurement was the individual patient (Table 3), a detailed comparison of individual lesions detected by either modality suggested that ^{131}I-3F8 detected significantly more abnormalities than [^{131}I]MIBG, especially for metastatic sites in marrow (or bone) (Table 2). More lesions were evident because there was either more tumor heterogeneity with respect to the uptake of [^{131}I]MIBG, or that the tumor-to-non-tumor ratio was superior for ^{131}I-3F8. For soft-tissue abnormalities, chest and abdominal CT or MRI showed strong correlation with antibody imaging (Table 4) and histologic confirmation of hot spots was obtained in seven patients. As we have previously reported (*19*), 3F8 did not localize to ganglioneuroma. In addition, microscopic neuroblastoma foci also escaped detection (*19*). The nature of increased uptake in a few patients who had apparent clinical remissions may become clear with longer follow-up. Nine patients who had negative or focally positive initial antibody studies, showed multiple sites of abnormalities (either new or with increased intensity) during the subsequent imaging studies when their clinical status deteriorated.

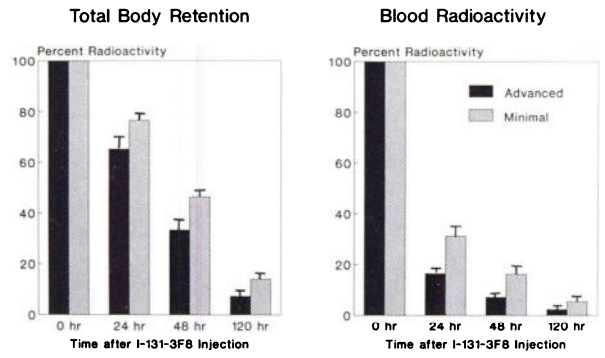

FIGURE 6. Clearance of ^{131}I-3F8. Both total-body retention (left) and plasma radioactivity (right) were expressed as percentages of the initial counts at time 0 hour after antibody injection.

In the past few years, a large number of patients with neuroblastoma have been imaged with ^{131}I- or [^{123}I]MIBG. Although excellent sensitivity and specificity of MIBG in detecting neuroblastoma were reported in the early studies (*2–4*), subsequent experience has demonstrated some failures in patients with active disease (*9*). Recently, it was reported that [^{123}I]MIBG underestimated the skeletal in-

volvement in neuroblastoma. Four patients who had negative [^{123}I]MIBG studies later died of disseminated disease (31). It is likely that MIBG may not be able to detect all tumor sites in neuroblastoma, even when [^{123}I]MIBG or a larger dose of [^{131}I]MIBG is used. Iodine-131-MIBG appears to be effective in the treatment of malignant pheochromocytoma (*32*). The results of [^{131}I]MIBG therapy in advanced neuroblastoma has been less encouraging (*5–6*). Since ^{131}I-3F8 has a higher tumor uptake (0.08% ID/g) than [^{131}I]MIBG (0.002%) (*11*) and appears to have less heterogeneity sites, this antibody is currently used as our standard for staging patients with advanced neuroblastoma. In addition, ^{131}I-3F8 with its relative low background activity in normal tissues has been utilized in targeted radioimmunotherapy of neuroblastoma (*33*).

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REFERENCES

1. Kushner BH, Cheung NKV. Treatment of neuroblastoma. In: DeVita V, Rosenberg S, Hellman S, eds. *Cancer principles and practice of oncology: updates, volume 2.* Philadelphia: Lippincott, 1988:1–11.
2. Munkner T. I-131-meta-iodobenzylguanidine scintigraphy of neuroblastomas. *Semin Nucl Med* 1985;15:154–160.
3. Hadley GP, Rabe E. Scanning with iodine-131-MIBG in children with solid tumors. An initial appraisal. *J Nucl Med* 1986;27:620–626.
4. Feine U. Metaiodobenzylguanidine in the diagnosis of neuroblastomas. In: Winkler C, ed. *Nuclear medicine in clinical oncology.* Berlin, Heidelberg: Springer-Verlag, 1986:122–128.
5. Voute PA, Hoefnagel CA, de Kraker J. I-131-meta-iodobenzylguanidine in diagnosis and treatment of neuroblastoma. *Bull Cancer* 1988;75:107–111.
6. Beierwaltes WH. Application of I-131-meta-iodobenzylguanidine. *Nucl Med Biol* 1987;14:183–189.
7. Geatti O, Shapiro B, Sisson J, et al. Iodine-131-metaiodobenzylguanidine scintigraphy for the localization of neuroblastoma: preliminary experience in ten cases. *J Nucl Med* 1985;26:736–742.
8. Yeh SDJ, Helson L, Benua RS. Correlation between iodine-131-MIBG imaging and biological markers in advanced neuroblastoma. *Clin Nucl Med* 1988;13:46–52.
9. Bouvier JF, Philip T, Chauvot P, et al. Pitfalls and solutions in neuroblastoma diagnosis using radioiodine MIBG. Our experience about 50 cases. In: Evans AE, D'Angrio GJ, Knudson AG, Seeger RC, eds. *Advances in neuroblastoma research.* New York: Alan R. Liss; 1988:707–720.
10. Schmiegelow K, Simes MA, Agertoft L, et al. Radio-iodobenzylguanidine scintigraphy of neuroblastoma: conflicting results, when compared with standard investigation. *Med Ped Oncol* 1989;17:126–130.
11. Moyes JS, Babich JW, Carter R, et al. Quantitative study of radioiodinated metaiodobenzylguanidine uptake in children with neuroblastoma: correlation with tumor histopathology. *J Nucl Med* 1989;30:474–480.
12. Cheung NKV, Saarinen U, Neely J, et al. Development of neuroblastoma antibodies for potential utilization in diagnosis and therapy. In: Evans AE, D'Angrio GJ, Seeger RC, eds. *Advances in neuroblastoma research.* New York: Alan R. Liss; 1985:501–505.
13. Goldman A, Vivian G, Gordon I, et al. Immunolocalization of neuroblastoma using radiolabeled monoclonal antibody UJ 13A. *J Ped* 1984;105:252–256.
14. Baum RP, Maul FD, Schwarz A, et al. Diagnosis and treatment of stage IV neuroblastoma with Tc-99m- and I-131-labeled monoclonal antibody BW 575/9. *J Nucl Med* 1989;30:904.
15. Cheung NKV, Saarinen UM, Neely JE, et al. Monoclonal antibodies to a glycolipid antigen on human neuroblastoma cells. *Cancer Res* 1985; 45:2642–2649.
16. Wu ZL, Schwartz E, Seeger R, et al. Expression of G_{D2} ganglioside by untreated primary human neuroblastomas. *Cancer Res* 1986;46:440–443.
17. Cheung NKV, Neely JE, Landmeier B, et al. Targeting of ganglioside G_{D2} monoclonal antibody to neuroblastoma. *J Nucl Med* 1987;28:1577–1583.
18. Cheung NKV, Landmeier B, Neely J, et al. Complete tumor ablation with iodine-131-radiolabeled disialoganglioside G_{D2} specific monoclonal antibody against human neuroblastoma xenografted in nude mice. *J Natl Cancer Inst* 1986;77:739–745.
19. Miraldi FD, Nelson AD, Kraly C, et al. Diagnostic imaging of human neuroblastoma with radiolabeled antibody. *Radiology* 1986;161:413–418.
20. Munn DH, Garnick M, Cheung NKV. Effects of parenteral recombinant human macrophage colony-stimulating factor on monocyte number, phenotype, and antitumor cytotoxicity in nonhuman primates. *Blood* 1990;75:2042–2048.
21. Kushner BH, Cheung NKV. GM-CSF enhances 3F8 monoclonal antibody-dependent cellular cytotoxicity against human melanoma and neuroblastoma. *Blood* 1989;73:1936–1941.
22. Munn DH, Cheung NKV. Phagocytosis of tumor cells by human monocytes cultured in recombinant macrophage colony stimulating factor. *J Exp Med* 1990;172:231–237.
23. Kushner BH, Gulati SC, Cheung NKV. Effective purging of neuroblastoma from bone marrow (BM) using IgG3 monoclonal antibody (MoAb) that mediate human complement-dependent as well as cell-mediated cytotoxicities [Abstract]. *Blood* 1988;72(suppl 1):394a.
24. Cheung NKV, Burch L, Kushner BH, et al. Monoclonal antibody 3F8 can effect durable remissions in neuroblastoma (NB) patients (pts) refractory to chemotherapy: a Phase II trial. *Proc Am Assoc Can Res* 1990;31:288.
25. Kemshead JT, Goldman A, Jones D, et al. Therapeutic application of radiolabelled monoclonal antibody UJ13A in children with disseminated neuroblastoma—a Phase I study. In: Evans AE, D'Angrio GJ, Seeger RC, eds. *Advances in neuroblastoma research.* New York: Alan R. Liss; 1985:533–544.
26. Berthold F, Waters W, Sieverts H, et al. Immunoscintigraphic imaging of MIBG-negative metastases in neuroblastoma. *Am J Ped Hemat Oncol* 1990;12:61–62.
27. Smolarz K, Waters W, Sieverts H, et al. Immunoscintigraphy with Tc-99m-labeled monoclonal antibody BW575 compared with I-123-MIBG scintigraphy in neuroblastoma [Abstract]. *Radiology* 1989;173:152a.
28. Cheung NKV, Von Hoff DD, Strandjord S, et al. Detection of neuroblastoma cells in bone marrow using G_{D2} specific monoclonal antibodies. *J Clin Oncol* 1986;4:363–369.
29. Allan PM, Garson JA, Harper E, et al. Biological characterization and clinical applications of a monoclonal antibody recognizing an antigen restricted to neuroectodermal tissues. *Int J Cancer* 1983;31:591–598.
30. Berthold F, Schneider A, Schumacher R, et al. Detection of minimal disease in bone marrow of neuroblastoma patients by immunofluorescence. *Pediatr Hematol Oncol* 1989;6:73–83.
31. Gordon I, Peters AM, Gutman A, et al. Skeletal assessment in neuroblastoma—the pitfalls of iodine-123-MIBG scans. *J Nucl Med* 1990; 31:129–134.
32. Sisson JC, Shapiro B, Beierwaltes WH, et al. Radiopharmaceutical treatment of malignant pheochromocytoma. *J Nucl Med* 1984;25:197–206.
33. Cheung NKV, Yeh SDJ, Gulati S, et al. I-131-3F8 targeted radiotherapy of neuroblastoma (NB): a phase I clinical trial. *Proc Am Assoc Can Res* 1990;31:284.