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The diagnostic and therapeutic utility of radioiodinated metaiodobenzylguanidine (MIBG)

5 years of experience*

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Abstract. The authors' experience of more than 5 years in the diagnostic and therapeutic use of radioiodinated MIBG in neural crest tumors is reported. $^{123}I/^{131}I$-MIBG scintigraphy was performed in 158 patients: 75 suspected (24 proven) pheochromocytomas (pheos), 43 neuroblastomas (NB), 20 medullary thyroid carcinomas (MTC), 6 ganglioneuromas, 5 carcinoids and 1 insulinoma. Eight cases of tumors not originating from the neural crest were also investigated. The diagnostic sensitivity of the method was above 90% both in pheos and NB (primary tumors and bone metastases). The examination was less effective in localizing MTC (sensitivity = 64.4% in primary or residual/recurrent tumors). The scintigraphic outcome was negative in ganglioneuromas, carcinoids and insulinoma. Specificity was very high (> 95%), and no false positive results were found in tumors not deriving from the neural crest.

^{131}I-MIBG treatment was administered to four patients with malignant pheo, nine with NB and four with MTC. Therapy resulted in a complete response in one pheo, two NB and one MTC treated after surgery or at diagnosis (one NB); it gave partial response and prolonged remission in five advanced cases (one pheo, two NB and two MTC); it resulted in temporary stabilization of the disease in one pheo and two NBs; it was ineffective in four cases.

Key words: Radioiodinated metaiodobenzylguanidine – Neural crest tumors – Diagnosis – Therapy

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Introduction

Radioiodinated meta-iodobenzylguanidine (MIBG labelled with ^{131}I or ^{123}I), originally proposed for the localization and treatment of pheochromocytomas (pheos) (Sisson et al. 1981, 1984; Sutton et al. 1982; Ackery et al. 1984; Horne et al. 1984; McEwan et al. 1985; Shapiro et al. 1985), has recently been extended to a wide spectrum of tumors originating from the neural crest (Endo et al. 1984; Fischer et al. 1984a; Kimmig et al. 1984; Smit et al. 1984; Hoefnagel et al. 1987; Von Moll et al. 1987). Favourable results have been obtained in neuroblastomas (NB) (Geatti et al. 1985; Hoefnagel et al. 1985; Munkner 1985), whereas somewhat less consistent results have been reported in medullary thyroid carcinomas (MTC) (Gétin et al. 1985; Hilditch et al. 1986; Poston et al. 1986), carcinoid tumors (CA) (Feldman et al. 1986) and oat cell lung carcinomas (Nakajo et al. 1986; Hoefnagel et al. 1987).

The therapeutic potential of the radiopharmaceutical has been repeatedly emphasized. Encouraging results have been obtained in this field in limited numbers of highly selected patients with pheos, NB and CA (Fischer et al. 1984b; Sisson et al. 1984; Adolph et al. 1986; Feine et al. 1986; Hoefnagel et al. 1986, 1987).

In order to gain further knowledge regarding the use of the radiopharmaceutical we studied its utility in the diagnosis and therapy of neuroendocrine tumors, and report in this publication our overall experience gained over a period of more than 5 years.

Materials and methods

Diagnostic studies. From the beginning of 1983 up to the 1st semester of 1988, 158 cases were investigated, mostly using ^{131}I-MIBG; in 6 cases the compound labelled with ^{123}I was used. In all 275 studies were performed. The series included 75 cases of suspected

pheos (96 studies: 21 repeated either because of an uncertain diagnosis or as follow up of malignant pheos). In 24 of the cases the presence of a tumor was proven; 43 NB (119 studies in different clinical phases); 20 MTC (39 studies); 5 CA (6 studies); 1 insulinoma (1 study), 6 ganglioneuromas (6 studies), and 8 tumors not originating from the neural crest (1 anaplastic thyroid carcinoma, 1 Ewing's sarcoma, 1 nephroblastoma, 1 rhinopharingeal epithelioma, 2 retroperitoneal sarcomas, 1 cervical sarcoma and 1 lung adenocarcinoma).

Patients were investigated on the basis of clinical and laboratory data (urinary catecholamines, vanillyl mandelic acid, homovanilic acid, serotonin, 5-hydroxy-indolacetic acid, calcitonin, CEA, TPA, etc.). Calcitonin (Ct) and tissue polypeptide antigen (TPA) were determined by radioimmunoassay and carcinoembryonic antigen (CEA) by an immunoradiometric assay. All patients underwent a variety of conventional diagnostic examinations including computed tomography (CT) and/or ultrasound or angiography. Many of them also had surgical and histological confirmation. In selected cases immunohistochemical stains (to identify products of the tumor), and electron microscopy (to demonstrate the presence of neurosecretory granules) were used.

The $^{123}I/^{131}I$-MIBG examination was performed according to previously described procedures (Troncone et al. 1984, 1986). Essentially it consists of: 1) thyroid blockade with Lugol's solution (30–60 mg/day of free iodine) starting 3 days before tracer administration and continuing for 7 days; 2) IV injection of 18.5–37 MBq (0.5–1 mCi) ^{131}I-MIBG; 3) whole body scans performed over 2–3 consecutive days. When ^{123}I-MIBG was used, 74–148 MBq (2–4 mCi) were administered intravenously and scintigraphy was carried out at 4, 24 and occasionally 46 h after tracer injection.

Scintigraphy was performed using a LFOV gamma camera equipped with a high-energy collimator and interfaced to a minicomputer (Philips P/855M).

Renal and/or hepatic and/or bone and/or thyroid scintigraphy, following an i.v. injection of ^{99m}Tc-DMSA, ^{99m}Tc-phytate, ^{99m}Tc-MDP and ^{131}I or ^{99m}Tc-pertechnetate respectively, were performed where required and these images were superimposed on those with MIBG.

Metabolic radiotherapy. In four cases of malignant pheo, nine NB and four MTC, ^{131}I-MIBG was found to concentrate sufficiently in the neoplastic lesions so that treatment with the radiopharmaceutical was undertaken. High specific activity ^{131}I-MIBG (> 1.11 GBq/mg, i.e. >30 mCi/mg) was used. In pheos and MTC the therapeutic procedure substantially followed that proposed for the treatment of pheos by the group of the Michigan University Medical Center (Sisson et al. 1984). For NB therapy a previously described therapeutic protocol was followed (Troncone et al. 1987). In synthesis after a thyroid blockade with Lugol's iodine solution, single doses varying from 2.6–9.2 GBq (70–250 mCi) ^{131}I-MIBG were administered by slow i.v. infusion (2–8 h). In NB patients doses were split into 2 parts and administered with a 2–7 day interval. The treatment was repeated at 1–4 month intervals. Patients were kept in an isolated room for 4–5 days and were subjected to continuous ECG and blood pressure monitoring during the infusion.

Dosimetric estimates were performed on the basis of the methodology of Sisson et al. (1984) and Shulkin et al. (1988). This took into account the volume of the tumor (determined by means of a 3 dimensional CT scan and ultrasound evaluation), the initial tumor uptake (% of the administered dose at 24 h), and retention ($T_{1/2}$ effective) (determined by means of conjugate views, and daily quantification of radioactivity in the tumor). Calculations were performed according to the MIRD formalism.

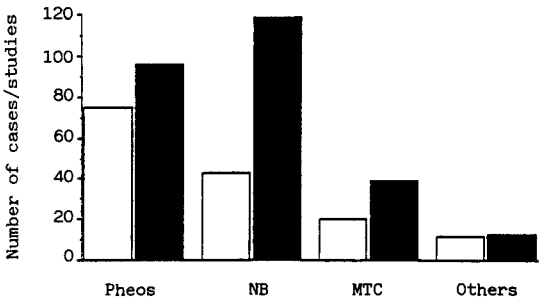


Fig. 1. Histogram showing the number of cases (*blank area*) and studies (*black area*) performed in various neural crest tumors. Cases of suspected pheos are the most numerous, followed by NB. On the other hand, the latter are more prevalent in the studies performed

Results

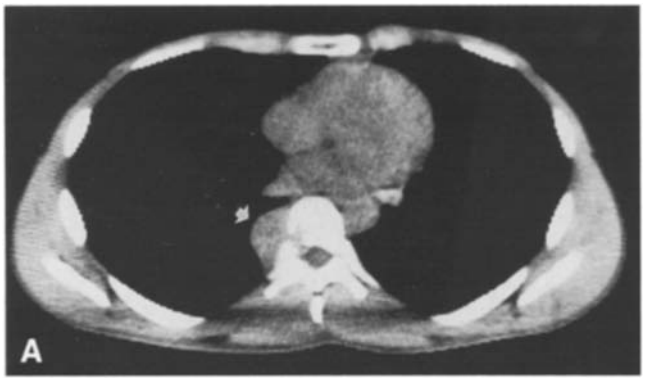
Diagnostics

Throughout the 5 years of this project, a constantly progressive increase in the request for scintigraphy with radioiodinated MIBG has been observed (from 5 cases scanned in 1983 to 100 studies performed in 1987, in the first 6 months of 1988 61 studies have been performed). The use of the new agent was initially limited to the localization of pheos, but was then extended to the detection of various other tumors originating from the neural crest. Cases of suspected pheos were the most numerous and they were followed by NB. When the number of imaging procedures were taken into account, the most numerous were those for NB (Fig. 1).

The diagnostic results obtained for the various histological types of tumor investigated are reported separately in the following paragraphs.

Pheochromocytomas. In the 24 cases with proven pheos, scintigraphy yielded diagnostic imaging in 22. It appeared particularly useful in the detection of extra adrenal pheos (1 located near the posterior bladder wall, 1 pelvic, 1 thoracic, 2 at the renal hilum, 3 retroperitoneal) (Fig. 2) and malignant pheos, the locations of which were not fully revealed by the conventional diagnostic techniques. Some difficulties were met in imaging ectopic pheos situated at the renal hilum. In these cases the use of ^{123}I-MIBG was very helpful as it succeeded in giving a representation of the tumoral mass where the compound labelled with ^{131}I failed (Fig. 3).

The results obtained in 47 cases, 24 with proven pheos and the remainder without evidence of the tumor, were compared with those obtained with CT. The overall reliability of scintigraphy was quite high, not significantly different from that of CT (Table 1). It was superior to CT in diagnostic specificity both in the sense of having very few false positive results (one case of adrenocortical nodular hyperplasia with no histological evidence of adrenomedullary enlargement) and in tumor specificity, i.e. allowing the identification of the nature of the tumor



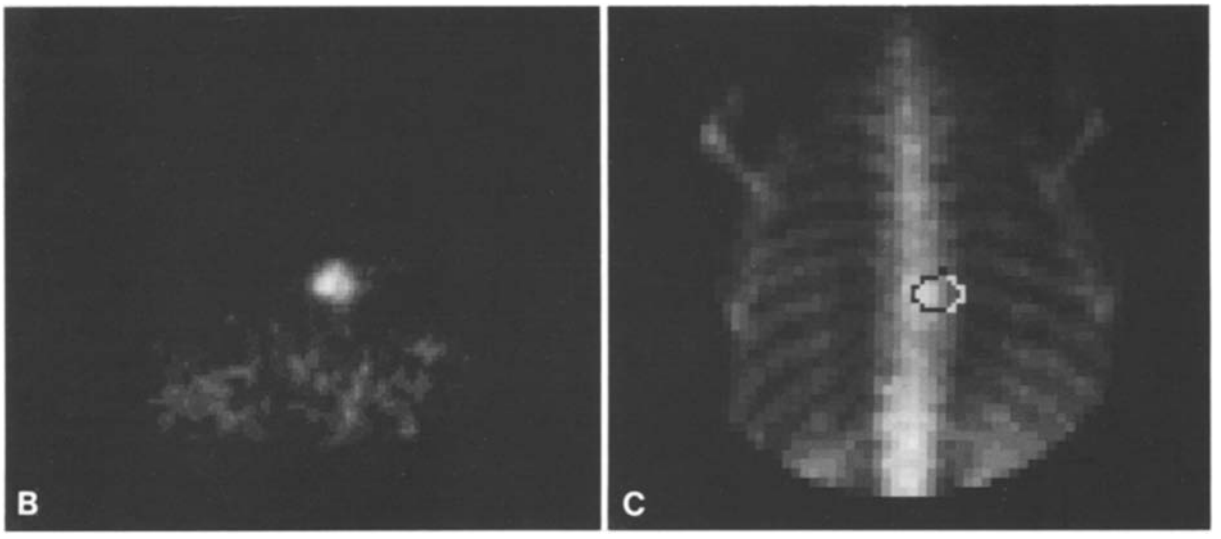


Fig. 2A–C. Extra adrenal malignant pheo. **A** CT scan of the lower chest showing a right paraspinal mass in the posterior mediastinum, characterized by homogeneous density similar to that of soft tissues, and sharp borders (*arrow*). The eight dorsal vertebra is eroded with no apparent intra spinal involvement. **B** ^{131}I-MIBG scan. Posterior view of the chest showing an area of abnormal uptake. **C** The region of interest selected over the focus of abnormal MIBG uptake is superimposed on the bone scan and it appears localized in the right side of spine (eight dorsal vertebra)

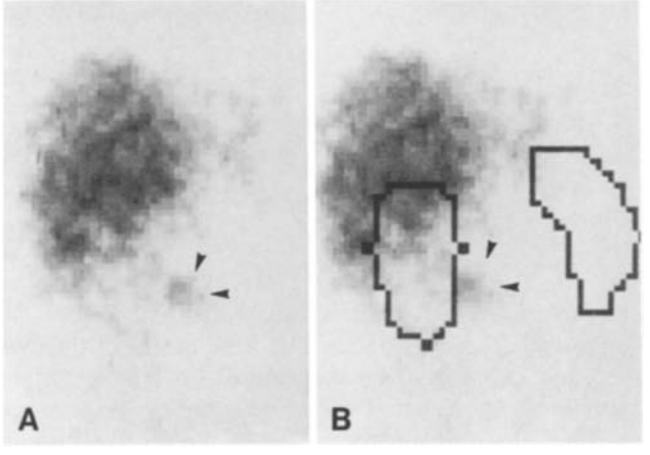


Fig. 3. Extra adrenal benign pheo. Scintigraphy with ^{123}I-MIBG (**A**) performed after a negative ^{131}I-MIBG scan shows an area of abnormal MIBG uptake (*arrows*) corresponding to the hilum of right kidney (**B**). Outlines of kidneys obtained by ^{99m}Tc-DMSA are superimposed on MIBG images

(not possible except on a presumptive basis with CT). Just one case of a tumoral mass with large necrotic areas, and an exceptional case of a dopamine-secreting malignant pheo, were missed by scintigraphy (false negative results).

Owing to the high reliability of the examination, an algorithm was developed in which radioiodinated MIBG labelled with either ^{131}I or ^{123}I, is presented as the first choice diagnostic modality. CT maintains its essential role as a further diagnostic technique in order to better detail the morphological aspects of the lesions detected by scintigraphy and to plan surgery. CT has a secondary role in locating those lesions with no ^{123}I/^{131}I-MIBG uptake (Fig. 4).

Neuroblastomas. An overall assessment of the results obtained with radioiodinated MIBG imaging is reported in Table 2. Scintigraphy was effective mainly in detecting primary tumors and bone metastases, whereas it was less effective in imaging soft tissue metastases and bone marrow involvement. The overall sensitivity was quite high (92%). However, when an accurate evaluation of the extent of the disease was made (including bone marrow involvement), in only 50 out of 81 studies (61.7%) were all the lesions present visualized.

The positive results did not strictly correlate with elevated catecholamine levels. In fact in 30 out of 81 positive scans (37%), primary and/or metastatic lesions were diagnosed by scintigraphy in spite of normal catecholamine levels.

After a more detailed analysis, the examination appeared to be particularly effective, and, to a certain ex-

Table 1. $^{123}I/^{131}I$-MIBG imaging and CT results in patients with a suspected pheo. Comparison in 47 cases

	Positive scan	
	$^{123}I/^{131}I$-MIBG	CT
Benign pheos		
Adrenal	12/13	13/13
Extra adrenal	5/5	4/5
Malignant pheos		
Adrenal	2/3	3/3
Extra adrenal	3/3	3/3
Absence of pheo	1/23	3/23
Sensitivity	91.6% (74.0%–99.0%)	95.8% (79.2%–99.9%)
Specificity	95.6% (79.0%–99.9%)	87.0% (67.0%–97.0%)
False positive results	4.4%	13.0%
False negative results	8.4%	4.2%
Accuracy	93.6%	91.4%
Prevalence of disease	51%	51

(In brackets are reported the confidence limits 95%)

Table 2. Reliability of ^{131}I-MIBG imaging in NB (43 cases – 119 studies)

	^{131}I-MIBG scintigraphy					
	Number of studies	Positive	Negative	Sensitivity	Specificity	Accuracy
1. *Global assessment*						
Tumor lesion +	88	81	7			
Tumor lesion –	31	0	31			
				92%	100%	94%
2. *Assessment of individual lesions*						
Primary tumor		29	3	90.6%		
Recurrence		4	1	–		
Bone metastases		30	1	96.7%		
Soft tissue metastases		20	12	62.5%		
Bone marrow infiltation		11[a]	7	61.1%		

[a] All showed 90% malignant cells

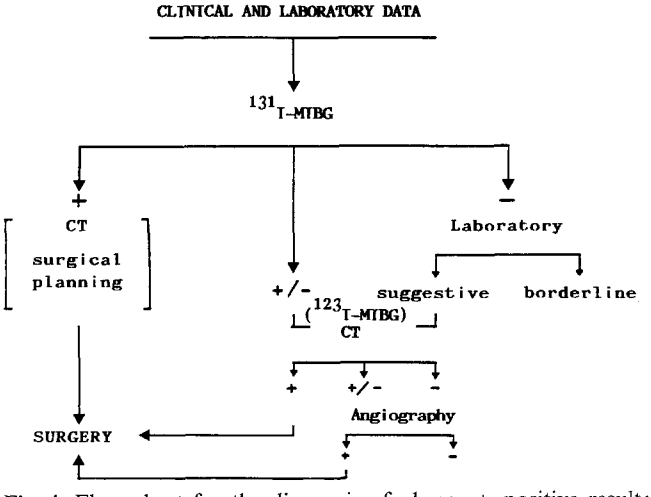


Fig. 4. Flow chart for the diagnosis of pheos. + positive result; +/– equivocal result; – negative result

tent, superior to conventional diagnostic modalities: at diagnosis, it correctly documented the extent of the disease, thus proving to be very useful for staging; after surgery, it demonstrated either the complete surgical removal of the tumor or the extent of the residual tumor (Fig. 5); in patients no longer on therapy, it demonstrated in a few cases (3/12) that the apparent remission of the disease was really only partial.

In at least 11 cases it was able to give information usually obtained only by the combination of multiple diagnostic techniques. Although scintigraphy was not able to offer the same morphological details as CT, it was especially useful in giving evidence of the functional nature of the lesions. It may be for this reason that in some cases (four patients) it failed to clearly detect the tumoral lesions during chemotherapy, when the uptake had been altered by the treatment.

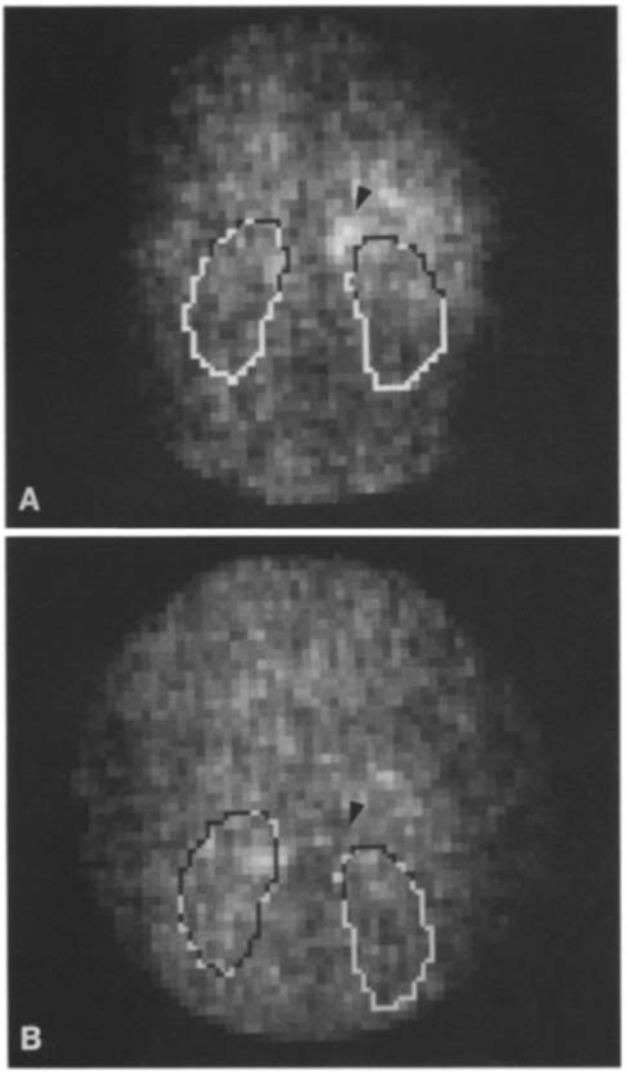


Fig. 5A, B. ^{131}I-MIBG scintigrams in a 5-year-old child with a right adrenal neuroblastoma. Posterior views of the abdomen. **A** ^{131}I-MIBG scan following chemotherapy shows a small area of uptake due to a residual tumor in the right adrenal (*arrow*). **B** ^{131}I-MIBG scan performed after the complete surgical removal of the residual tumor (*arrow* indicates the site from which the tumor was removed) shows no uptake in the region

Medullary thyroid carcinoma. ^{123}I/^{131}I-MIBG successfully imaged the primary or residual/recurrent MTC in 1 out of 2 cases investigated at diagnosis, in 1 case studied after a previous hemithyroidectomy (2 months earlier) and in 4 out of 6 cases studied after total thyroidectomy (Table 3). Furthermore, the examination succeeded in detecting minimal residual lesions in two out of six patients considered free of disease by conventional diagnostic imaging methods, but still with persistently abnormal levels of calcitonin. The outcome was negative in the remaining four cases. Two of these had previously undergone a hemithyroidectomy and further surgery had excluded the presence of neoplastic lesions in the residual lobe, while the various examinations performed on the other 2, together with a follow up of 5 and 7 months

Table 3. ^{123}I/^{131}I-MIBG imaging in MTC

Cases	Ct levels	Tumoral lesions	^{123}I/^{131}I-MIBG positive
10	Elevated	Primary tumor residual/recurrent tumor Distant metastases	1/2 5/7 3/5
6	Elevated	Not evident (at conventional imaging modalities)	2/6
4	Normal	Not evident (at conventional imaging modalities)	0/4

respectively, did not reveal the presence of a tumor (these 2 patients did not attend for the last follow up). Scintigraphy was correctly negative in four cases with normal calcitonin values. On the other hand, ^{123}I/^{131}I-MIBG scintigraphy was less accurate in the search for distant metastases, some but not all of which were visualized in three out of five cases. At a preliminary assessment of the effectiveness of the method a sensitivity of 64.4% was calculated.

Other tumors. The results of ^{123}I/^{131}I-MIBG scintigraphy were falsely negative in the five cases of proven carcinoid tumor, in the six cases of ganglioneuroma and in the one case of insulinoma. They were correctly negative in the above listed eight cases of tumors not originating from the neural crest.

Therapy

Malignant pheochromocytomas. The clinical status, doses administered, dosimetry, and responses of the patients treated are listed in Table 4. A complete regression of the residual tumor and the normalization of blood pressure and catecholamine levels were achieved in a 35-year-old woman (patient 2), after 11.1 GBq (300 mCi) ^{131}I-MIBG were given post surgically in 2 courses at 3-month intervals (estimated radiation dose 56 Gy). There is still no evidence of disease 20 months after the start of therapy (Fig. 6).

Distinct and persistent benefits were achieved in another 2 patients with disseminated pheos (patients 1 and 4); 24.8 GBq (670 mCi) ^{131}I-MIBG were given in 9 courses (cumulative estimated dose 79 Gy) in patient 1, with a persistent remission of the disease (however, after having refused any further treatment the patient relapsed and after 18 months of sustained remission died from progression of the disease 24 months from the start of therapy); 12.5 GBq (340 mCi) ^{131}I-MIBG were given in 3 courses to the other patient (estimated dose 30 Gy) with a stabilization of the disease lasting 15 months. No change was observed in patient 3 who received only

Table 4. ^{131}I-MIBG therapy in pheochromocytomas

Case	Age (years)	Sex	Clinical status	Uptake %	Courses/ total dose (number/mCi)	Gy	Response	Follow up (months)
1	35	M	Primary (360 g) + metastases	8.2	9/670	79	– Partial remission with pain relief and decrease (50%) in tumor volume – Relapse after 18 months Refused further therapy – Died after 24 months from the beginning of therapy	24
2	35	F	Residual tumor (30 g)	1.5	3/300	56	– Complete remission with normalization of catecholamine levels and regression of the residual tumor – Alive	20
3	39	F	Recurrence (420 g) (abdominal)	3.8	2/150	8.6	– Pain relief – Died for progression of the disease after 2 months from the beginning of therapy	2
4	43	M	Recurrence (130 g) (pelvic)	3.5	3/340	30	– Pain relief – Arrest in tumor growth, deterioration after 6 months – External radiotherapy and chemo following MIBG therapy – Died after 15 months	15

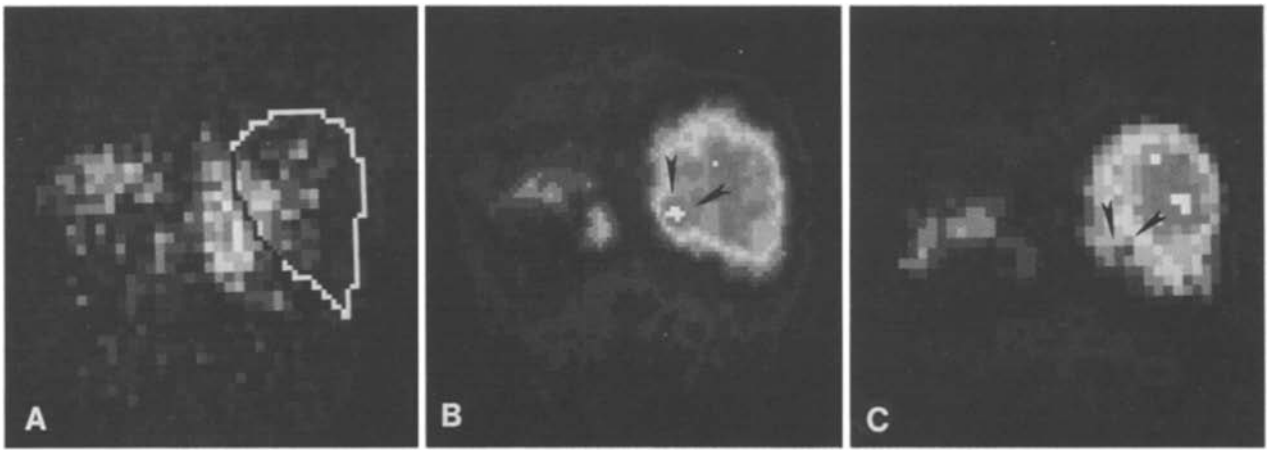


Fig. 6. A ^{131}I-MIBG image of posterior mid abdomen showing a large area of abnormal uptake corresponding to an ectopic malignant pheochromocytoma (the tumor was located behind the liver, between the aorta and vena cava) (number 2, Table 4). The outline of liver obtained by ^{99m}Tc-phitate is superimposed on the MIBG image. **B** ^{131}I-MIBG scan performed 4 months after surgery showing minimal tracer uptake due to residual tumor (*arrow*). **C** After ^{131}I-MIBG treatment (11.1 GBq = 300 mCi), a complete regression of the residual tumor was achieved and MIBG uptake in this region was no longer evident (*arrows*). The patient is still free of disease at 20 months from the beginning of therapy

5.55 GBq (150 mCi) ^{131}I-MIBG (she died 2 months later).

No side effects were recorded in these patients.

Neuroblastomas. Eight cases (one adult) out of nine treated were evaluable (Table 5). Two children had a complete response after 17.0 GBq (460 mCi) and 5.55 GBq (150 mCi) ^{131}I-MIBG were given in 3 and 2 courses respectively (estimated dose 65 and 35 Gy). One of them had a residual tumor and vertebral metastases (patient 5) and the other (patient 9) was treated at diagnosis – this case has been reported elsewhere

Table 5. ^{131}I-MIBG therapy in neuroblastoma

Case	Age/sex (years)	Stage	Clinical status	Previous treatment	Uptake %	Course/ Total dose (number/mCi)	Gy	Response	Follow up (months)
1.	1/M	4	Primary (230 g) bone meta, BMI	Chemo	17.8	1/80	23	NE	–
2.	1.2/M	4	Primary bil. (130 g) bone meta, BMI	Chemo	3.5	1/80	11	DS.Refused further therapy. Died	2
3.	9/M	4	Primary (320 g) Bone, liver meta	Chemo	8.2	4/588	78	PR.Surgical removal of primary. Died following relapse	8
4.	2/M	4	Primary (220 g) BMI	Chemo	6.7	2/178	15	PR. Died following relapse	8
5.	8/M	4	Residual tu. (60 g) Bone meta	Chemo	2.8	3/460	65	CR. Alive	34
6.	38/F	4	Residual tu. (110 g)	Chemo	1.2	3/450	14	DS. Lost at Follow up	17
7.	3/M	4	Bone meta (25 g)	Chemo	1.7	2/365	41	DP. Died	9
8.	2/M	4	Lymph nodes Bone meta (30 g)	Chemo 60-Co	1.2	1/168	22	DP. Died	2
9.	0.8/M	3	Primary (75 g)	–	7.0	2/150	35	CR. Alive	24

BMI, bone marrow involvement; *DS*, disease stabilization; *NE*, non evaluable; *PR*, partial remission; *DP*, disease progression; *CR*, complete response

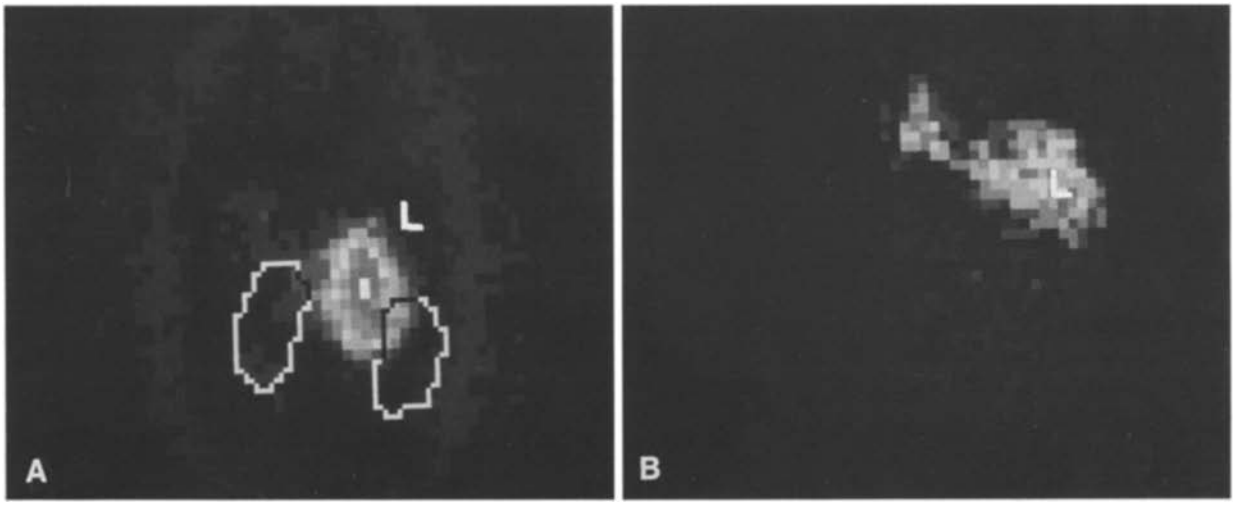


Fig. 7. A ^{131}I-MIBG scan, posterior lumbar view in a case of neuroblastoma (number 9, Table 5) showing a large area of abnormal MIBG uptake. This corresponds to a voluminous right retroperitoneal NB displacing the right kidney downwards (outlines of kidneys obtained by ^{99m}Tc-DMSA are superimposed on the MIBG images) (L = liver activity slightly recognizable due to the intense uptake of the tumor). **B** After a total dose of 4.5 GBq (150 mCi) given in 2 courses, there was no evidence of uptake in the region. The complete regression of the tumor was confirmed by surgical exploration and subsequent 24 month follow up (L = liver activity)

(Mastrangelo et al. 1989). They are at present in complete remission with a follow up of approximately 34 and 24 months respectively (Fig. 7).

Two other patients (3 and 4) had objective responses with a shrinking of the primary tumor (30% and 50% respectively) and (in case 3) a partial regression (30%) of the metastatic lesions. They died, however, 8 months after treatment. Two patients (2 and 6) showed tempo-

Table 6. ^{131}I-MIBG therapy in an integrated treatment of medullary thyroid carcinoma

Case	Sex	Age (years)	Pathology Previous therapy	Clinical status	Treatment performed	^{131}I-MIBG therapy		Response	Follow-up (months)
						Course/ Total dose (n./mCi)	Gy		
1.	M	39	M T C + Papillary ca (1971). Thyroidectomy + Lymphadenectomy ^{131}I ablative dose	Recurrence after 15 years sustained response	Lymphadenectomy External radiotherapy. ^{131}I-MIBG therapy	2/360	20	– Complete response to integrated treatment – Markers normalized – Alive	20
2.	M	36	M T C + Papillary ca. Thyroidectomy + Lymphadenectomy	Residual/ recurrent tumor	^{131}I ablative dose ^{131}I-MIBG Mediastinal lymph adenectomy.	2/430	46	– Partial response to integrated treatment – Markers sill elevated – Alive	23
3.	M	54	M T C (1979) Thyroidectomy Local recurrences and distant metastases External radiotherapy on sacrum (1979). Chemotherapy	Local recurrences Distant metastases still present	^{131}I-MIBG ^{131}I ablative dose	6/891	50 (neck) 56 (sacrum)	– Partial response on neck lesions – Arrest in growth of remote meta – Alive	24 (105)[a]
4.	F	66	M T C Thyroidectomy Distant metastases	Multiple skeletal metastases	^{131}I-MIBG External radiotherapy on ilium	2/236	15	– No change. Relief of pain – Died for progression of disease	9

[a] From external radiotherapy

rary stabilization of the disease (4 weeks and 17 months respectively) and two patients (7 and 8) were completely unresponsive to treatment.

The major side effects recorded in these patients were: several hypertensive crises (from 150/95 up to 280/140 mmHg) over a 6-day period from the beginning of treatment in case 2 (temporarily controlled with α-blockade), and bone marrow depression in 2 cases (3 and 7) previously treated with high dose chemotherapy and harboring persistent bone marrow involvement; it was severe in case 7 (WBC 2.9×10^9/l; PLT $= 5 \times 10^9$/l; absolute number of neutrophils $< 0.5 \times 10^9$/l), mild in the other (WBC $= 3.7 \times 10^9$/l; PLT 35×10^9/l). However, a slight hematologic toxicity was observed in almost all cases, mainly thrombocytopenia which never reached levels of any clinical importance ($100–150 \times 10^9$/l).

Medullary thyroid carcinomas. In four patients affected by MTC, an integrated treatment including ^{131}I-MIBG was given. The clinical data of patients, the treatment performed and its outcome are reported in Table 6.

A complete regression of the local recurrences, proven both by the conventional diagnostic techniques and by the normalization of tumoral markers, was obtained in patient 1 who underwent an integrated treatment including surgery (cervical lymphadenectomy), external radiotherapy (60 Gy) and ^{131}I-MIBG therapy 13.3 GBq (360 mCi) (estimated dose 20 Gy). In the 2nd case, 15.9 GBq (430 mCi) were administered (estimated dose 46 Gy); ^{131}I-MIBG was effective in reducing the residual/recurrent tumor visualized by scintigraphy and CT by about 50% (Fig. 8). This improvement was confirmed by conventional diagnostic procedures and by the continuing decrease of Ct levels (even though they still have not reached normal limits) and the normalization of CEA. The patient is still undergoing treatment.

Two cases were in a very advanced stage with widespread bone metastases. In case 4 it was possible to administer only 8.7 GBq (236 mCi) ^{131}I-MIBG (estimated dose 15 Gy). The treatment was essentially ineffective (only pain relief was achieved) and the patient died 9 months after the beginning of therapy. In the other

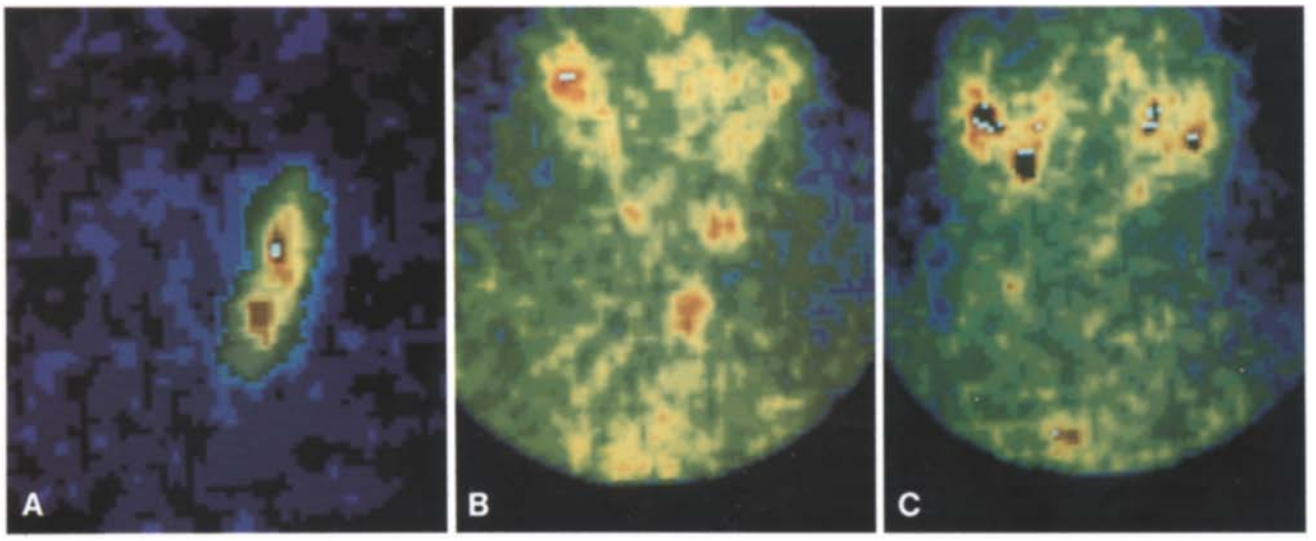


Fig. 8A–C. A 36-year-old man with medullary thyroid carcinoma (number 2, Table 6). **A** Following right hemithyroidectomy, the ^{131}I-MIBG scintigraphy imaged the tumor involved residual lobe. The tumoral involvement was subsequently confirmed by surgery (free radioiodine uptake was blocked by administration of triiodothyronine and Lugol's solution). **B** Multiple foci of abnormal uptake corresponding to the residual tumor were detected in the neck after total thyroidectomy. **C** Partial regression of the residual disease demonstrated by scintigraphy after administration of a total dose of 15.9 GBq (430 mCi) ^{131}I-MIBG

case (patient 3), treatment with 32.9 GBq (891 mCi), given in 6 courses (estimated dose 50 Gy to the neck lesions and 56 Gy to the sacral lesion) produced an arrest in growth of the voluminous metastasis on the sacral bone and also resulted in a partial regression (about 70%) of local recurrences. This patient is still alive 2 years after the initiation of ^{131}I-MIBG therapy. The Ct values, however, remain abnormal.

No side effects were recorded in any of these patients.

Comment

The 5-year clinical experience in the use of ^{123}I/^{131}I-MIBG supports this new technique which was introduced by the research group at the Michigan University Medical Center (Wieland et al. 1980, 1981).

As reported in the literature, patients with pheo and NB are those which gain the most benefit from the examination (Ackery et al. 1984; Horne et al. 1984; Kimmig et al. 1984; Sutton et al. 1982; Troncone et al. 1984, 1986; Geatti et al. 1985; Hoefnagel et al. 1985; Munkner 1985; Shapiro et al. 1985). In the former disease the test has a high reliability, equal to that of CT (Francis et al. 1983; Chatal et al. 1985; Rufini et al. 1988). The scintigraphic examination has the advantage over CT in that it permits the screening of the whole body in a single procedure, it gives fewer false positive results, and has a high specificity which allows the nature of the neoplastic lesion to be identified.

The examination has also proved reliable in NB, especially in the initial staging, in the postoperative phase, in the monitoring of the response to different treatments and in off-therapy patients (for an early diagnosis of otherwise occult metastases or recurrent tumors). In the above situations the examination seems superior to individual conventional imaging modalities, and can offer diagnostic information which can only be obtained by a combination of several diagnostic techniques. Its outstanding feature is not that of revealing morphological details, but rather of imaging the functional aspect of the neoplastic lesions.

Our data obtained in medullary thyroid carcinoma are controversial, but appear more reliable than those found in the literature (Hilditch et al. 1986; Poston et al. 1986; Clarke et al. 1988; Perdrisot et al. 1988). The well known histological heterogeneity of these neoplasms, as well as the possible anaplastic transformation of some metastases, may explain these controversial findings.

As was expected, the scintigraphic results in the eight cases with tumors not deriving from the neural crest were negative. This confirmed the high diagnostic specificity of the examination for sympathomedullary tumors.

Lastly, the results obtained in a small series of other tumors of neuroectodermal origin have been rather disappointing, which is at variance with some data in the literature (Feldman et al. 1986; Hoefnagel et al. 1987; Von Moll et al. 1987). A wider utilization of the modality and a better knowledge of the pathways of the radiopharmaceutical uptake and storage, can probably clarify many of the uncertain aspects of the technique. It nevertheless seems capable of playing an important role in the location and diagnosis of tumors originating from the neural crest.

The therapeutic potential of ^{131}I-MIBG has been evident since its first clinical application (Fischer et al.

1984b; Sisson et al. 1984). Our experience substantially confirms the encouraging initial results obtained by various authors (Adolph et al. 1986; Feine et al. 1986; Maul et al. 1986; Hoefnagel et al. 1987) and also offers further interesting data. Our best results have been observed in the early postsurgical treatment of residual tumors, both in pheochromocytomas and neuroblastomas. The outcome of therapy was the normalization of symptomatology and complete regression of some of the neoplastic lesions. The dramatic regression of the primary tumor obtained (with relatively limited therapeutic doses) in a case of neuroblastoma treated at diagnosis, may confirm the importance of taking action as soon as possible in untreated patients to ensure a good response.

In MTC, preliminary data point towards the need to continue exploring this mode of treatment. To our knowledge only a few cases have been reported as having been treated with this agent (Hoefnagel et al. 1988). We have had the opportunity to treat four patients with ^{131}I-MIBG. In two advanced cases, ^{131}I-MIBG therapy offered a further therapeutic option (successful in one) to those who otherwise would have had no other therapy available. In both cases it provided worthwhile relief of pain. As a complement to surgery, ^{131}I-MIBG therapy resulted in a regression of local recurrence in the other two cases: complete in one and partial in the other (still in treatment).

No adverse reactions were recorded in any of the cases scanned, except for a hypertensive crisis which occurred during injection in one case of suspected (not α-blocked) pheo. Of the cases treated, only children with neuroblastomas suffered any severe side effects. Apart from the hypertensive crises observed in one child, probably due to catecholamine release following radiation induced damage, a hematologic toxicity was recorded in almost all cases: in two cases it was quite severe. This is probably due to the extensive bone marrow infiltration by the tumor cells and to the heavy dosages required.

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