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Extra-adrenal and Metastatic Pheochromocytoma: The Role of ^{131}I Meta-Iodobenzylguanidine (^{131}I MIBG) in Localization and Management

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From June, 1980, to August, 1983, ^{131}I MIBG scintiscans were performed in 353 patients with suspected pheochromocytomas. Extra-adrenal pheochromocytomas were identified in 15 of 18 patients who at operation were proven to have such tumors and normal adrenal glands. Conventional localization studies, often repeated, had failed to localize these tumors in nearly all cases. Nine of the extra-adrenal pheochromocytomas were found within the middle mediastinum. This group of unique tumors required further specialized localization studies with augmented computed tomography (CT) scans for specific anatomical delineation. These complementary studies allowed for precise planning of surgical excision of the tumors, which required cardiopulmonary bypass in some patients. Extra-adrenal pheochromocytomas were identified in a family with no other endocrinopathies. The tumors in 3 patients from 3 different generations all were perirenal and involved the vena cava.

^{131}I MIBG scintiscans detected metastatic lesions in 40 patients with malignant pheochromocytomas. Metastases were not readily demonstrated in 4 patients. The diagnosis of malignant and metastatic pheochromocytoma was first made by the scintiscan findings in 5 patients. ^{131}I MIBG scans were not false-positive in any cases and were false-negative in 10.5% of 95 patients proven to have pheochromocytomas by biochemical evidence or operation.

Ten patients have been treated for malignant pheochromocytomas with therapeutic doses of ^{131}I MIBG. Five patients have had objective responses with diminution in size of metastases or primary malignant tumor and a decrease in the secretion of catecholamines.

This agent has been found to be of great value in detecting pheochromocytomas that often have defied all other means of localization. ^{131}I MIBG concentrates in most malignant pheochromocytomas, and preliminary results suggest that it will be very useful in the treatment of this disease.

The diagnosis of pheochromocytoma is frequently simpler than the anatomical localization of the tumor. Elevations in plasma and/or urinary catecholamine and their metabolites, coupled with a characteristic clinical picture can usually establish the diagnosis. The tumor localization, however, particularly when there is malignant, extra-adrenal, or bilateral disease, may be very difficult. Approximately 10% of pheochromocytomas arise from chromaffin tissue anywhere from the base of the skull to the bladder. Furthermore, some pheochromocytomas may be multiple, in extra-adrenal locations, or concurrently intra-adrenal and extra-adrenal. Third-generation computer assisted tomography is extremely accurate in localizing intra-adrenal lesions, but is not very helpful for identifying extra-adrenal or metastatic pheochromocytomas. Until recently, no available modality could provide both an anatomical and functional documentation of the tumor prior to surgical intervention. The synthesis of ^{131}I meta-iodobenzylguanidine (^{131}I MIBG) has made it possible to obtain scintigraphic images of pheochromocytomas and hyperplastic chromaffin tissue. This compound, a guanidine analogue with molecular structure similar to that of norepinephrine, was found by Wieland et al. [1] to

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have a strong affinity for adrenergic tissue. For the past 3 years, ^{131}I MIBG scintiscans have been used at The University of Michigan for the localization of pheochromocytomas and for screening patients with multiple endocrine neoplasia type II and other neuroectodermal dysplasias. ^{131}I MIBG has also been used in the management of inoperable and metastatic pheochromocytomas. This report describes our experience with this agent.

Methods and Materials

Patient Populations

During the 3-year period from August 1980, to August, 1983, a total of 353 patients with suspected pheochromocytomas was studied at The University of Michigan Medical Center. Nearly a third of the patients had the diagnosis established by biochemical studies. These patients were referred for localization and possible treatment of their pheochromocytomas. Many other patients had hypertension that was labile, difficult to control, or paroxysmal, and underwent scintiscans because to do so expedited their pheochromocytoma evaluation when they had been treated with a drug such as alpha-methyldopa that interferes with biochemical testing. Some patients had suspicious but not diagnostic catecholamine elevations in either plasma or urine. Other patients with proven MEN IIa or IIb syndromes, without hypertension or biochemical evidence of pheochromocytoma, underwent scintiscans with ^{131}I MIBG as part of a screening protocol. Although ^{131}I MIBG scans were used primarily for localization, in a few cases the scan was the first diagnostic proof that a pheochromocytoma was present.

The 95 patients with proven pheochromocytomas ranged in age from 9 to 69 years. Fifty-one were males and 44 were females. With the exception of 2 MEN IIa patients who were asymptomatic except for episodes of palpitations and anxiety, all were hypertensive. There were 18 patients with familial disease associated with pheochromocytomas including 8 with MEN IIa, 3 with MEN IIb, 5 with neurofibromatosis, 1 with von Hippel-Lindau, and 1 with Carney's triad (pheochromocytoma, gastric leiomyoblastoma, and pulmonary chondroma) [3].

All patients with proven pheochromocytomas had at least 1 urinary catecholamine or catecholamine metabolite level within the diagnostic range. Many patients also had diagnostic elevations in their plasma catecholamines as well. In addition to undergoing the ^{131}I MIBG scan, patients were screened for pheochromocytoma by CT scanning.

Technique for Scanning with ^{131}I MIBG

^{131}I MIBG was synthesized and prepared for intravenous injection as previously described [1, 2]. Lugol's iodine, 30 mg, was given orally for 5 days beginning 24 hours before the injection of ^{131}I MIBG in order to block uptake of ^{131}I by the thyroid gland. A dose of 0.5 mCi per 1.7 m^2 of body surface area (not to exceed a total dose of 0.5 mCi) was injected intravenously over 10–20 seconds on the day prior to the first scan. Scanning was performed at 24, 48, and 72 hours after injection. In cases in which anatomic orientation was uncertain, (^{99}mTc) pentetic acid or (^{99m}Tc) diethylene triaminepentacetic acid was also administered to visualize the kidney.

Administration of ^{131}I MIBG for the Treatment of Metastatic or Inoperable Malignant Pheochromocytomas

Ten patients with unresectable metastases or inoperable primary tumors that showed uptake by ^{131}I MIBG scintography were administered therapeutic doses of this agent. Early in the experience with therapy, approximately 100 mCi was given as the initial dose. During the last year, however, patients have been given 200 mCi as a initial dose. The majority of patients have been given 2 or 3 doses with maximum of 600 mCi. When administered therapeutically, ^{131}I MIBG was given as a 100 mCi dose of ^{131}I on 5 mg of MIBG and infused at the rate of 3 mg/30 min, intravenously. It was calculated that each dose of 100 mCi of MIBG would deliver approximately 3,400 rad. A therapeutic dose is now considered to be a total of 300 mCi or 10,200 rad delivered to the tumor.

Results

^{131}I MIBG Localization

Of 95 patients proven to have pheochromocytomas by operation or consistently diagnostic biochemical determinations, 85 were visualized by ^{131}I MIBG scintigraphy (Table 1). The false-negative rate was, therefore, 10.5%. There were no false-positive studies. Eighteen of 19 patients with intra-adrenal sporadic pheochromocytomas had localizing scintiscans. In the single false-negative case, a 51-year-old man had a large easily identifiable left adrenal pheochromocytoma that was cystic on CT scanning. The excised lesion was a fluid-filled neoplastic cyst with a maximum wall thickness of 0.5 cm. It is possible that cystic degeneration of

Table 1. ^{131}I MIBG detection of pheochromocytoma or metastases.

	No. shown (No. proven) with ^{131}I MIBG
Intra-adrenal (sporadic)	18 (19)
Extra-adrenal	15 (18)
Malignant (sporadic)	34 (38)
Familial	18 (18)
Bilateral	12
Malignant	6
Total	85 (93)[a] 95%

[a]Location of pheochromocytomas in 2 patients with biochemical proof, undetermined.

this pheochromocytoma was responsible for its failure to take up ^{131}I MIBG.

Fifteen of 18 patients had extra-adrenal pheochromocytomas that were visualized by ^{131}I MIBG scanning. Six of these were in intra-abdominal locations. Five were periaortic and one was perirenal. In 1 patient, 2 periaortic pheochromocytomas were visualized. This 30-year-old man had, 1 year previously, undergone a left adrenalectomy for an intra-adrenal pheochromocytoma. Because of recurrent hypertension, he was extensively studied for a possible extra-adrenal lesion. Plasma venous catecholamine levels, repeated abdominal and mediastinal CT scans, and abdominal aortography with selective studies failed to identify his tumor sites. An ^{131}I MIBG scan readily showed 2 tumors in the periaortic region as depicted in Fig. 1.

Nine patients had pheochromocytomas found in the middle mediastinum. With 1 exception, all were initially discovered after ^{131}I MIBG scintiscanning. In 1 case, a tumor blush was initially seen as a result of coronary angiography. Three of these patients were males and 6 were females, ranging in age from 18 to 61 years. Five tumors were excised using cardiopulmonary bypass. In each of these, the left atrium was the site of origin of the tumor. Three of the 5 patients are considered cured. One patient died on the first postoperative day with diffuse intravascular coagulation. One patient has persistent disease because of skeletal metastases. One tumor was stripped from the atrium without the need for cardiopulmonary bypass and is cured. Another patient's tumor was in the aorticopulmonary window and could be excised without difficulty. One patient with Carney's syndrome has not undergone operation for pheochromocytoma because she has proven liver metastases with gastric leiomyoblastoma. Another patient is awaiting operation. These rare middle mediastinal pheochromocytomas have been reported in detail elsewhere [3]. Ten of 18 extra-adrenal pheochromocytomas proved to be malignant.

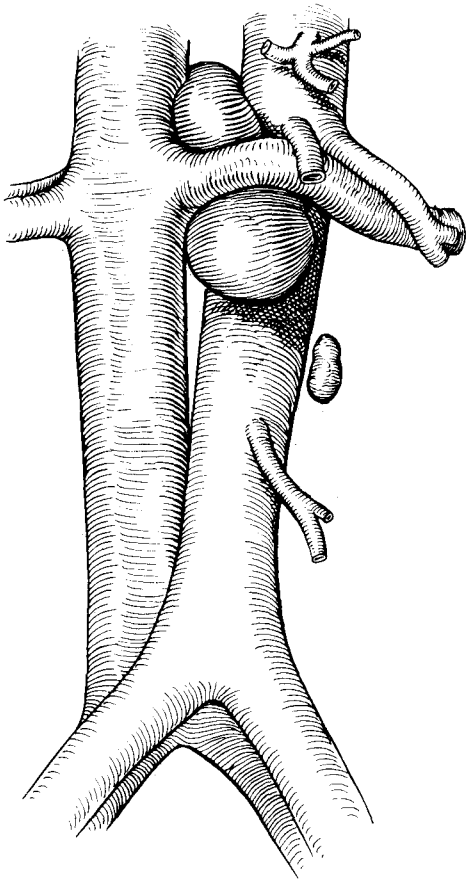

Fig. 1. A 30-year-old male patient with 2 extra-adrenal primary pheochromocytomas localized by ^{131}I MIBG scan after other studies failed to show the tumors.

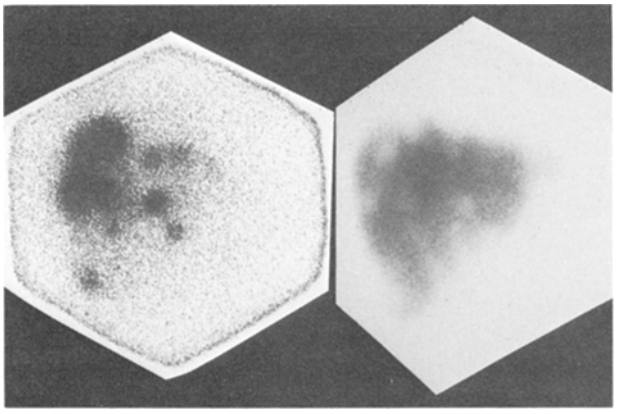

Fig. 2. Liver metastases in a 27-year-old woman with MEN IIa demonstrated by ^{131}I MIBG scan *(left)* and ^{99}mTc sulfur colloid scan *(right)*.

There were 44 patients with malignant pheochromocytomas as determined by metastases in lymph nodes, liver, lung, or bone. In 18 of these, the primary tumor was extra-adrenal. In several cases the primary tumor was identified as malignant because metastases were discovered by the

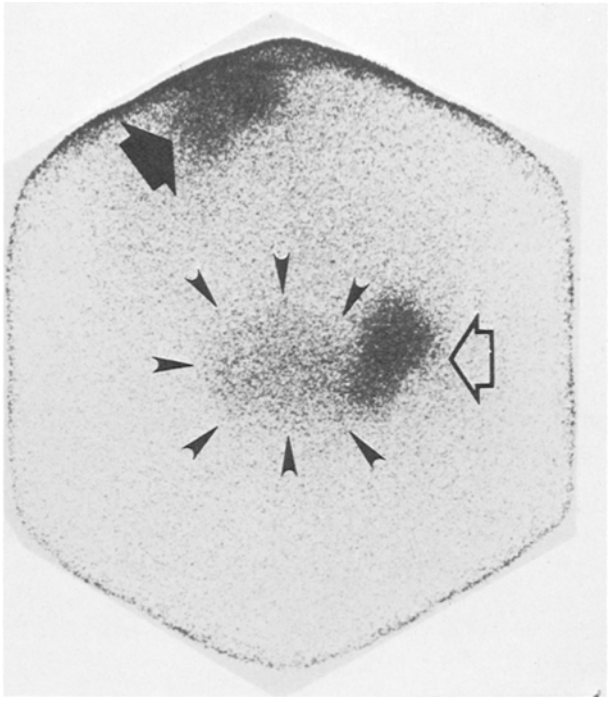

Fig. 3. A ^{131}I MIBG scan of the pelvis showing the primary pheochromocytoma periaortic focus *(solid arrow)* and a metastatic deposit in the left acetabulum *(open arrow)*. Normal bladder activity is outlined by small arrows.

scintiscan (Fig. 2). Malignant pheochromocytomas were identified by scintiscanning in 40 cases. Thirty-four of these were malignant sporadic pheochromocytomas. In addition, pheochromocytomas in 6 patients with familial disease were malignant. Two were MEN IIa patients and both had liver metastases that were visualized. Four additional patients had malignant pheochromocytomas that did not appear with MIBG scanning. In 3 of these cases the metastases were in bone and had been previously treated with external irradiation. In 1 patient, hepatic metastases did not appear although in several others they were easily identified.

In addition to the false-negative scan in 1 patient with an intra-adrenal pheochromocytoma, 3 patients, with surgically proven pheochromocytomas in the region of the right renal hilus, had negative ^{131}I MIBG scans. Two of these pheochromocytomas were localized by CT scans. Selective aortography localized the third lesion. These 3 patients all had elevations of urinary catecholamine levels, diagnostic of pheochromocytoma. There were 4 patients with malignant disease whose metastases did not visualize. Two patients have persistently diagnostic levels of catecholamines but these tumors have not as yet been localized by any study.

Therapeutic Use of ^{131}I MIBG

Thus far, 10 patients with metastatic pheochromocytomas or inoperable primary tumors have been treated with therapeutic doses of ^{131}I MIBG. Five patients have shown objective responses as determined by decrease in tumor size to less than 50% of the original volume and/or significant decrease in urinary catecholamine levels. The most dramatic response has been seen in a 62-year-old male patient who had a large inoperable periaortic pheochromocytoma completely encircling his upper abdominal aorta and vena cava, extending from the diaphragm to the bifurcation of the aorta. This patient had severe pain radiating to his scrotum, severe hypertension, and intractable angina. During an attempted resection at another hospital, he had had a cardiac arrest and myocardial infarction. During a 2-year period (1980–1982), he was given 3 doses of ^{131}I MIBG (500 mCi). His tumor size and urinary catecholamines have decreased to a third of pretreatment levels. In 1983 he underwent a successful triple coronary artery bypass without adrenergic blockage at another hospital. He has no hypertension.

Discussion

^{131}I MIBG scintigraphy represents an important advance in the diagnosis and treatment of pheochromocytoma. Until now, adrenal lesions, if large enough, could be documented with computed tomography or angiography, but their functional status could not be readily assessed without selective plasma catecholamine sampling, which was often inaccurate. If a patient with the clinical and biochemical features of pheochromocytoma had an adrenal lesion on CT scan, it was presumed to be a pheochromocytoma. Preoperative assessment of metastatic involvement was difficult and frequently lesions in extra-adrenal sites were not visualized. In our series, the mean time interval from the diagnosis of pheochromocytoma to the diagnosis or identification of metastatic disease was 9 years (range 0–33 years). Among patients with a history of pheochromocytoma, the duration of symptoms due to metastases was 3.7 years (range 0–18 years) before identification by the ^{131}I MIBG scintiscan.

Extra-adrenal metastatic lesions could be visualized in most cases. Until ^{131}I MIBG became available, the discovery of an intra-thoracic pheochromocytoma was a rare and reportable event. Until 1980 only 24 cases of intra-thoracic pheochromocytomas were reported in the world literature [7]. In this series, 9 intra-pericardial lesions were identified by ^{131}I MIBG scintiscanning. None was pro-

spectively found by CT scanning, although one was suspected by the serendipitous appearance of a tumor blush during coronary angiography done for the evaluation of angina. It was further determined, once middle mediastinal lesions could be localized by ^{131}I MIBG scintiscan, that augmented dynamic computer assisted tomography could precisely define the anatomical site of the lesion. As experience with ^{131}I MIBG scanning increased, the usefulness of combined localization modalities became more apparent. Composite scanning techniques using technetium and other agents to identify kidneys, bone, and major blood vessels in conjunction with ^{131}I MIBG have made preoperative localization even more accurate than previously achieved.

The specificity of this test as well as its sensitivity make it ideal for total body screening. Besides the adrenal medulla, uptake 3 hours after injection of ^{131}I MIBG is significant only in the thyroid [1]. Blockage of iodine uptake with Lugol's iodine minimizes uptake of ^{131}I MIBG by the thyroid.

The 10 patients with false-negative scans have brought attention to some technical points. First, cystic lesions may not be visualized with ^{131}I MIBG. Second, lesions that cannot be seen with ^{131}I MIBG may be visualized with ^{123}I MIBG since a larger dose may be given. The short half-life and greater cost of ^{123}I as compared to ^{131}I make its routine use impractical. In difficult cases, however, it may prove to be the more sensitive agent.

Although 90% of adrenal pheochromocytomas may be visualized using CT scanning, this is not the case with extra-adrenal and metastatic lesions.

The success of ^{131}I MIBG in localizing lesions not found by computed tomography proves it the better agent when metastatic lesions, small lesions, or extra-adrenal lesions are suspected. Pheochromocytomas as small as 0.5 cm in diameter have been visualized [2].

The extremely high incidence of malignancy in this series of patients reflects the selectivity of patient referrals with malignant or occult pheochromocytomas because of the availability of MIBG as a scanning agent. There was a surprisingly high incidence of malignant extra-adrenal tumors found in this series (18 of 44 primary tumors). In most series, such tumors comprised no more than 10%. In a few cases, malignancy was first determined because of the extra-adrenal uptake of ^{131}I MIBG in locations where chromaffin tissue should not normally be present. These lesions might have remained undetected for long periods of time without the use of this scanning agent.

The number of patients thus far treated with ^{131}I MIBG for unresectable and metastatic lesions is small but the results are promising. To date, surgical ablation is the mainstay of treatment. Chemotherapeutic agents and radiation therapy have not been successful in arresting metastatic disease [8, 9]. Until now, treatment of metastases that were not surgically resectable has been palliative. Alphamethyl tyrosine, phenoxybenzamine, and in some cases beta adrenergic blocking drugs have been used. ^{131}I MIBG is not blocked by phenoxybenzamine. Consequently, patients may continue this drug during treatment with ^{131}I MIBG.

In conclusion, ^{131}I MIBG scintigraphy is a safe, noninvasive diagnostic and therapeutic advance in the management of pheochromocytoma. It supplants other scintigraphic techniques for localization of pheochromocytomas and augments data obtained from computed tomography and angiography by providing functional as well as anatomic information.

Résumé

De juin 1980 à août 1983, 353 malades suspects d'être porteurs de phéochromocytomes ont été soumis à la scintigraphie à l'iode marqué: I^{131} métaiodobenzylguanidine (I^{131} MIBG). Des phéochromocytomes extra-surrénaliens ont été découverts chez 15 des 18 sujets suspects d'être porteurs de telles lésions extra-surrénaliennes, ce qui fut constaté lors de l'intervention qui démontra que les surrénales étaient normales. Les autres méthodes conventionnelles n'avaient pas permis de localiser ces tumeurs dans la majorité des cas. Neuf des phéochromocytomes extra-surrénaliens furent découverts dans la partie moyenne du médiastin. Ce groupe de tumeurs implique la mise en oeuvre de techniques particulières en plus du scanner pour localiser la tumeur. Ces explorations complémentaires permettent de planifier l'intervention chirurgicale qui peut nécessiter l'emploi d'une circulation extra-corporelle. Des phéochromocytomes extra-surrénaliens ont été découverts dans une famille qui ne présentait pas d'autres endocrinopathies. Les tumeurs chez 3 malades appartenant à 3 générations différentes siégeaient hors de la surrénale et intéressaient la veine cave.

La scintigraphie à l'I^{131} marqué a permis de découvrir des métastases chez 40 malades porteurs d'un phéochromocytome malin, mais fut en défaut dans 4 cas. Le diagnostic de phéochromocytome malin avec métastase fut porté initialement chez 5 malades. La scintigraphie ne se solda par aucun faux positif mais 10,5% de faux négatifs furent constatés chez 95 malades où la présence d'un phéochromocytome fut prouvée par les données biologiques ou opératoires.

Dix malades atteints de phéochromocytomes

malins ont été traités par l'I^{131} marqué. Cinq d'entre eux accusèrent une diminution de volume de la tumeur et des métastases et une diminution de la sécrétion des catécholamines. L'iode marqué: I^{131} méta-iodobenzylguanidine permet de déceler les phéochromocytomes qui échappent aux autres explorations. Le fait qu'il s'accumule électivement au niveau de la tumeur permet de penser qu'il pourra jouer un rôle actif dans le traitement de l'affection.

Resumen

El diagnóstico de feocromocitoma con frecuencia es más simple que establecer la localización anatómica del tumor, lo cual es difícil, especialmente cuando el feocromocitoma es maligno, extra-adrenal o bilateral. Aproximadamente el 10% de los feocromocitomas se origina en tejido cromafino ubicado en algún lugar entre la base del cráneo y la vejiga. La tomografía computadorizada de tercera generación es extremadamente precisa en la localización de lesiones intra-adrenales, pero no es muy útil en la identificación de feocromocitomas extra-adrenaleso metastásicos. Hasta muy recientemente no existía modalidad alguna capaz de proveer documentación anatómica y funcional del tumor con anterioridad a la intervención quirúrgica. La síntesis de la I^{131} metayodo-benzilguanidina (I^{131} MIBG) ha hecho posible obtener imágenes scintigráficas de feocromocitomas y de tejido cromafino hiperplásico.

Entre junio de 1980 y agosto de 1983, scintigramas con I^{131} MIBG fueron realizados en 353 pacientes con sospecha de feocromocitoma. Se identificaron feocromocitomas extra-adrenales en 15 de 18 pacientes quienes ulteriormente demonstraron tener tales tumores, con glándulas suprarrenales normales. Los estudios convencionales de localización, con frecuencia realizados en forma repetida habían fallado en casi todos los casos. Nueve de los feocromocitomas extra-adrenales fueron hallados en el mediastino medio. Este grupo especial de tumores requirió estudios de localización adicionales con tomografía computadorizada aumentada para el logro de la delineación anatómica específica. Tales estudios complementarios hicieron posible la planeación precisa de la excisión quirúrgica, la cual necesitó circulación extracorpórea en algunos casos. Feocromocitomas extra-adrenales fueron identificados en una familia, la cual no exhibió otras endocrinopatías. Los tumores en 3 pacientes provenientes de 3 generaciones diferentes fueron todos de ubicación peri-renal con compromiso de la vena cava.

Los estudios con I^{131} MIBG detectaron lesiones metastásicas en 40 pacientes con feocromocitomas malignos. En sólo 4 pacientes las metástasis no pudieron ser fácilmente demostradas. El diagnóstico de feocromocitoma maligno y metastásico fue hecho en forma primaria por la scintigrafía en 5 pacientes. Los scintigramas con I^{131} MIBG no han dado resultados positivos falsos, en caso alguno, y han dado resultados negativos falsos en 10,5% de 95 pacientes con feocromocitoma comprobado por evidencia bioquímica o por operación.

Diez pacientes han sido tratados para feocromocitoma maligno con dosis terapéuticas de I^{131} MIBG. Cinco pacientes han manifestado respuesta objetiva con reducción del tamaño de las metástasis o del tumor primario maligno con disminución en la secreción de catecolaminas.

Este agente ha demostrado ser de gran valor en la detección de feocromocitomas que han desafiado todos los otros métodos de localización. La I^{131} MIBG se concentra en la mayoría de los feocromocitomas malignos, y los resultados preliminares sugieren que habrá de ser de gran utilidad en el tratamiento de esta enfermedad.

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Invited Commentary

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The use of ^{131}I metaiodobenzylguanidine (^{131}I MIBG) in the localization and management of pheochromocytoma represents a major advance in the treatment of this disease. The preliminary results were presented in 1980 as a result of a long-term search for a suitable radiopharmaceutical agent. Since then a large clinical experience has been evaluated. To have studies on 95 patients with proven pheochromocytomas as well as 40 patients with malignant pheochromocytoma within a 3-year period is outstanding for one institution and will probably never be repeated. This fortunate opportunity to evaluate the method is unique. The results presented make it quite clear that this method for localization of pheochromocytoma and for treatment of metastatic disease will be widely used in most centers of endocrine surgery. Particularly, the treatment of malignant disease is of great importance since other modalities apart from radical surgery have shown a low degree of efficacy.

The place for ^{131}I MIBG scan in the routine treatment of pheochromocytoma has still to be ascertained. The diagnosis of pheochromocytoma is primarily biochemical and, with the combination of a positive biochemical diagnosis and computed tomography showing an adrenal tumor, most of us proceed with surgical intervention. However, since roughly 10% of the lesions are extra-adrenal, a long transverse upper abdominal incision is mandatory. This approach gives access to both adrenals and permits exploration of the para-aortic regions and the perihilar renal zones as well.

I have found the anterior approach hazardous in a few adequately blocked patients with right-sided adrenal pheochromocytoma and, therefore, I subsequently preferred a posterolumbar incision. ^{131}I MIBG scans offer a distinct advantage in this connection. In patients in whom the scan excludes multiple tumors, this surgical approach can be performed with better exposure of the adrenal, allowing a meticulous dissection and early ligation of larger veins—important details when handling these capricious neoplasms.