

9-1989

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Luigi Troncone

Vittoria Rufini

Giovina De Rosa

Amerigo Testa

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### Recommended Citation

Troncone, Luigi; Rufini, Vittoria; De Rosa, Giovina; and Testa, Amerigo (1989) "Diagnostic and Therapeutic Potential of New Radiopharmaceutical Agents in Medullary Thyroid Carcinoma," *Henry Ford Hospital Medical Journal* : Vol. 37 : No. 3 , 178-184.

Available at: <https://scholarlycommons.henryford.com/hfhmedjournal/vol37/iss3/28>

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# Diagnostic and Therapeutic Potential of New Radiopharmaceutical Agents in Medullary Thyroid Carcinoma

Luigi Troncone,\* Vittoria Rufini,\* Giovina De Rosa,† and Amerigo Testa†

*Recently developed radiopharmaceuticals have been proposed for imaging medullary thyroid carcinoma (MTC) with some having therapeutic potential. This study compares the imaging results obtained with radioiodinated meta-iodo-benzylguanidine (MIBG), <sup>99m</sup>Tc (V) DMSA, and <sup>131</sup>I F(ab')<sub>2</sub> anti-carcinoembryonic antigen (anti-CEA) in a group of MTC patients. In 23 patients <sup>131</sup>I MIBG imaging showed a high specificity (no false-positive results) but a less satisfactory sensitivity (50%). In 12 patients <sup>99m</sup>Tc (V) DMSA revealed a better sensitivity (77%) but a lower specificity (three false-positive results). Positive results were obtained in two of three patients studied with <sup>131</sup>I F(ab')<sub>2</sub> anti-CEA. These data suggest that the highly sensitive <sup>99m</sup>Tc (V) DMSA should be considered as a first choice procedure followed by the highly specific radioiodinated MIBG to confirm the initial results. Since radioiodinated MIBG imaging may have therapeutic usefulness, <sup>131</sup>I MIBG was evaluated in an integrated treatment protocol in four cases of proven MTC. The preliminary results obtained were encouraging. (Henry Ford Hosp Med J 1989;37:178-84)*

Medullary thyroid carcinoma (MTC) presents particular diagnostic problems. Detection of local or regional and distant metastases both preoperatively and postoperatively is difficult even when these tumors are known to be present because of elevated levels of calcitonin (CT) and other tumor markers. Recently developed radiopharmaceuticals which selectively concentrate in MTC can allow both the primary and secondary lesions to be scintigraphically imaged and thereby provide obvious advantages in terms of diagnosis and prognosis.

Three radiopharmaceuticals currently of interest are: 1) <sup>123</sup>I/<sup>131</sup>I meta-iodo-benzylguanidine (MIBG), which is specific for tumors originating from the neural crest including MTC (1-7); 2) <sup>99m</sup>Tc (V) DMSA, a new preparation which is able to concentrate in several types of tumors including MTC, even though its mechanism of action is unclear (8-10); and 3) labeled monoclonal antibodies to carcinoembryonic antigen (CEA) which have been utilized because of their highly specific antigen-antibody reactivity and because of the capability of MTC to produce CEA as well as CT (11). Because of the therapeutic potential attributed to <sup>131</sup>I MIBG (6,12,13), this radiopharmaceutical may provide additional advantages for MTC patients. However, because very few patients have had this metabolic treatment, its efficacy is still uncertain (6,14,15). To understand the possible applications of these radiopharmaceuticals in MTC, we compared diagnostic data and report preliminary therapeutic results.

## Materials and Methods

### Diagnostics

Twenty-three patients (ten males and 13 females ranging in age from 17 to 72 years) with proven MTC were studied. Scin-

tigraphic studies were performed in the initial evaluation of MTC (three cases) and/or in the postsurgical follow-up. One case was hereditary without the features of multiple endocrine neoplasia (MEN), three cases were MEN 2B, and 19 cases were sporadic.

All patients underwent the usual imaging modalities (including <sup>131</sup>I thyroid scintigraphy, chest roentgenogram, cervical/thoracic/abdominal computed tomography, bone scan, etc). Serum CT was measured by radioimmunoassay (when necessary after pentagastrin stimulation), and plasma CEA levels were measured by immunoradiometric assay. Clinical data on the patients studied are reported in Table 1.

All patients with proven MTC were studied with radioiodinated MIBG (labeled with <sup>131</sup>I or <sup>123</sup>I). A total of 26 studies were performed; three patients had the examination both before and after total thyroidectomy. Scintigraphy was performed according to the previously described procedure (16,17). A total of 37 MBq of <sup>131</sup>I MIBG was injected intravenously, and whole body images were obtained at 24, 48, and sometimes 72 hours. When <sup>123</sup>I MIBG was used, 148 MBq of the tracer was administered intravenously, and whole body imaging was performed at 4, 24, and sometimes 48 hours. Thyroid uptake was prevented by administration of Lugol's iodine solution (60 mg/day of free iodine for six to eight days beginning two days before tracer injection).

Submitted for publication: October 23, 1989.

Accepted for publication: November 20, 1989.

\*Department of Nuclear Medicine, Università Cattolica del Sacro Cuore, Rome, Italy.

†Department of Endocrinology, Università Cattolica del Sacro Cuore, Rome, Italy.

Address correspondence to Dr. L. Troncone, Istituto di Medicina Nucleare, Università Cattolica del Sacro Cuore, L.go A. Gemelli 8 Rome 00168, Italy.



**Table 1**  
**Data on Patients Including Scintigraphic Results**

Case	Age (years)/Sex	Tumor Markers		Known Lesions	MIBG	Agents	
		CT	CEA			DMSA	anti-CEA
1	17/F	++	++	Primary tumor	TP	—	—
				DM (bone)	FN		
2	32/M	++	++	DM (bone, lung)	TP	—	—
				Primary tumor	FN		
3	63/F	++	++	LN involvement	—	—	—
				Primary tumor	FN		
4	36/M	++	++	LN involvement	FN	—	—
				Residual tumor	FN		
5	39/M	++	++	Local recurrence	TP	—	—
				Rib fractures	TN		
6	64/F	+	+	LN involvement	TP	—	—
				Local recurrence	FN		
7	72/M	++	++	Dental abscesses	TN	—	—
				LN involvement	FN		
8	62/M	++	++	LN involvement	FN	—	—
				Local recurrence	FN		
9	36/M	++	++	Local recurrence	TP	—	—
				DM (bone, lung, liver)	FN		
10	54/M	++	++	Local recurrence	TP	—	—
				DM (bone)	TP		
11	66/F	++	—	DM (bone)	TP	—	—
				DM (lung)	FN		
12	52/M	++	++	Local recurrence	FN	—	—
				DM from breast cancer	FN		
13	68/F	+	++	DM from breast cancer	TN	—	—
				None	FN		
14	60/F	++	—	None	FN	—	—
				None	FN		
15	41/F	+	—	None	TP	—	—
				None	TP		
16	36/F	++	++	None	TP	—	—
				None	TP		
17	32/F	++	+	None	TP	—	—
				None	TP		
18	19/M	++	++	None	FN	—	—
				None	FN		
19	58/F	+	—	None	FN	—	—
				None	FN		
20	20/F	—	—	None	TN	—	—
				None	TN		
21	65/M	—	—	None	TN	—	—
				None	TN		
22	62/F	—	—	None	TN	—	—
				None	TN		
23	52/F	—	—	None	TN	—	—
				None	TN		

Note: "++" indicates highly elevated levels, "+" indicates moderately elevated levels, "-" indicates normal levels, DM = distant metastases, LN = lymph node, TP = true positive, TN = true negative, FP = false-positive, and FN = false-negative.

All data were obtained after total thyroidectomy except for cases 1, 2, 3, and 4. For cases 1, 2, and 3, data were obtained presurgery and after total thyroidectomy. For case 4, data were obtained after hemithyroidectomy and total thyroidectomy.

All cases were sporadic except cases 1, 2, and 18 which were MEN 2B and case 20 which was hereditary MTC.

In 12 patients (two MEN 2B and ten sporadic) <sup>99m</sup>Tc (V) DMSA whole body scintigraphy was carried out two to three hours after intravenous injection of 370 MBq of the tracer. A total of 13 studies were performed; one patient was studied both before and after surgery. In three patients (one MEN 2B and two sporadic) <sup>131</sup>I F(ab')<sub>2</sub> anti-CEA whole body scintigraphy was performed 72 and 96 hours after intravenous injection of 111 MBq of the tracer.

### Therapy

Four patients (three males and one female, aged 36 to 66 years) were treated with high specific activity <sup>131</sup>I MIBG (> 1.11 GBq/mg) (Table 2). The therapeutic procedure followed that for the treatment of pheochromocytomas proposed by the University of Michigan Medical Center group (12). Single doses varying from 3.7 to 8.5 GBq were administered by slow intravenous infusion (90 to 100 minutes) at two- to four-month intervals. Patients were isolated for four to five days and subjected to electrocardiographic and blood pressure monitoring during the infu-

sion. Dosimetric estimates were performed according to the methods of Sisson et al (12) and Shulkin et al (18). Two patients had had an ablative dose of <sup>131</sup>I after thyroidectomy, and in two cases external radiotherapy had also been carried out.

## Results

### Diagnostics

The scintigraphic results obtained with <sup>131</sup>I MIBG are summarized in Table 3. Radioiodinated MIBG scintigraphy was correctly negative in four cases with normal tumor markers and negative results from conventional diagnostic modalities. Tumor uptake was found in six of 13 patients (eight of 16 studies positive) who had high levels of CT and clinical and/or radiologic evidence of disease (Fig 1).

In one of the three cases of MEN 2B (case 1, Table 1), the primary tumor as well as, postoperatively, the lung and bone metastases were detected. The other two cases had negative results: one patient (case 2, Table 1) had clinically evident lesions (pri-

**Table 2**  
**Data on Patients Requiring Integrated Treatment Including <sup>131</sup>I MIBG**

Case (Age/Sex)	Pathology Previous Therapy	Clinical Status	Treatment Performed	<sup>131</sup> I MIBG Courses/GBq (Gy)	Follow-up (months)
5 (39/M)	MTC + papillary cancer (1971) Thyroidectomy Lymphadenectomy <sup>131</sup> I ablative dose	Recurrence after 15 years	Lymphadenectomy External radiotherapy <sup>131</sup> I MIBG	2/13.3 (20)	23
Outcome: Complete response, markers normalized.					
4 (36/M)	MTC + papillary cancer (1986) Thyroidectomy Lymphadenectomy	Residual/local recurrence	<sup>131</sup> I ablative dose <sup>131</sup> I MIBG Mediastinal lymphadenectomy	2/15.9 (46)	26
Outcome: Partial response, markers still elevated.					
10 (54/M)	MTC (1979) Thyroidectomy Local recurrence & distant metastases External radiotherapy to the sacrum Chemotherapy	Local recurrence Distant metastases	<sup>131</sup> I MIBG <sup>131</sup> I ablative dose	6/32.9 (50 to neck) (56 to sacrum)	27
Outcome: Partial response on neck lesions, arrest in growth of remote metastases.					
11 (66/F)	MTC (1987) Thyroidectomy Distant metastases	Multiple bone metastases	<sup>131</sup> I MIBG External radiotherapy to the ilium	2/8.7 (15)	9
Outcome: No change. Relief of pain. Died from progression of disease.					

**Table 3**  
<sup>123/131</sup>I MIBG Imaging Outcome in MTC

Number of Cases	Calcitonin	Clinical Status	MIBG Positive
4	Normal	No evidence of disease	0
13	Elevated	Primary tumor	1/3*
		Recurrent tumor: local	5/10†‡
		distant	3/6§
6	Elevated	No evidence of disease	3/6

\*In one case distant metastases were also present.

†In two cases distant metastases were also present.

‡Two cases were studied twice (before and after total thyroidectomy).

§One case was studied twice (before and after total thyroidectomy).

||Not all the tumor sites were visualized.

mary tumor and lymph node involvement), and the other patient (case 18, Table 1) had high levels of CT but no clinically evident lesions. Although the former patient's primary MTC did not image, MIBG scintigraphy visualized bilateral adrenal pheochromocytomas. MIBG scintigraphy detected small residual lesions in three of six patients with abnormal levels of CT (CEA was elevated in three patients) who had no evidence of disease by conventional imaging (Fig 2).

The overall sensitivity of the method was estimated to be 50% (11 of 22 studies positive).

The scintigraphic results obtained with <sup>99m</sup>Tc (V) DMSA are summarized in Table 4. High uptake of <sup>99m</sup>Tc (V) DMSA was shown in most of the MTC sites in nine of 12 patients (ten of 13 studies positive) who had high CT levels. Lesions were detected in known tumor sites of seven of eight patients (eight of nine studies positive) and in two of four patients with high CT levels but no clinical or radiologic evidence of disease. In one of two MEN 2B cases the outcome of <sup>99m</sup>Tc (V) DMSA scintigraphy was positive. The primary tumor not previously imaged by radioiodinated MIBG was correctly identified (case 2, Table 1) (Fig 3). The other patient (case 18, Table 1) had high levels of CT but no detectable tumor.

The overall sensitivity of the method was 77%. Abnormal <sup>99m</sup>Tc (V) DMSA uptake was also seen in rib fractures (case 4), dental abscesses (case 6) (Fig 4), and bone metastases from breast carcinoma (case 13).

<sup>131</sup>I F(ab')<sub>2</sub> anti-CEA scintigraphy was correctly positive in two of three cases (one MEN 2B). The method was not able to identify the lateral cervical lymph node involvement in the third case.

A comparative analysis of the scintigraphic results obtained with the three radiopharmaceuticals is shown in Table 1. In three



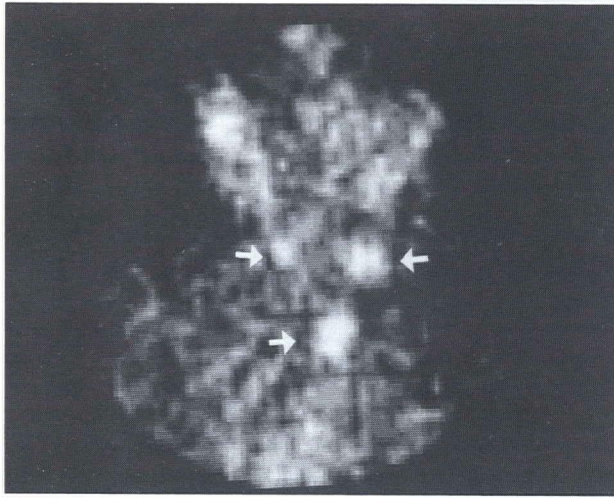


Fig 1—<sup>131</sup>I MIBG scan after total thyroidectomy in case 4 (Table 1), presenting high levels of CT and CEA. Anterior view of the neck (48 hrs after injection) shows multiple foci of abnormal <sup>131</sup>I MIBG uptake, corresponding to local recurrent tumor (arrows).

cases all three scintigraphic procedures were performed: in one patient (case 10) all tests were positive (Fig 5), in another patient (case 2) <sup>99m</sup>Tc (V) DMSA and <sup>131</sup>I F(ab')<sub>2</sub> were positive but <sup>131</sup>I MIBG was negative, and in the patient (case 8) with palpable lateral cervical lymph nodes all tests were negative. In nine cases only <sup>99m</sup>Tc (V) DMSA and radioiodinated MIBG procedures were performed: both tests were positive in four cases, <sup>123/131</sup>I MIBG was negative but a high uptake of <sup>99m</sup>Tc (V) DMSA in the tumors was observed in three cases, <sup>123</sup>I MIBG detected a local residual tumor not visualized by <sup>99m</sup>Tc (V) DMSA scintigraphy in one case, and both <sup>131</sup>I MIBG and <sup>99m</sup>Tc (V) DMSA were negative in one patient who had elevated CT levels and no evidence of disease.

### Therapy

In four cases <sup>131</sup>I MIBG was included in an integrated treatment protocol of MTC. The treatments and outcomes are reported in Table 2.

A complete regression of the local recurrent tumor was obtained in one patient (case 5, Table 2) who underwent an integrated treatment which included surgery (cervical lymphadenectomy), external radiotherapy (60 Gy), and <sup>131</sup>I MIBG therapy (13.3 GBq, estimated dose 20 Gy). In this case <sup>131</sup>I MIBG played an important role in destroying the recurrent tumor (according to radiologic and scintigraphic techniques and CT and CEA levels).

In another patient (case 4, Table 2), <sup>131</sup>I MIBG therapy (15.9 GBq, estimated dose 46 Gy) was apparently effective in reducing by about 50% the residual tumor visualized by computed tomography and scintigraphy. A continuing decrease of CT and CEA levels was observed in this case, even though these levels remained above normal.

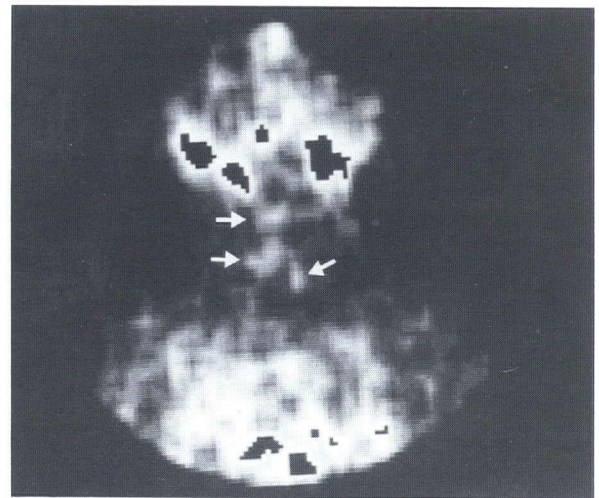


Fig 2—<sup>131</sup>I MIBG scan after total thyroidectomy in case 15 (Table 1) with no clinical or radiologic evidence of disease but persistent elevation of CT. Anterior view of the neck (48 hrs after injection) shows abnormal minimal foci of <sup>131</sup>I MIBG uptake (arrows).

Table 4  
<sup>99m</sup>Tc (V) DMSA Imaging Outcome in MTC

Number of Cases	Calcitonin	Clinical Status	DMSA Positive
8	Elevated	Primary tumor	1/1
		Recurrent tumor: local	7/8*†
		distant	1/1
4	Elevated	No evidence of disease	2/4

\*In one case distant metastases were also present.

†One case studied twice.

The other two patients (cases 10 and 11, Table 2) were in a very advanced stage with widespread bony metastases. In one patient (case 10), after a total dose of 32.9 GBq (estimated dose 50 Gy to the neck and 56 Gy to the sacral lesion) given in six courses, a partial response with marked regression of the cervical lesions and arrest of growth of the bony metastases occurred. Subjective improvement with relief of diarrhea and pain was noted. In this case an ablative dose of <sup>131</sup>I had been given. The treatment program did not decrease tumor marker levels.

In the other patient (case 11) with widespread bony metastases, it was possible to administer a total dose of only 8.7 GBq (estimated dose 15 Gy). The patient had a significant though temporary relief of pain but showed no objective response and died of rapidly progressive disease nine months after therapy was initiated. No adverse reactions were noted in any of the cases treated with <sup>131</sup>I MIBG except for a reversible thrombocytopenia in case 10.

### Discussion

The diagnosis and follow-up of patients with MTC depend mainly on the determination of CT (basal and/or pentagastrin-



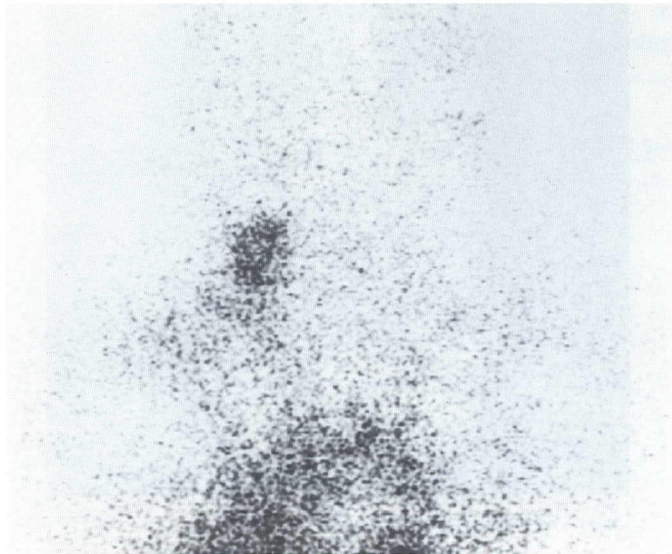


Fig 3— $^{99m}\text{Tc}$  (V) DMSA scan at diagnosis in case 2 (Table 1), MEN 2B. Anterior view of the neck shows an area of abnormally increased uptake corresponding to the nodule in the right thyroid lobe.

stimulated) and CEA levels and on the use of various imaging modalities which have a high spatial resolution but a low specificity for this tumor.

The diagnostic value of tumor markers, especially CT, has been further confirmed by our data. All patients with normal levels of both CT and CEA exhibited no evidence of disease by radiologic and scintigraphic investigations. Diagnostic problems arose in cases with high levels of CT and occasionally of CEA. In several of these cases the detection of tumor sites was difficult or inconclusive. This difficulty in detection of tumor sites, well known in clinical practice and reported in the literature (19), is usually attributed to the limitations in spatial resolution of current imaging techniques.

Recently introduced radiopharmaceuticals which have been demonstrated to concentrate selectively in MTC provide new possibilities for localization of residual MTC as well as therapeutic possibilities. Radioiodinated MIBG has been shown to have a high specificity in detecting MTC as well as other tumors in which it has been applied (2,4). No false-positive results were recorded: all patients with normal CT levels had negative MIBG scans. The diagnostic effectiveness remains controversial although the sensitivity in our series was better than that reported by some authors (20-23). Sensitivity appears to be greater for primary or residual/recurrent tumor than for metastatic lesions. The heterogeneity of MIBG uptake within and between patients seems to limit the utility of MIBG scintigraphy, but in some cases (three in our series) residual tumor not otherwise identifiable could be detected. Furthermore,  $^{131}\text{I}$  MIBG may provide an alternative treatment for patients who show uptake of the tracer in tumors.

$^{99m}\text{Tc}$  (V) DMSA gave better diagnostic results. It exhibited a higher sensitivity (77%) in the detection of local recurrent tu-

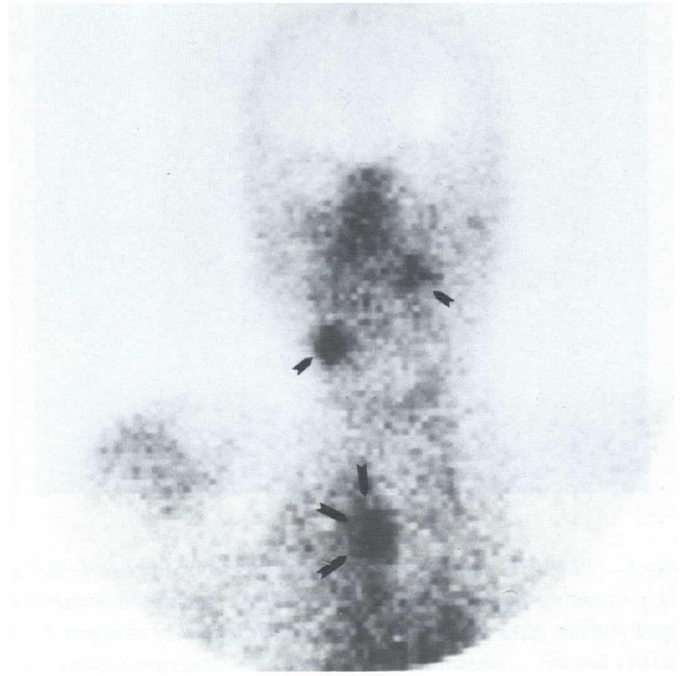


Fig 4— $^{99m}\text{Tc}$  (V) DMSA scan after total thyroidectomy in case 6 (Table 1) with high levels of CT and CEA. Anterior view of head and neck shows a round area of abnormal uptake in the suprasternal notch region (large arrows), corresponding to a local recurrent tumor (subsequently confirmed by surgery). Two additional areas of abnormal uptake were seen in the left upper jaw and in the right lower jaw corresponding to dental abscesses (small arrows).

mor, giving a positive outcome in four patients who had negative MIBG scans. Moreover,  $^{99m}\text{Tc}$  (V) DMSA has the advantages of low cost, availability, high-quality images, single photon emission computed tomography feasibility, and low radiation burden to the patient. Its limits include the complexity of the radiopharmaceutical preparation (22) and the problem of false-positive results. High uptake of  $^{99m}\text{Tc}$  (V) DMSA was observed in three patients who had lesions not related to MTC. This finding, on the basis of the most recent acquisitions (24), was in some way expected even though contradictory to the initial experience reported with this agent (23,25).

The use of monoclonal antibodies to CEA (or fragments) in MTC is based on the high specificity of the immunologic reaction and on the biologic characteristics of MTC which can produce CEA as well as CT (11). Our preliminary results with  $\text{F(ab')}_2$  anti-CEA labeled with  $^{131}\text{I}$  are promising. In two of three patients with high levels of CT, a significant uptake of the radiocompound was observed. The negative outcome was questionable because even  $^{131}\text{I}$  MIBG and  $^{99m}\text{Tc}$  (V) DMSA scintigraphy gave negative results despite clinically evident disease. The high specificity of radiolabeled monoclonal antibodies, together with its therapeutic potential, make this an attractive agent in the management of patients with MTC. Further studies are in prog-



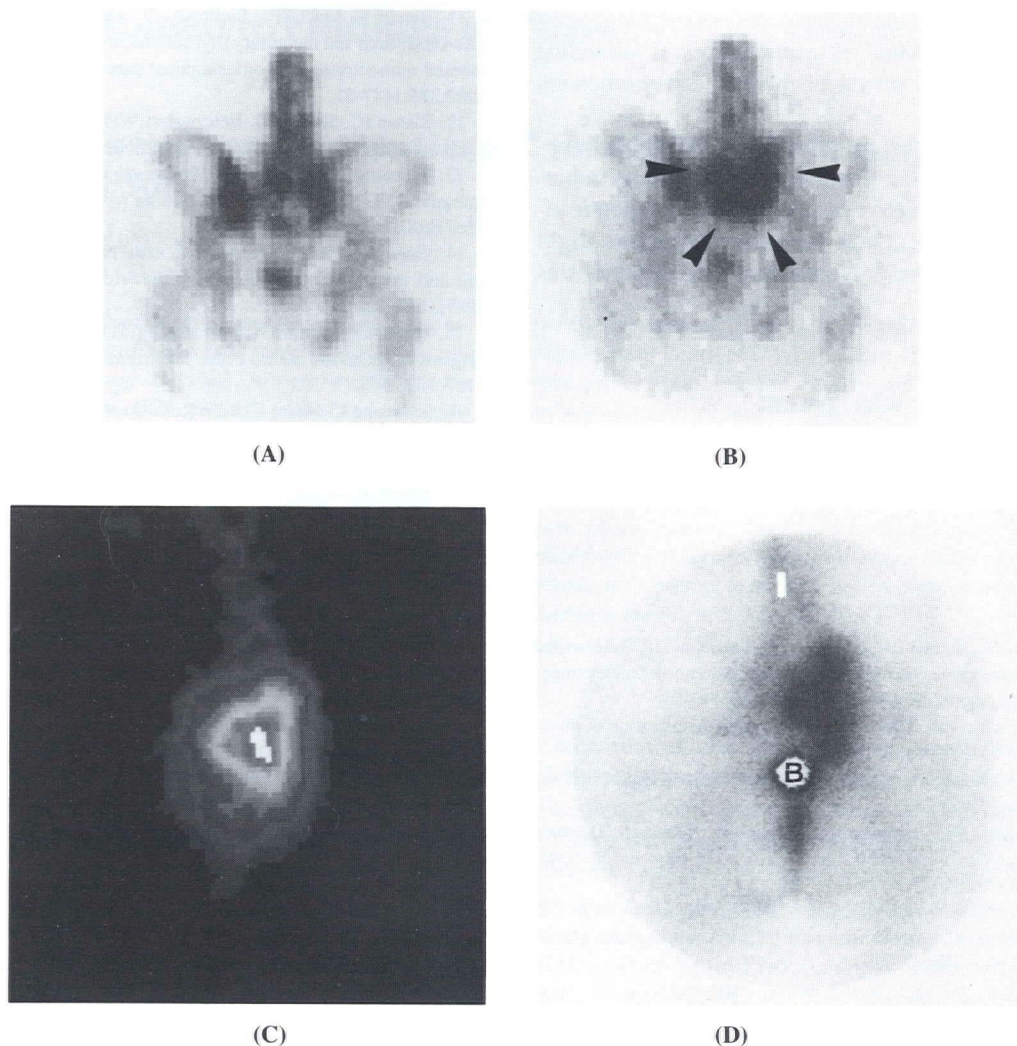


Fig 5—Case 10 (Table 1) (sporadic MTC) after total thyroidectomy. Posterior view of the pelvis. Bone scintigraphy (A) showing a large photopenic area in the sacrum, corresponding to a voluminous bone deposit. The lesion is well imaged by  $^{131}\text{I}$  MIBG (B) (here superimposed to bone scan) as well as by  $^{131}\text{I}$   $\text{F}(\text{ab}')_2$  (C) and  $^{99\text{m}}\text{Tc}$  (V) DMSA (D) (I = iliac vessels; B = bladder).

ress to establish the diagnostic and therapeutic value of this procedure.

The favorable results obtained with these new radiopharmaceuticals suggest a new diagnostic approach in the detection and follow-up of MTC:

1. Due to its relatively high sensitivity and previously mentioned advantages,  $^{99\text{m}}\text{Tc}$  (V) DMSA should be performed as a first choice examination. However, the problem of possible false-positive results cannot be overlooked.

2.  $^{123/131}\text{I}$  MIBG imaging, even though less sensitive, is more specific. It can be used to confirm the results obtained with  $^{99\text{m}}\text{Tc}$  (V) DMSA. Moreover, a positive scan may provide treatment possibilities.

The therapeutic potential of  $^{131}\text{I}$  MIBG has been proposed since its first diagnostic application in MTC. However, only a few cases have been treated with this radiopharmaceutical (6,14,15). The preliminary data from our previously published

four cases (15,26,27) suggest that  $^{131}\text{I}$  MIBG therapy may be useful for MTC patients (Table 2).  $^{131}\text{I}$  MIBG treatment provided further therapeutic options in two patients who otherwise would have had no other therapy available, and, as a complement to conventional treatment, resulted in a regression of local recurrences in the other two cases (complete regression in one patient and partial regression in the other patient who is still in a treatment program).

While these preliminary results are encouraging, only a small number of patients were studied and evaluation of such combination programs without a longer follow-up period is difficult. The data collected confirm the need for early and appropriate surgery to avoid residual or recurrent tumors which require further treatment. The use of complementary radiotherapy alone remains controversial. After a long-term follow-up, radiotherapy was not able to prevent late recurrences in at least one of the cases reported. An integrated treatment which includes  $^{131}\text{I}$



MIBG may be of greater benefit. Favorable results were obtained in two cases with residual/recurrent tumors. Radioiodine therapy may help make the treatment more effective when residual MTC is present.

In advanced cases with distant metastases,  $^{131}\text{I}$  MIBG represents the only treatment available and has provided some important subjective and even objective responses. For therapeutic effect very high doses of the agent were necessary, but slight hematologic toxicity was the only observed side effect of this approach.

### Acknowledgment

This work was supported by a grant of the National Research Council, Special Project "Oncology," contract number 88.00909.44.

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