

A Scintigraphic Comparison of Iodine-123-Metaiodobenzylguanidine and an Iodine-Labeled Somatostatin Analog (Tyr-3-Octreotide) in Metastatic Carcinoid Tumors

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A number of neoplasms are known to express somatostatin receptors, and the use of somatostatin receptor imaging in their localization has recently been described. We compared an ^{123}I -labeled somatostatin analog Tyr-3-octreotide (TOCT) and ^{123}I -labeled metaiodobenzylguanidine (MIBG) scintigraphy in seven patients with histologically proven metastatic carcinoid tumors. The optimum time for identifying tumor uptake on scanning after [^{123}I]MIBG was 24–48 hr, and after ^{123}I -TOCT 10–30 min postinjection. Both radiopharmaceuticals showed a varying spectrum of tracer uptake ([^{123}I]MIBG showed no uptake in one patient; minimal in two; moderate in two; and intense in two; ^{123}I -TOCT showed no uptake in two patients; minimal uptake in one; moderate uptake in two; and intense uptake in two). In two patients, ^{123}I -TOCT identified metastatic lesions not seen by [^{123}I]MIBG scintigraphy. These preliminary results suggest that [^{123}I]MIBG and ^{123}I -TOCT are useful and complementary imaging techniques for detecting metastatic carcinoid tumors.

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Carcinoid tumors are slow growing neoplasms of enterochromaffin cells. The tendency for these tumors to metastasize to the liver and the subsequent hepatic failure are well recognized. The diversity of the biologically-active substances produced by these tumors and their clinical manifestations have always posed a diagnostic and therapeutic challenge.

Isotopic scanning techniques have tried to address the problems encountered in the localization and therapy of this disease principally by the use of radiolabeled metaiodobenzylguanidine (MIBG) (1–4). However, the accuracy of localization is not great (1–3), and attempts at using [^{131}I]MIBG therapy have produced variable results (5,6). This has prompted further search for suitable radiophar-

maceuticals. It is known that carcinoid tumor tissue frequently possesses binding sites for somatostatin and therapy with a somatostatin analog (octreotide) may control symptoms (7). Therefore an analog of octreotide, which was successfully radiolabeled, has been used for imaging carcinoid and other endocrine tumors (8,9). In this study, we describe a scintigraphic comparison between ^{123}I -labeled MIBG and the ^{123}I -labeled somatostatin analog Tyr-3-octreotide (TOCT) for imaging in a small group of carcinoid tumors.

MATERIALS AND METHODS

Patients

Seven patients with known metastatic carcinoid tumor were included in a study that had been approved by the City and Hackney District Research Ethics Committee. All subjects had had their primary tumor resected previously and had histologically confirmed metastatic disease and active disease at the time of the study, despite chemotherapy with CCNU and 5FU. The spread of the disease was verified by CT scanning and ultrasonography.

Iodine-123-MIBG and ^{123}I -TOCT scans were performed on all patients 1 wk apart. Prior to scintigraphy with [^{123}I]MIBG, a drug history was obtained to exclude any interfering medication (10). All subjects were taken off octreotide therapy for at least a week prior to ^{123}I -TOCT scintigraphy. Before each study, 120 mg/day of potassium iodide were administered orally, starting 24 hr prior to scintigraphy and continued up to 48 hr postinjection in order to block thyroid uptake of any free ^{123}I . The scans were assessed independently without knowledge of the results from other imaging modalities by two nuclear medicine clinicians (J.B., K.E.B.).

Radiolabeling

Iodine-123-MIBG was obtained from a commercial source (Amersham International plc, UK). Tyr-3-octreotide (500 $\mu\text{g}/\text{ml}$ in sodium acetate buffer pH 4.3) was obtained from Sandoz (Basel, Switzerland). For radiolabeling, approximately 370 MBq (10 mCi) of sodium (^{123}I) iodide in 0.01 M NaOH (Medgenix, Fleurus, Belgium) and 5 μl of a solution of potassium iodide (5 mg in 100 ml of water) were added to 50 μg of the peptide. The mixture was divided between two iodogen tubes (11) and incubated at room temperature for 30 min. The labeled material was

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TABLE 1
Clinical and Scintigraphic Results for [¹²⁵I]MIBG and ¹²³I-TOCT

Patient no.	Age	Sex	Primary tumor site	Urinary 5-HIAA levels in μ mols/24 hr	[¹²⁵ I]MIBG scans	¹²³ I-TOCT scans
1	70	M	Ileum	160	Grade 3	Grade 3
2	62	F	Ileum	1140	Grade 3	Grade 2
3	64	F	Bronchus	41	Grade 0	Grade 0
4	66	F	Pancreas	120	Grade 1	Grade 1
5	50	M	Ileum	248	Grade 1	Grade 0
6	51	F	Ileum	184	Grade 2	Grade 2
7	68	F	Pancreas	68	Grade 2	Grade 3

Normal range 16–73.

HIAA = Hydroxyindoleacetic acid; Grade 0 = no persistent uptake; Grade 1 = minimal, persistent, detectable uptake; Grade 2 = moderate, persistent uptake (equal to that in liver); and Grade 3 = intense, persistent uptake (greater than that in liver).

purified by passing it down a sterile ion exchange column (Dowex 1X8) prepared by the addition of 0.5 ml autoclaved Dowex resin to a 2-ml hypodermic syringe packed with a sterile gauze dressing. The column was washed before use and the radiolabeled peptide eluted with sterile 0.9% sodium chloride acidified to pH 5 by the addition of dilute hydrochloric acid before filtration through a 0.22- μ m filter (Millipore, Milford, MA). Labeling efficiency and radiochemical purity were checked before and after purification by reverse-phase HPLC radiochromatography on ODS with 40%–80% methanol in 0.9% sodium chloride solution (12). Labeling efficiency was typically 60%–70%. Final radiochemical purity was 90% monoiodinated Tyr-3-octreotide with less than 5% free iodide.

Imaging Protocol

Between 130–185 MBq of [¹²³I]MIBG were injected intravenously over 30 sec. Four hundred thousand count images were acquired for skull, chest and abdomen in anterior and posterior

projections at 10 min, 22 hr, and 48 hr post injection with a large field of view gamma camera with a high-resolution collimeter.

Scintigraphy with ¹²³I-TOCT was performed approximately a week after the [¹²³I]MIBG study. Fifty micrograms of TOCT labeled with 74–185 MBq (2–5 mCi) of ¹²³I were injected slowly over 60 sec. Images were acquired with the same equipment and a similar protocol to [¹²³I]MIBG, but imaging times were at 10–30 min, 2 hr, 4 hr and 24 hr postinjection.

Data Analysis

Imaging results of the two modalities were compared. All patients were classified with respect to their [¹²³I]MIBG and ¹²³I-TOCT uptake intensity using the following four grades: grade 0 = no persistent uptake; grade 1 = minimal, persistent, detectable uptake; grade 2 = moderate, persistent uptake (equal to that in liver); grade 3 = intense, persistent uptake (greater than that in liver). In all subjects the calculation of a tumor-to-background (T/Bkgd) ratio was attempted using appropriate regions of interest. In patients with liver metastases, a background region was identified over the ipsilateral lower lung field.

RESULTS

No side effects were observed in response to intravenous injections of either [¹²³I]MIBG or ¹²³I-TOCT. The clinical and scintigraphic details are summarized in Table 1. Both radiopharmaceuticals identified carcinoid tumor metastases (Figs. 1 and 2). The highest T/Bkgd ratio for [¹²³I]MIBG was 4.33, which was detected between 24–48 hr. For ¹²³I-TOCT, the highest T/Bkgd ratio was 4.10, which was seen between 10 and 30 min. In all patients imaged with ¹²³I-TOCT, biliary activity was seen from 10–30 min onwards, which subsequently emptied into the gut. There was no correlation between urinary 5-HIAA levels and uptake values for either [¹²³I]MIBG or ¹²³I-TOCT.

A total of five extrahepatic lesions were identified in these patients by both [¹²³I]MIBG and ¹²³I-TOCT. An

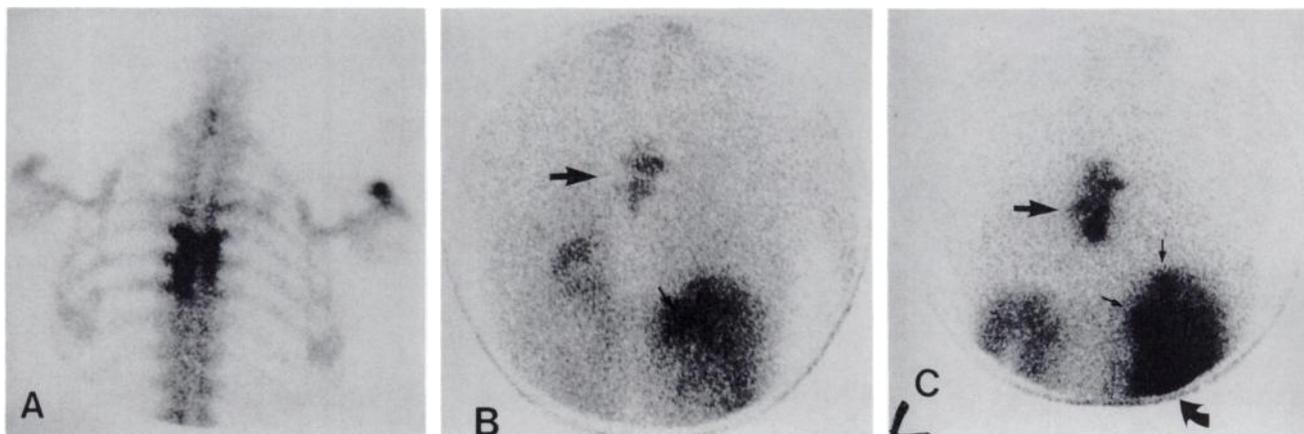


FIGURE 1. Patient 1, posterior chest views. Arrows indicate metastatic sites. (A) A ^{99m}Tc-MDP bone scan that shows uptake in the thoracic vertebrae, T5-7. Uptake is also observed in the right shoulder joint, which is degenerative in origin. (B) Iodine-123-MIBG scan (dose 170 MBq), posterior chest view, 22-hr postinjection shows intense uptake in the corresponding thoracic vertebrae (large arrow) and liver (small arrow) (Grade 3). (C) Iodine-123-TOCT scan (dose 74 MBq), posterior chest view, 4 hr postinjection, shows uptake at the corresponding sites in the thoracic spine (large arrow), which is more prominent than the [¹²³I]MIBG uptake on the corresponding image. Two lesions are seen in the liver (small arrows) (Grade 3). Tracer activity is also seen in the gall bladder (curved arrow).

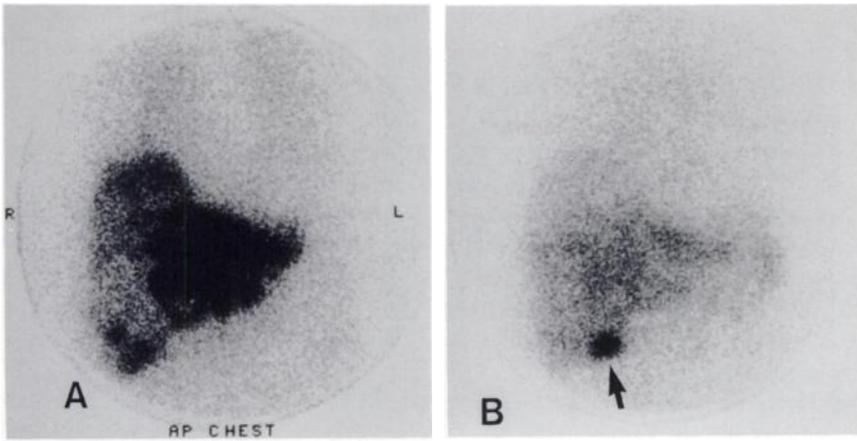


FIGURE 2. Patient 2, anterior view. (A) Iodine-123-MIBG scan (dose 185 MBq) 22-hr postinjection shows intense uptake in the liver (Grade 3). (B) Iodine-123-TOCT scan (dose 130 MBq) at 30 min shows moderate uptake in the liver (Grade 2). Arrow indicates activity in the gallbladder.

additional two lesions were identified by [¹²³I]MIBG, which were not identified by ¹²³I-TOCT (Patients 2 and 6): both lesions were in the soft tissue along the para-aortic region in the abdomen. Iodine-123-TOCT identified two sites of extrahepatic uptake: one in the abdomen lateral to the left kidney (Patient 1) and a second lesion in the tail of pancreas (Patient 7) not seen on [¹²³I]MIBG images (Fig. 3). In addition, ¹²³I-TOCT identified two discrete

hepatic lesions: one in Patient 1 (Fig. 1) and the second in Patient 7, which were not seen on [¹²³I]MIBG scans (Fig. 3).

DISCUSSION

The results show that both [¹²³I]MIBG and ¹²³I-TOCT can detect carcinoid tumor metastases. Both radiophar-

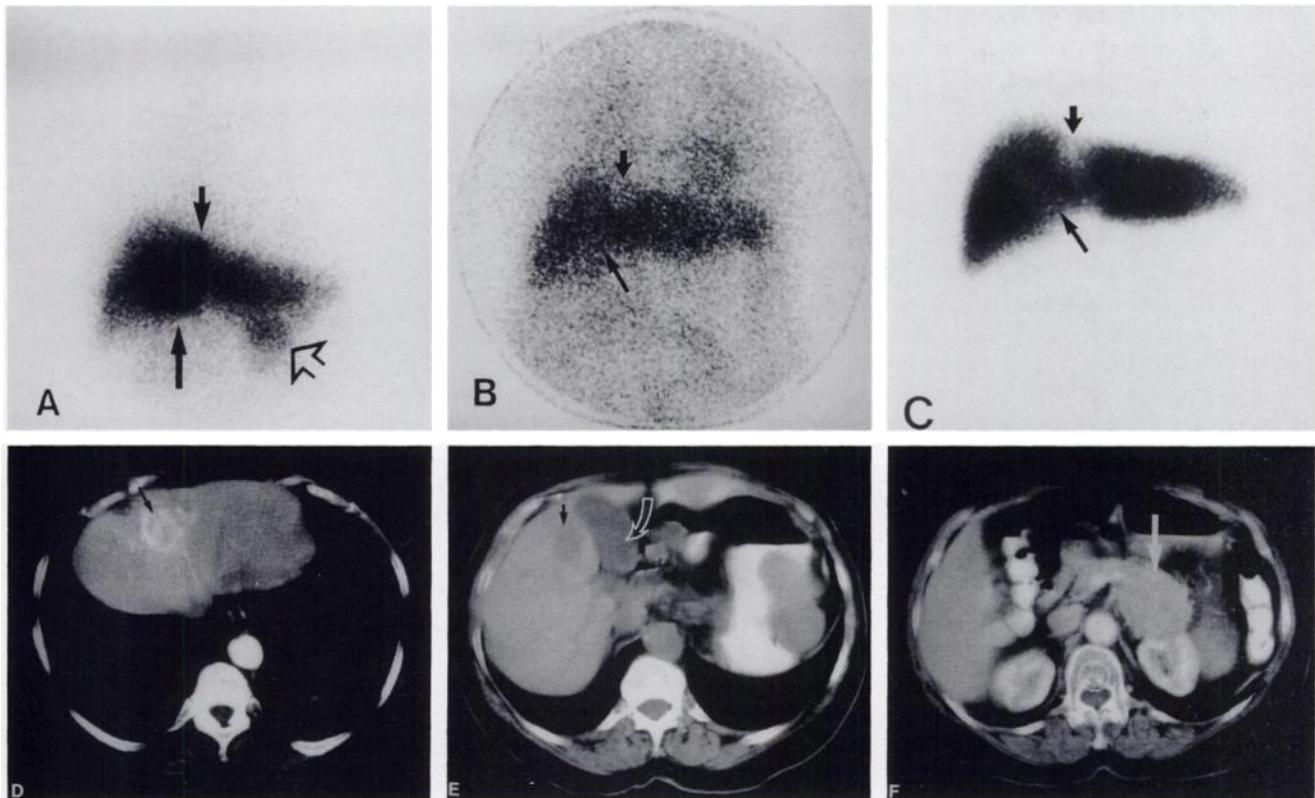


FIGURE 3. Patient 7, anterior view. (A) Iodine-123-TOCT scan (dose 185 MBq) at 20 min shows two metastatic sites in the liver (arrows). It is difficult to separate the activity in the lesion near the gallbladder (large arrow) from the adjacent biliary activity. Open arrow shows recurrence in the pancreatic tail. (B) Iodine-123-MIBG scan (dose 180 MBq) 48 hr postinjection. No uptake is seen in one of the liver metastases (small arrow), while the other shows Grade 2 uptake (large arrow). The site of tumor recurrence in the pancreatic tail is not visualized. (C) Technetium-99m-colloid liver scan shows two photon-deficient areas in the liver (arrows). (D) CT scan performed on the same patient at the same time shows a hepatic lesion (arrow) near the superior surface of the liver. (E) Closed arrow indicates a second metastatic site adjacent to the gallbladder and open arrow indicates gallbladder. (F) Arrow indicates recurrence in the pancreatic tail.

maceuticals show a spectrum of uptake ranging from no detectable activity to intense tracer uptake.

In this series, the total number of lesions detected by either modality was not counted, since it was difficult to quantify lesions in patients with diffuse liver disease. Detection of disease with ^{123}I -TOCT (five of seven) was marginally lower than [^{123}I]MIBG (six of seven). Others have observed a slightly higher detection rate (12 of 13) of carcinoid disease with ^{123}I -TOCT (9). This could be due to a difference in patient population, since the patients in our series had had previous chemotherapy.

In patients with detectable uptake, the highest T/Bkgd ratio with [^{123}I]MIBG was obtained on the 24–48-hr images. With ^{123}I -TOCT, the T/Bkgd ratio was optimal on 10–30-min images. This uptake persisted up to 24 hr postinjection. The intensity of uptake in tumor sites identified by both radiopharmaceuticals was similar. Grade 0–1 uptake images with ^{123}I -TOCT probably reflect a paucity of somatostatin binding sites on tumor cells (13), while for [^{123}I]MIBG, it is possibly due to a lack of neurosecretory granules (4). These findings further highlight the diverse nature of carcinoid tumor cells.

A poor correlation between MIBG uptake and urinary 5-HIAA levels has been described previously (2). This pattern was also observed with ^{123}I -TOCT uptake, suggesting that the serotonin secretory capacity of the tumor does not necessarily correspond to the somatostatin-binding status of tumor cells.

The main limitation of ^{123}I -TOCT scintigraphy is high biliary uptake (Fig. 2) and subsequent gut activity seen after approximately 30 min. The resulting degradation of the 2-hr and 4-hr diagnostic images impairs the ability to detect small tumor metastases with grade 1 and 2 uptake, particularly in the abdomen. However, in some cases, delayed 24-hr images may help. This has also been observed by others who have used ^{123}I -TOCT for imaging endocrine tumors (9). The use of ^{111}In -labeled [DTPA-D-Phe-1]-octreotide may overcome the problem of biliary activity (14).

In this series, Patients 1 and 2 had relapsed after chemotherapy prior to scintigraphy. After diagnostic imaging, these patients underwent [^{131}I]MIBG therapy. In both cases, a good clinical response was observed, which persisted for 8 mo. These patients are still under follow-up. Since high uptake and preferential retention of ^{123}I -TOCT were seen 24 hr after administration in Patient 1, there may be potential for ^{131}I -TOCT therapy as a complement to [^{131}I]MIBG treatment for carcinoid tumor metastases.

However, biliary and gut activity are obvious limitations for ^{131}I -TOCT therapy and further work is required to overcome these problems.

In conclusion, ^{123}I radiolabeled Tyr-3-octreotide may be useful for identifying carcinoid tumor metastases. With further work, the potential for radiolabeled targeted therapy with this agent could become a reality in the near future.

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