Imaging secondary neuroendocrine tumours of the liver: comparison of $^{123}$I metaiodobenzylguanidine (MIBG) and $^{111}$In-labelled octreotide (Octreoscan)

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Received 7 November 1995 and in revised form 14 March 1996

Summary

Functional imaging of neuroendocrine tumours with Octreoscan and $^{123}$I metaiodobenzylguanidine (MIBG) is important for assessment prior to various therapies and assessing response. The two imaging methods have not been directly compared in hepatic neuroendocrine tumours. Patients ($n = 18$) were studied with both imaging techniques. The sensitivity of Octreoscan was 94%, and that of MIBG 39%. No previously occult primary sites were detected.

Concurrent octreotide therapy did not reduce the sensitivity of Octreoscan. Widespread bone metastases were seen in two post-liver-transplant patients using Octreoscan. Octreoscan is a sensitive means of detecting hepatic neuroendocrine tumours, and the more specific technique. MIBG has poor sensitivity, reducing its clinical utility. Therapy with $^{131}$I-MIBG is likely to be applicable to relatively few patients.

Introduction

Functional imaging of neuroendocrine tumours has become possible as a result of two characteristics of the tumour cells. The first is that they express somatostatin receptors and therefore can be imaged with Indium$^{111}$-labelled octreotide (Octreoscan). The second characteristic of neuroendocrine tumours is that amine precursors are taken up into the cells by a specific amine precursor uptake/decarboxylase (APUD) pathway. Labelling of physiological amine precursors was unsuccessful, but metaiodobenzylguanidine (MIBG) is taken up by the same pathway and is concentrated in tumours cells, and thus $^{123}$I labelled MIBG can be used for imaging. Furthermore, tumours which concentrate MIBG on scanning may respond to local radiation therapy with $^{131}$I MIBG. Imaging is becoming increasingly important in order to document extrahepatic spread in those considered for hepatic surgery or transplantation or for monitoring responses to chemotherapy.

Methods

The 18 patients studied had either histologically-proven neuroendocrine tumours of the liver (by chromogranin staining and histological appearance) or positive urinary 5HIAA (at least three times normal range). Two of the patients (2 and 5) were scanned for the first time after liver transplant which had been performed for severe symptoms unresponsive to medical therapy.

All patients adhered to a standard protocol. Potassium iodate was administered 24 h prior to MIBG to block thyroid uptake. On day 1, 185 MBq $^{123}$I MIBG was given intravenously with scanning at
Immediate following the last MIBG scan, the subject was injected with 120 MBq $\text{In}^{111}$-DTPA-D-Phe-Octreotide with planar whole-body scans acquired at 24 and 48 h using an ADAC dual-head Genesys system. Single-photon emission tomography (SPEM) was used for all patients and this is particularly important for Octreoscan images since the octreotide $\text{In}^{111}$ is concentrated in renal tissue which may overlie tumour. Scans were interpreted by two independent observers.

Results

In 17 (94%) of the 18 patients, definite lesions within the liver were demonstrable with Octreoscan (Table 1). The one patient (patient 4) in which no liver lesion was identified by Octreoscan had Carney’s triad\textsuperscript{15} (of gastrointestinal leiomyoma, pulmonary chondroma and extra-adrenal apudoma) in which the neuroendocrine tumour of the liver may be atypical.

In 5/18 patients, Octreoscan identified a primary site although in all of these this site was previously known (Figure 1). In a further two cases with a known primary site this was not demonstrated by the Octreoscan. The known primary sites in these seven patients had previously been picked up by CT scanning of the pancreatic primary sites (four patients), and by small bowel barium studies (two patients) or laparotomy (one patient) in the cases with ileal lesions.

In the two patients (2 and 5) studied post-transplant, widespread bony metastases were seen as a result of tumour recurrence, and these had not been previously diagnosed. Both had liver lesions in addition to bony metastases (Figure 2). Ten of the patients were studied with Octreoscan while they were concurrently taking octreotide for relief of symptoms and this appeared not to interfere with uptake of the isotope within tumour.

Using MIBG scanning, only seven (39%) of the 18 cases had positive uptake within the liver lesions. Two of the primary sites were also positive for MIBG (Figure 2). In two further cases, photon-deficient areas were clearly seen within the liver, and the same lesions had been photon-dense on Octreoscan. None of the bone lesions in patients 2 and 5 shown on Octreoscan were positive with MIBG. In only two patients (10 and 11) were primary sites seen using MIBG, and no previously occult primary sites were revealed by this method.

Discussion

This study has confirmed the clinical use of Octreoscan scintigrams in defining intrahepatic neuroendocrine tumours shown previously\textsuperscript{3,4,5,6,7} and also in detecting extrahepatic spread. The sensitivity for detecting hepatic lesions using Octreoscan was 94%, rather better than the overall figures (for pooled results of 451 patients from all published series by 1994) of 86%.\textsuperscript{7} This imaging method is particularly

Table 1 Scan results in 18 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical</th>
<th>Primary site</th>
<th>Octreotide liver</th>
<th>Octreotide primary</th>
<th>MIBG liver</th>
<th>MIBG primary</th>
<th>On Octreotide?</th>
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*Resected prior to scan.
NK, not known; OLT, orthotopic liver transplantation.
Imaging secondary neuroendocrine tumours

**Figure 1.** Patient 11. *a* Octreoscan image at 24 h anterior view (L) and posterior view (R) showing one liver lesion and also a large primary site in the ileum (arrow). Uptake in the right kidney is seen to partially overlie the liver on posterior view. *b* MIBG images at 24 h showing uptake within the liver and the primary site (arrow) which were not as clearly demonstrated as with Octreoscan.

**Figure 2.** Patient 5 (post transplant recurrence of tumour). Octreoscan images at 24 h showing an enlarged liver with abnormal uptake and multiple hot spots throughout the pelvis and spine.

important prior to liver transplantation, which is now an accepted therapy for these tumours.\textsuperscript{12,17} When bone metastases occur, these are easily detected by Octreoscan, and the whole-body imaging facility makes it more useful than other imaging techniques in this respect. Octreoscan is not as sensitive at detecting sites of the primary tumour. Only 5/7 known primary lesions were detected by Octreoscan, and this did not identify any additional primary sites that were occult by other imaging methods.

Single photon emission tomography (SPET) scanning was shown to be important for correctly identifying liver metastases and separating these from the appearance of normal renal uptake. Areas within the hepatic tumours that accumulate labelled octreotide but leave photon-deficient areas on MIBG scans are of uncertain significance as yet. Concurrent administration of octreotide prior to scanning may improve visualization of lesions, as previously described.\textsuperscript{18}

Octreoscan is an important investigation for
detecting skeletal metastases, and will be useful in
detecting such recurrent tumour after liver trans-
plantation. The Octreoscan appearances of wide-
spread metastases in post-liver-transplant patients has
not been previously described. It is possible that
immunosuppression changes the normal behaviour
of the tumour, since asymptomatic widespread bony
metastases are unusual in non-transplanted patients.

Imaging with labelled MIBG in this series has
shown adequate visualization of metastases in only
39% of those scanned, and is clearly not useful in
diagnosis of the primary tumours. This figure is lower
than that of other series—6/7 lesions were positive in
Bomanji's series but only 70% of 275 patients
accumulated from other publications. In the present
series, only scans that had very clear lesions in the
liver were considered positive, which may explain
some of the differences. In those that are positive,
therapy using 111In MIBG may be possible, making
this a useful investigation for that reason alone.

In clinical use, the two techniques may be comple-
mentary. Octreoscan is more sensitive, but less
specific since it would be positive in many other
types of tumour—e.g. small-cell lung cancer or
metastatic breast cancer. Overall dosimetry with
the two techniques is similar but with different
distribution of absorbed dose. That of Octreoscan
presents a larger dose to renal tissue. In view of the
greater sensitivity of octreotide uptake into these
tumours, the possibility of a therapeutic radiolabel
being attached to the octreotide molecule has been
addressed. Currently this has not been used clinically
and some concerns exist with respect to radiation
doses to the kidney and pituitary.

MIBG scanning gives more information about
possible therapy and is more specific. Currently,
targeted radiotherapy with 131I is still under trial for
neuroendocrine liver tumours, although it may have
clearer role in the treatment of phaeochromocytoma.
The therapy has not produced objective reduction
in tumour size in significant numbers of patients but
may have a role in reducing hormone secretion.
Our results show that only a relatively small propor-
tion of patients could be treated in this way.

References
1. Lamberts SWJ, Bakker WH, Reubi JC, Krenning EP.
Somatostatin-receptor imaging in the localisation of
2. Westlin JF, Janson ET, Arnegger H, Ahlstrom H, Oberk
Nilsson S. Somatostatin receptor scintigraphy of carcinoma
tumours using the 111In-DTPA-D-Phe-octreotide. Acta
Localization of metastatic gastroenteropancreatic tumours
by somatostatin receptor scintigraphy with 111In-DTPA-D-
4. Scherubil H, Bader M, Fett U, Hamm B, Schmidt-Gayk H,
Koppenhagen K, Döpf F, Riecken E, Wiedenmann B.
Somatostatin-receptor imaging of neuroendocrine
gastroenteropancreatic tumours. Gastroenterology 1993;
5. Bomanji J, Ur E, Mather S, Moyes J, Ellison D, Britton KE,
Besser GM. A scintigraphic comparison of
iodine-123-metaiodobenzyl guanidine and an iodine-
labelled somatostatin analog (Tyr-3-octreotide) in metastatic
Utility of thallium-201 and iodine-123-metaiodobenzyl
guanidine in the detection of neuroendocrine neoplasia. Eur
7. Hoefnagel CA. Metaiodobenzylguanidine and somatostatin
in oncology: role in the management of neural crest
8. Castellani MR, Di Bartolomeo M, Maffioli L, Zilembo N,
Gasparini M, Buraggi GL. 131I Metaiodobenzylguanidine
35:349–51.
Results of 111In metaiodobenzylguanidine therapy in
GM. Treatment of malignant phaeochromocytoma,
paraganglioma and carcinoid tumours with 131I
Metaiodobenzylguanidine. Nucl Med Comm 1993;
14:856–61.
11. McIntee GP, Nagorney DM, Kvolks LK, Moettel CG, Grant
CS. Cytoreductive hepatic surgery for neuroendocrine
Orthotopic liver transplantation in the treatment of
neuroendocrine tumors of the liver. Liver Transplant Surg
13. Ramage JK, Catnach S, Williams R. Overview: The
management of carcinoid tumours. Liver Transplant Surg
14. Kvolks LK. Therapeutic considerations for the malignant
15. Carney JA. The triad of gastric epithelioid leiomyosarcoma,
functioning extra-adrenal paraganglioma and pulmonary
16. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WAP,
Kooij PPM, Oei HY, van Hagen M, Postema PTE, de
Jong M, Reubi JC, Visser TJ, Reijs AEM, Hofland LJ, Koper
JW, Lamberts SWJ. Somatostatin receptor scintigraphy with
[111In-DTPA-D-Phe and [111In-Tyr]-octreotide: the Rotterdam
experience with more than 1000 patients. Eur J Nucl Med
17. Makowka L, Tzakis AG, Mazzocco V, Teperman L,
Demetris J, Iwatsuki S, Starzl TE. Transplantation of the liver
for metastatic endocrine tumours of the intestine and
Adrian H-J, Bihl H. Improved visualisation of carcinoid liver
metastases by Indium-111 pentetreotide scintigraphy
following treatment with cold somatostatin analogue. Eur