Pergamon

European Journal of Cancer Vol. 32A, No. 11, pp. 1924–1932, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00241-9

Original Paper

Combined Diagnostic Imaging with ^{131}I-Metaiodobenzylguanidine and ^{111}In-Pentetreotide in Carcinoid Tumours

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Carcinoid tumours derived from the neural crest are usually associated with the symptoms of flushing and diarrhoea in the presence of liver metastases. Scintigraphs with ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) which is accumulated in the argentaffin granules of the cell, as well as with ^{111}In-pentetreotide for the imaging of somatostatin receptors on the cell surface, are positive in a large proportion of carcinoid patients. To evaluate the complementary role of both radionuclide tests, we studied 20 consecutive carcinoid patients: 14 with the characteristic carcinoid syndrome and 6 with tumour symptoms, such as pain or obstruction. A positive test was found in 84% with either ^{131}I-MIBG or ^{111}In-pentetreotide; the combination yielded a sensitivity of 95%. A positive correlation was found with the presence of the carcinoid syndrome, but not with 5-HIAA excretion. A positive test may help in adjusting treatment: either to predict the response to octreotide or to select patients for ^{131}I-labelled MIBG treatment. Application of a therapeutic dose of ^{111}In-pentetreotide may be limited by the high normal uptake in the kidneys. Copyright © 1996 Elsevier Science Ltd

Key words: radionuclide imaging, carcinoid, somatostatin, ^{131}I-MIBG

Eur J Cancer, Vol. 32A, No. 11, pp. 1924–1932, 1996

INTRODUCTION

CARCINOID TUMOURS are derived from the argentaffin cells in the base of the intestinal crypts. These tumours belong to the amine precursor uptake and decarboxylation (APUD) cells that originate from the neural crest [1]. The characteristic symptoms of the carcinoid syndrome, such as episodes of flushing, diarrhoea and vomiting, are mainly found in patients with liver metastases.

^{131}I-Metaiodobenzylguanidine (^{131}I-MIBG), an analogue of a biogene amine precursor, is taken up by chromaffin cells and stored in the neurosecretory storage granules. Radionuclide imaging, employing this uptake mechanism, has been applied to the diagnosis and treatment of several neuroendocrine tumours. The first report of a positive diagnostic scan in carcinoid tumours dates from 1984 [2]. Soon thereafter, we described the beneficial effect of a higher, therapeutic dose of ^{131}I-MIBG [3]. Pooled experience in the literature indicates that MIBG scans have been positive in 70% of 275 cases [4–7].

Apart from the neuroendocrine features, carcinoid tumours are well-known for their receptor binding sites for somatostatin. The radiolabelled analogue of somatostatin, ^{123}I-Tyr-octreotide, may detect carcinoid tumour deposits in half the liver metastases and in approximately 60% of extrahepatic sites [8]. A newer compound, labelled with ^{111}indium (^{111}In-DTPA-D-Phe^{1}-octreotide), was introduced in 1990 and has the advantages of easy peparation and an absence of major interference of imaging in the upper abdomen. Enhanced diagnostic accuracy has been reported [9], leading to a positive test in 86% of 451 carcinoid patients [7].

Little is known of the possible gain in diagnostic accuracy or therapeutic efficacy of the combination of ^{131}I-MIBG and ^{111}In-DTPA-D-Phe-Octreotide (^{111}In-pentetreotide) in carcinoid tumours. Preliminary results of a study in 7 patients suggest that these tests may complement each other [10]. To evaluate the role of the two nuclide imaging tests

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Received 18 Dec. 1995; revised 9 May 1996; accepted 19 Jun. 1996.

Table 1. Clinical and scintigraphic findings in 20 patients with a carcinoid tumour and/or carcinoid syndrome

Number	Age	Gender	Primary tumour*	Metastases	Carcinoid syndrome‡	5-HIAA urinary levels§	^{131}I-MIBG scan‖	^{111}In-pentetreotide scan‖	Octreotide treatment¶
1	50	m	stomach†	liver	–	21	+	0	–
2	81	m	rectum	abdominal	–H	62	0	+ + +	–
3	38	f	x	liver	+	1665	+ + +	+ + +	–
4	66	f	x	liver	+H	1712	+ + +	+ + +	+
5	49	m	x	liver	+H	2284	+ +	+ +	–
6	56	m	pancreas?	abdominal	+H	510	+ + +	+ + +	±
7	70	m	pancreas	–	–	42	0	0	–
8	41	f	ileum	liver	+H	688	+ +	+ + +	–
9	45	m	ileum†	liver/peritoneal	+H	1429	+ +	0	–
10	62	f	ileum†	liver/peritoneal	+	393	+ +	+ +	–
11	42	m	x	liver	+H	237	+	+ +	–
12	72	f	duodenum	liver	–	0	0	+ + +	–
13	49	m	ileum†	liver/abdominal	+H	834	+ +	+ + +	–
14	44	f	x	liver	+	348	+ +	+ + +	–
15	83	f	x	liver	+H	250	+ + +	+ + +	+
16	63	m	ileum†	liver/peritoneal	+H	1080	+ + +	+ + +	+
17	59	m	pancreas?	liver	–	137	+ + +	+ + +	–
18	38	f	x	liver/abdominal	+	1763	+ +	+ + +	–
19	64	f	x	liver	–	156	+ +	+ +	–
20	61	f	kidney	liver	+	194	+	+ +	+

* Primary tumour: x, unknown, † resected: ‡ H hospitalisation required for severe attacks of carcinoid syndrome: § urinary 5-HIAA excretion (normal is up to 40 μmol/24 h); ‖ grading system: 0, negative; +, minimal uptake; + +, moderate uptake (equal to that in the liver): + + +, intense uptake (more than in the liver); ¶ octreotide injection (three times daily): –, no treatment; +, treatment continued at the time of the scan; ±, stopped 1 day before the octreoscan. 5-HIAA, 5-hydroxyindoleacetic acid; ^{131}I-MIBG, ^{131}I-metaiodobenzylguanidine; m, male; f, female.

and the possible implications for treatment, we performed an imaging study with both ^{131}I-MIBG and ^{111}In-pentetreotide in 20 patients with a carcinoid tumour.

PATIENTS AND METHODS

20 consecutive patients (10 men, 10 women) with a median age of 60 years (range 41–83) and with either a histologically confirmed ($n = 19$) carcinoid tumour and/or the typical carcinoid syndrome were treated at the Netherlands Cancer Institute between 1992 and 1994 (Table 1). A single patient refused liver biopsy; in this case the diagnosis was based on findings from a computer tomography (CT) scan and an elevated urinary 5-HIAA level. In 8 patients, the primary site of the carcinoid tumour remained unknown. In the other 12 patients, the carcinoid tumour was derived from the foregut in 5, the mid-gut in 6 and the hind-gut in 1. In all patients, tumour deposits were present on a CT scan of the abdomen. As one of the patients experienced severe flushes and diarrhoea when taken off octreotide temporarily, octreotide treatment was continued in the subsequent patients, who received s.c. injections of the long-acting somatostatin analogue, octreotide, when the ^{111}In-pentetreotide scanning was performed.

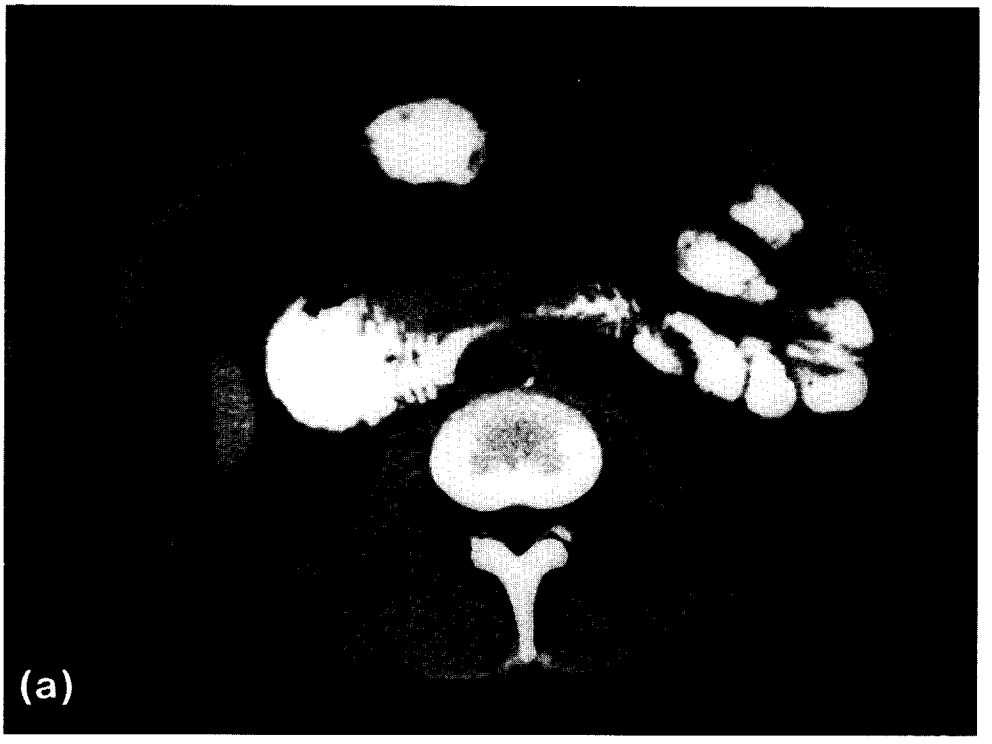
Radionuclide imaging

Patients received oral potassium iodide, 200 mg daily for 5 days, starting 1 day before ^{131}I-MIBG administration to avoid radioiodine uptake by the thyroid. The patients received 37 MBq (1 mCi) of ^{131}I-MIBG by i.v. injection over 5 min. Total body imaging was performed 24, 48 and 72 h later, using a dual head extra large field-of-view gamma camera with a high energy collimator. Planar images with an acquisition of 10 min using a 512 × 512 matrix were made of the whole body. On the 48 hr scintigram, the uptake of ^{131}I-MIBG was graded from 0 to + + + as previously used by Hoefnagel and colleagues (0, no uptake; +, minimal upake, less than in the liver; + +, moderate uptake, equal to the liver; + + +, intense uptake, greater than in the liver) [11].

For somatostatin receptor imaging, 110 MBq (3 mCi) ^{111}In-pentetreotide (Octreoscan, Mallinckrodt) was administered i.v. This second scintigraphic procedure was performed at least 1 week later because of the long half-life of I-131. Total body imaging was performed at 24 h, using the same gamma camera equipped with medium energy collimators, using a running speed of 6 cm/min and a 512 × 1024 matrix. Tumour uptake was scored as applied in ^{131}I-MIBG imaging. The scintigraphic studies were read 'blind', with merely the information of the diagnosed carcinoid tumour available, but without details of the tumour localisation from the CT scan and other procedures.

RESULTS

In half the patients, a primary tumour localisation was not identified (Table 1). In 17 of the 20 patients, liver metastases were found at presentation. This relatively large subgroup of patients may explain the high incidence of symptoms of the carcinoid syndrome (14 of 20). These consisted of flushes and varying degrees of diarrhoea in all, for which 8 patients required medication. Periodic vomiting occurred in 4. Bronchospasm was not observed in any of the patients. Severe symptoms requiring hospitalisation were present in 9 patients, 6 of whom had very high levels of urinary 5-HIAA excretion (>500 μmol/24 h), despite octreotide therapy in 3 of them. In all patients, tumour deposits were demonstrated on abdominal CT scans. Liver



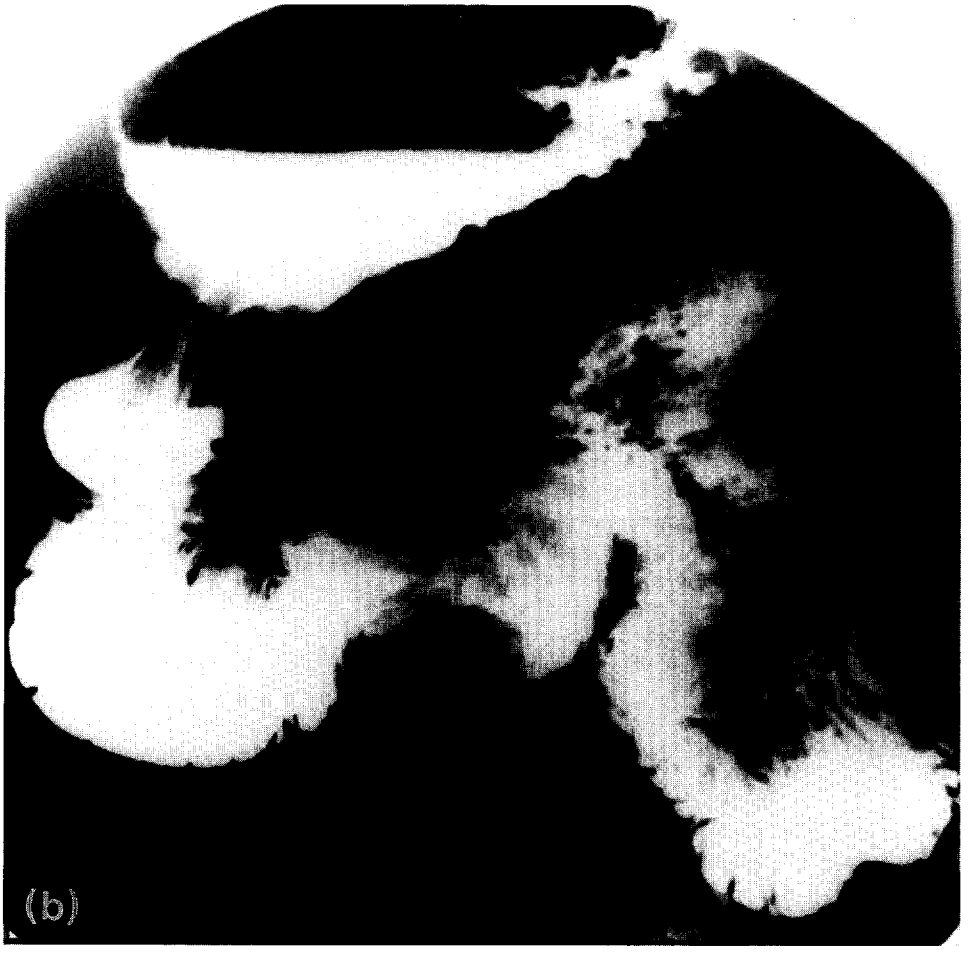


Figure 1a, b

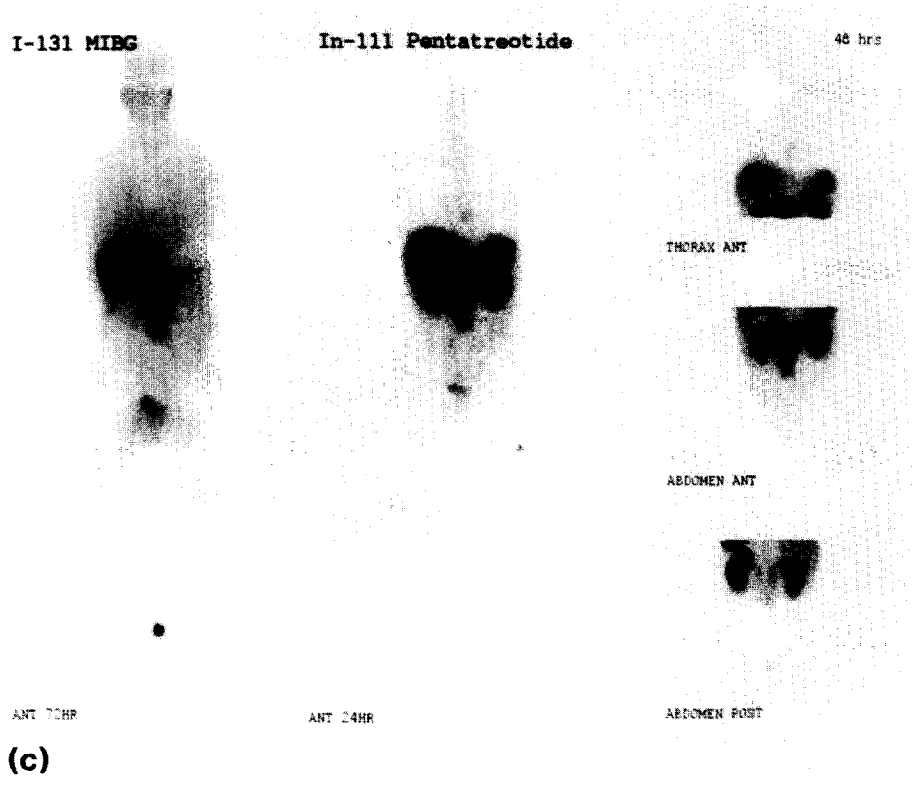


Figure 1. Patient (number 6) with carcinoid syndrome with flushes and diarrhoea also suffered from pain and vomiting due to severe obstruction of the horizontal part of the duodenum as demonstrated in a CT scan (a) and with a barium meal (b). The radionuclide imaging tests (c) were both positive, showing the large tumour mass as a mid-abdominal triangle. Clearly prolonged uptake in both kidneys is shown in the ^{111}In-pentetreotide scan.

metastases were pesent in all patients with the carcinoid syndrome ($n = 14$), except 1 who had a large retroperitoneal tumour mass invading the duodenum (Figure 1). All 14 patients with the carcinoid syndrome had repeatedly elevated 5-HIAA excretion levels.

The ^{131}I-MIBG scan correctly identified carcinoid localisations in the liver of 15 of 17 patients (88%). Figure 2 shows an example of a positive ^{131}I-MIBG scan in a patient with severe attacks of the carcinoid syndrome, but only a moderately elevated 5-HIAA excretion. A large metastatic area in the liver with central necrosis caused a 'cold' area of diminished uptake at tomography within a clearly positive region. The MIBG scan was negative (number 12) or minimally positive (number 1) in 2 patients, both with liver metastases on a CT scan, but without symptoms of the carcinoid syndrome. The MIBG scan was positive in two of the four extrahepatic abdominal lesions. In Figure 1, a large tumour with duodenal obstruction is visible as a large triangle in the mid-abdomen. The sensitivity of the ^{111}In-pentetreotide scan was equally good: liver metastases were correctly identified in 14 of 17 patients (82%). Although it is recommended that administration of somatostatin is stopped before imaging studies, the simultaneous use of octreotide injections did not apparently interfere with the pentetreotide scan: in the 4 patients who continued with their octreotide treatment, the test was clearly positive. New localisations other than those already known from the CT scan were not detected with either radionuclide imaging technique.

Combination of ^{131}I-MIBG and ^{111}In-pentetreotide scans was of additive value in 4 patients (20%), in whom either one of the tests was positive, as illustrated in Figure 3. Only the lateral view of the ^{111}In-pentetreotide scan showed the large obstructing tumour (T) hidden behind the urinary bladder (BL), while the ^{131}I-MIBG scan was definitely negative. Both radionuclide tests gave a false-negative in only 1 patient (number 7), who had a solitary pancreatic mass and obstructive jaundice without the carcinoid syndrome. In 15 patients, both the ^{131}I-MIBG and the ^{111}In-pentetreotide were positive. A representative example is shown in Figure 4. This young woman with carcinoid syndrome, diffuse liver metastases on the CT scan and elevated 5-HIAA excretion refused a liver biopsy to prove the diagnosis of a carcinoid tumour. The ^{111}In-pentetreotide scan revealed retention in the kidneys and bowel, which were considered as normal retention, different from the spots in the left abdomen that were suggestive of extrahepatic lesions. Whenever there was a difference in the degree of positive labelling, it was always in favour of the ^{111}In-pentetreotide scan. In 6 of the 15 patients (40%) in whom both tests were positive, the ^{111}In-pentetreotide scan was clearly more strongly positive than the ^{131}I-MIBG scan. The prolonged, normal renal uptake in all patients following ^{111}In-pentetreotide administration is worth noting (Figure 1 and Figure 4).

No correlation between urinary 5-HIAA excretion and the uptake of ^{131}I-MIBG or ^{111}In-pentetreotide was found. However, in patients with the carcinoid syndrome, both radionuclide imaging tests were significantly more often

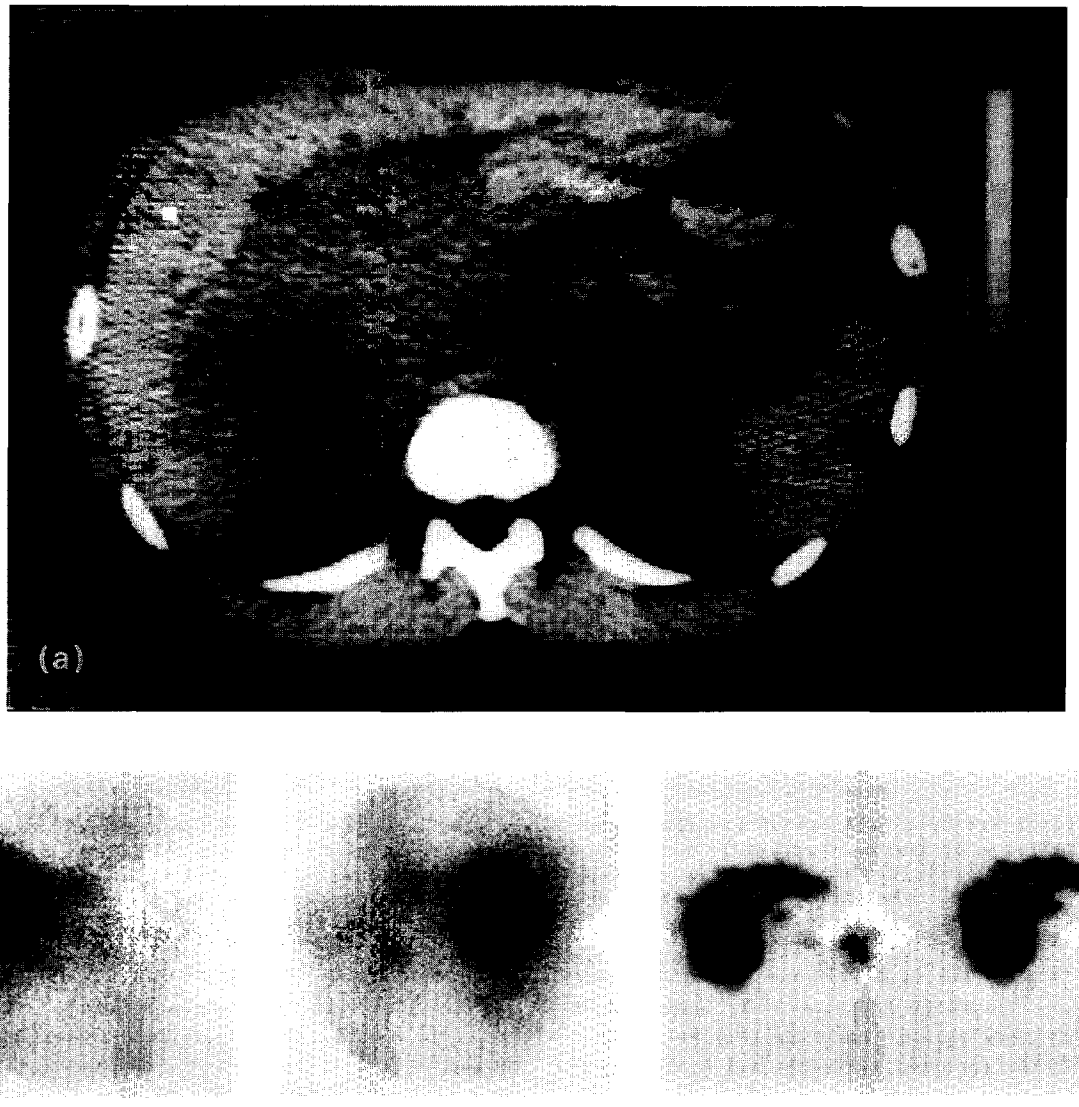


Figure 2. (a) The CT scan of the liver of a 42-year old man (number 11), suffering severe episodes of flushing, diarrhoea and vomiting leading to dehydration with the need for hospitalisation, revealed massive liver involvement. A large metastatic area with central necrosis is shown on the ^{131}I-MIBG scan as an area of positive uptake with a central cold area representing the necrotic part. (b) With more detail, various positive areas with a cold region in the middle of the largest metastases can be seen.

positive (13/14 or 93%) than in patients without the specific symptoms of the carcinoid syndrome (2/6 or 33%).

DISCUSSION

Carcinoid tumours belong to the group of neuroendocrine tumours and arise from the enterochromaffin cells of the glands of Lieberkuhn that contain neurosecretory granules [1], demonstrable by silver impregnation techniques. The release of various gastrointestinal hormones and vasoactive substances may lead to the characteristic carcinoid syndrome, which is most commonly associated with liver metastases, but may also occur if hormones drain directly into the systemic circulation as in retroperitoneal tumour masses or in ovarian tumours. In 17 of 20 patients (85%) in our series, liver metastases were found at first presentation and 14 patients reported signs of the carcinoid syndrome, especially flushes and diarrhoea. Symptoms usually fluctuated, but were severe enough to require hospital treatment in 9 patients (45%).

Radionuclide imaging tests may be helpful in detecting tumour localisation. In the present series, we found a sensitivity of 84% for both the ^{131}I-MIBG test and the ^{111}In-pentetreotide scan using CT scanning as the 'gold' standard. These figures compare favourably with those found in the literature. In a compilation of all published data [7], the cumulative sensitivity in carcinoid tumours was 70% for the ^{131}I-MIBG scan ($n = 275$) and 88% for the ^{111}In-pentetreotide scan ($n = 451$). Whether there was a difference in the accuracy of detection of hepatic or extrahepatic lesions is difficult to determine from our series, because liver metastases were far more frequent than extrahepatic localisations. The apparently higher sensitivity of ^{131}I-MIBG scintigraphy in this particular series could also be explained by a referral phenomenon (i.e. patients with liver metastases and carcinoid syndrome are more likely to be referred to a specialist

cancer centre), as well as by our technique of delayed imaging (up to 72 h) for ^{131}I-MIBG. When ^{123}I-MIBG and 24 h images are used, liver metastases may be obscured by normal liver uptake [11].

It is usual to advocate discontinuation of octreotide injection therapy 1 week before the ^{111}In-pentetreotide scan to avoid the saturation of somatostatin receptors, which could hypothetically lead to a false-negative scan [8, 9]. Contrary to expectations, Dürr and colleagues [12] reported an increased visualisation of hepatic metastases in 5 patients on somatostatin therapy, partly ascribed to changes in biodistribution with decreased background radioactivity in the liver, spleen and kidneys. Similar results with a clear positive uptake in liver metastases were found in 4 patients on somatostatin therapy in the present series. A similar phenomenon for MIBG was not observed, possibly because there was no simultaneous use of drugs known to interfere with ^{131}I-MIBG uptake, such as labetalol and calcium channel blockers [7].

As described earlier for both the ^{111}In-pentetreotide scan [8] and the ^{131}I-MIBG scan [5–7], the correlation between urinary 5-HIAA excretion and the imaging tests was poor. This suggests that production of vasoactive and/or hormonal substances other than serotonin is responsible for the syndrome. The clear positive correlation between a positive

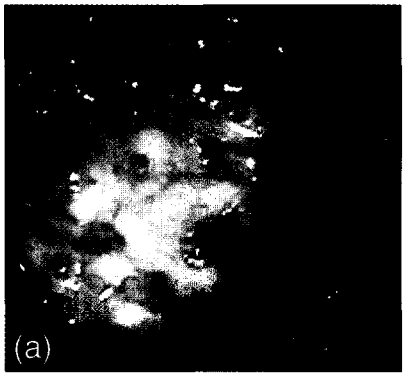
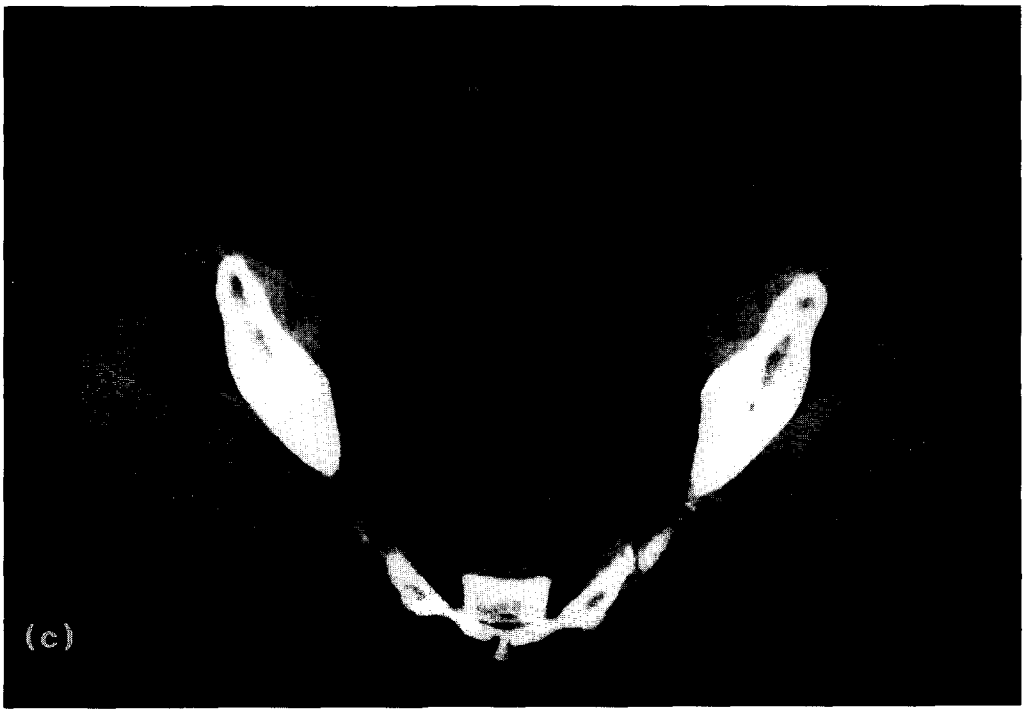


Figure 3. In an 81-year old man (number 2) presenting with rectal bleeding and cramps, an obstructive, whitish tumour was found at endoscopy (a) and with a barium enema (b), representing a very large tumour mass in the small pelvis on the CT scan (c). ^{131}I-MIBG was negative, but the ^{111}In-pentetreotide scan revealed the primary tumour (T) at the level of the urinary bladder (BL) only detected in lateral view. In retrospect, a double contour can be seen at the arrow in the anterior and posterior images. (Continued overleaf).


(c)

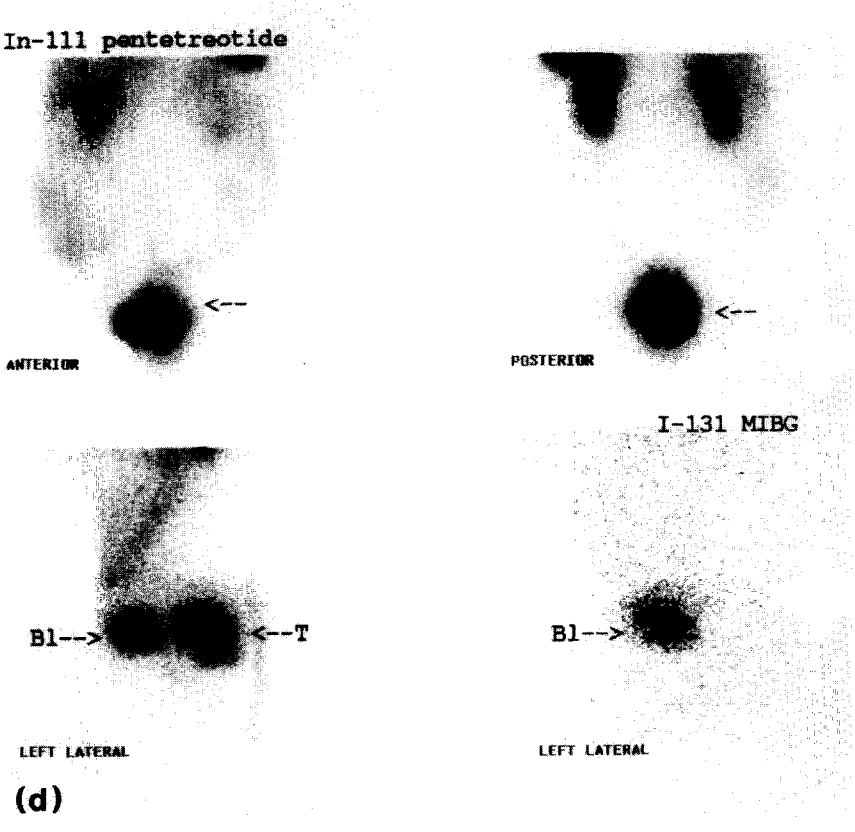

In-111 pentetreotide
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Figure 3c, d.

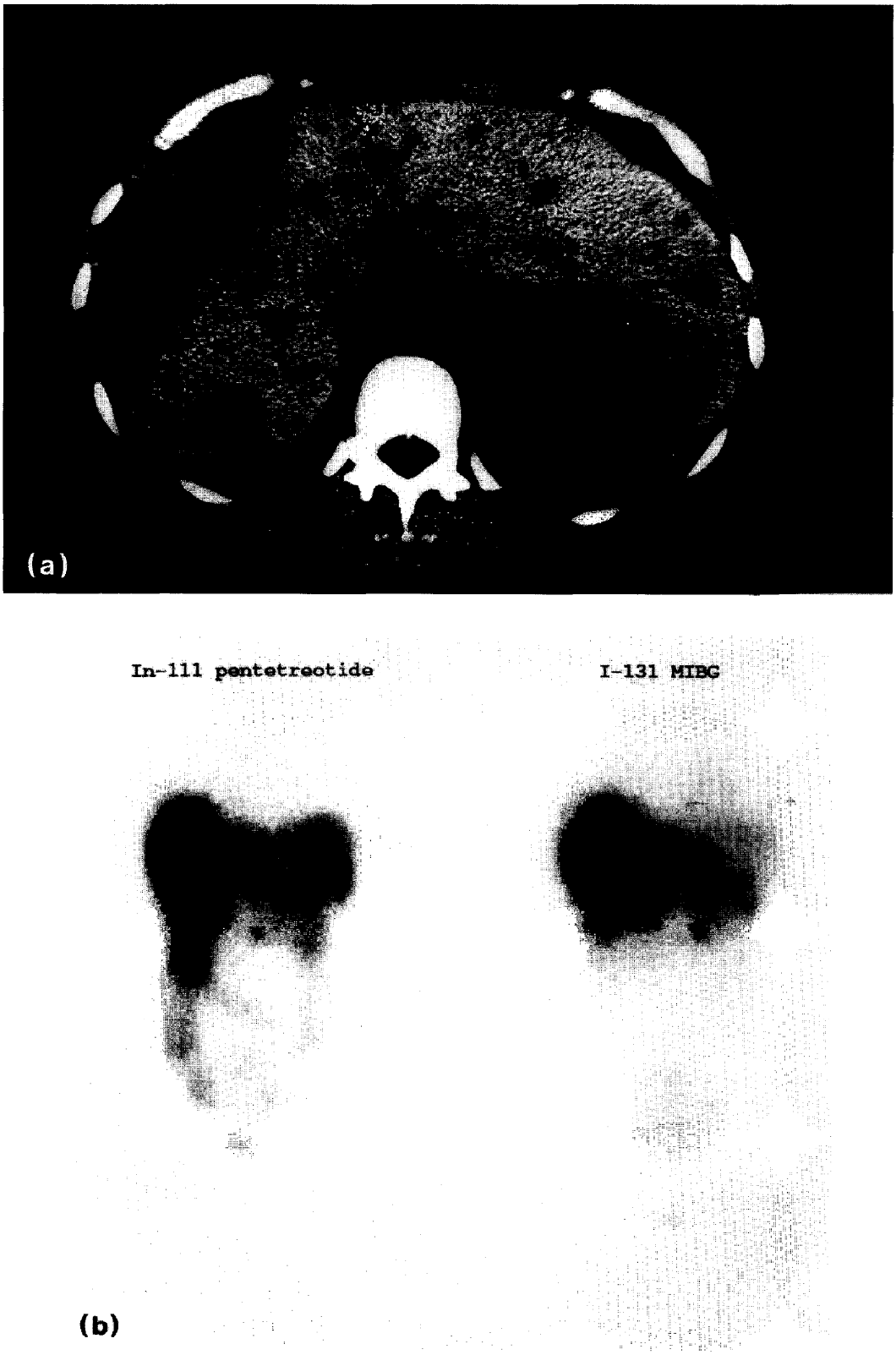

Figure 4. Diffuse liver metastases as shown with a CT scan (a) in a young woman (number 14) suffering from flushes. (b) The ^{111}In-pentetreotide scintigraphy was positive, revealing a large positive area, matching the largest metastasis on the CT scan, accompanied by normal uptake in the kidneys and intestine. The ^{131}I-MIBG scan was also positive, but without the interference of normal uptake in other organs.

^{131}I-MIBG scan and the presence of the carcinoid syndrome seen here supports this assumption.

The combination of both radionuclide scans was of additive value and led to a further increase in the true positive rate from 85 to 95%. Only one study reported preliminary data that support the complementary role of both radionuclide tracers in a small number ($n = 7$) of patients with a carcinoid tumour [10]. Similar comparative studies are only available for other neurocrest-derived tumours, such as phaeochromocytoma, paraganglioma and neuroblastomas, in all of which the combination of scan shows an increased sensitivity [7].

In addition to the detection of tumour localisation by the radionuclide tests, the impact on treatment choices is probably most important. For MIBG, the imaging procedure consists of measurements on 3 consecutive days; the uptake and biological half-life in the tumour are assessed in relation to the normal tissues. For pentetreotide, only the tumour uptake is relevant to treatment with the unlabelled octreotide analogues; as no radionuclide is given, imaging at one time point is sufficient. A positive ^{111}In-pentetreotide test is thought to predict a favourable response to octreotide treatment [8]. The main disadvantages of this treatment are the high cost, and relatively short biological half-life and therefore the need for injections to be repeated three to five times per day. However, new compounds with a prolonged half-life are currently under investigation. The use of a therapeutic dose of radiolabelled ^{111}In-pentetreotide, which targets the somatostatin receptor sites on the cell surface and delivers radiation directly to the tumour cells, is limited, in our opinion, by the high concentrations that accumulate in the kidneys. In contrast, the ^{131}I-MIBG scan identifies patients who may benefit from a therapeutic dosage of radiolabelled ^{131}I-MIBG, which is concentrated intracellularly; such a radioactive treatment is not limited by high uptake or retention in normal tissues as seen following the ^{111}In-pentetreotide scan. The mechanism of action also differs from that of ^{111}In-pentetreotide. It consists of several steps: uptake of ^{131}I-MIBG into the cell by active transport or passive diffusion, followed by intracellular transport and storage in the granules, subsequent release from the granules and re-uptake [7]. A therapeutic dose of 200 mCi ^{131}I-MIBG has been used in various centres, leading to a good and usually long-lasting (up to 1 year) palliative effect in 65% of all reported series that includes a total of 52 patients [7]. The main disadvantage of this treatment is the relatively high cost and the need to isolate patients for 5–7 days depending on local rules. ^{131}I-MIBG treatment is not associated with significant side-effects. Therefore, MIBG treatment is a simple means of inducing long-lasting palliation, even after failure with octreotide. The effect of MIBG is being examined in more detail in a prospective study [13].

In conclusion, ^{131}I-MIBG and ^{111}In-pentetreotide are both sensitive indicators of carcinoid tumour deposits. Their role is complementary in the diagnostic work-up, but the combination of both tests may be helpful in determining the optimal palliative treatment strategy.

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Acknowledgements—The authors wish to thank Mrs E. Peetam-Brugman for her help in preparing the manuscript and Dr S. Rodenhuis and Dr E. Rankin for their critical review.