Anti-Cancer Drugs 1996, **7**, Suppl 1, pp. 33–44

Radiolabelled somatostatin analogue scintigraphy in oncology

Kenneth J O'Byrne[1] and Desmond N Carney[2]

[1]ICRF Clinical Oncology Unit, Churchill Hospital, Headington, Oxford OX3 7LJ, and [2]Mater Misericordiae Hospital, Dublin, Ireland

Somatostatin analogue scintigraphy represents a new technique employing radiolabelled peptides to detect specific receptor-bearing lesions. ^{111}Indium diethylenetriaminopentaacetic acid-linked octreotide (^{111}In-DTPA-D-Phe^1-octreotide), also known as [^{111}In]pentetreotide or OctreoScan, is now established in the management of patients with neueroendocrine gastrointestinal tract and pancreatic tumours, and has proved effective in localizing disease sites in lung, breast and medullary thyroid carcinomas, lymphomas, meningiomas and others. In these conditions (a) the imaging of all disease sites at a single sitting (in a proportion of patients) thereby making further investigations unnecessary, (b) the localization of otherwise unexpected metastatic deposits and (c) the detection of residual disease not found by other means suggest that [^{111}In]pentetreotide may be a useful adjunct in the diagnostic evaluation of patients with somatostatin receptor-bearing tumours.

Key words: Somatostatin analogue, scintigraphy, somatostatin receptor, diagnosis.

Introduction

First discovered as a growth hormone release inhibitory factor in the hypothalamus in 1968, somatostatin was successfully sequenced as a tetradecapeptide in 1973. Somatostatin has since been found throughout the body, particularly in the central, peripheral and autonomic nervous system, the D or δ cells of the pancreas and gastrointestinal tract and the parafollicular C cells of the thyroid.

Somatostatin functions as an inhibitor of hormone release from somatotrophs and thyrotrophs in the pituitary and α, β and δ cells in the pancreas. Somatostatin also inhibits the release of all known gastrointestinal tract hormones. Somatostatin is an immunomodulator, inhibiting lymphocyte and thymocyte proliferation and lymphocyte colony formation while increasing the inhibition of human leukocyte migration following exposure to antigen. Somatostatin affects cytokine production and function, reducing, for example, the production of interferon-γ from activated normal blood T lymphocytes. As a neurotransmitter, somatostatin appears to play an important role in sensory perception and learning, circadian rhythm, pain control and normal respiration.[1–3] Finally, somatostatin is an endogenous inhibitor of cell growth.[4]

Somatostatin acts by binding to specific receptors on target tissues. Somatostatin receptors (hSSTR) have been found throughout the nervous system, on somatotrophs, thyrotrophs and lactotrophs in the pituitary, α, β and δ cells of the pancreas, activated immune cells and lymphoid follicles and the adrenal gland. Recently, five hSSTR subtypes have been cloned. One or more of these have been detected in most of the abovementioned tissues as well as in the lung and kidney.[3,5–10]

Somatostatin receptor expression in tumours

Recent attention has focused on hSSTR expression in both benign and malignant tumours. As expected, hSSTR are expressed by tumours derived from tissues that are targets for somatostatin, including somatotroph, thyrotroph and endocrine inactive pituitary adenomas, central nervous system tumours (meningiomas, astrocytomas, oligodendrogliomas and medulloblastomas), gastroenteropancreatic (GEP) neuroendocrine tumours and medullary thyroid carcinoma.[3,5,11–14]

Through membrane-binding assays, autoradiography and *in situ* hybridization, hSSTR have been detected in small-cell lung cancer (SCLC), breast, renal, prostatic, ovarian, exocrine pancreatic and

Our studies reported here were made possible by the support of the Irish Cancer Society.

Correspondence to KJ O'Byrne

colorectal carcinomas and malignancies of the reticulo-endothelial system. Furthermore, venules in the region of malignant tumours tend to express high concentrations of hSSTR. Evidence from studies in breast cancer and neuroblastoma suggest that hSSTR expression is associated with a favourable prognosis.[3,5,11–15]

Growth-inhibitory actions

On binding to their extracellular domains, many growth factors induce intracellular receptor tyrosine kinase activity. Furthermore, a number of oncogene products are truncated growth factor receptors, lacking an extracellular binding domain but having permanent endogenous intracellular tyrosine kinase activity. This tyrosine kinase activity results in phosphorylation of a number of tyrosine residues on the intracellular portion of the receptor. The phosphorylated tyrosine residues then interact with guanine nucleotide-binding proteins and subsequently *ras*, inducing a phosphorylation cascade which activates transcription factors and ultimately results in cell proliferation.[16] Dephosphorylation of tyrosine residues blocks this growth pathway. The antiproliferative effects of somatostatin in hSSTR-positive cell lines has been shown to be closely linked to activation of tyrosine phosphatase activity *in vitro* .[17,18] Further direct effects of somatostatin on hSSTR-positive cells which may contribute to growth inhibition include inhibition of the accumulation of intracellular cyclic AMP[19,20] and of the mobilization of intracellular calcium.[21] Somatostatin may also have indirect growth-inhibitory effects by blocking the release of trophic factors from other tissues such as growth hormone and insulin-like growth factor-1,[22] inhibiting angiogenesis[23] and reducing the ability of cancer cells to adhere to blood vessel walls.[24]

Somatostatin analogues

The best studied octapeptide analogues of somatostatin, SMS 201 995 (octreotide), BIM 23014 C (somatuline) and RC-160 (vapreotide), have high affinity for and functionally activate hSSTR2. They have an intermediate to low affinity for the other receptor subtypes. Despite this, RC-160 functionally activates at least one of these, the hSSTR1 receptor.[24] Somatostatin analogues have been shown to inhibit the growth of hSSTR-positive breast cancer, SCLC, exocrine pancreatic, colorectal, gastric and prostatic carcinomas *in vitro* and/or *in vivo* and hSSTR-negative tumours such as non-SCLC *in vivo*.[3,25]

SMS 201 995 (octreotide) is established in the treatment of acromegaly and GEP tumours.[26–29] Recent studies have suggested that octapeptide somatostatin analogues may also be useful in the management of solid tumours, including gastrointestinal tract and exocrine pancreatic, prostatic, SCLC and breast cancers, either alone or in combination with cytotoxic agents. Disease response and/or stabilization with somatostatin analogue treatment has been observed in all tumour types.[29–34]

Radiolabelled somatostatin analogue imaging

Recent work has evaluated the potential role of radiolabelled somatostatin analogues for the detection and localization of hSSTR tumours in patients through scintigraphic imaging techniques. The initial studies focused on [^{123}I-Tyr^3]octreotide. This agent was successfully applied in patients to visualize meningiomas, GEP tumours, paragangliomas and SCLC.[35–38]

There were several problems with this radiolabel. The labelling of [Tyr^3]octreotide with ^{123}I is cumbersome and requires special skills. Na^{123}I of high specific activity is expensive and not readily available worldwide. [^{123}I-Tyr^3]octreotide has a short effective half-life in the circulation due to rapid clearance by the hepatobiliary system. Also, substantial accumulation of the radiolabel is seen in the intestines, since a major part of [^{123}I-Tyr^3]octreotide is excreted, unchanged, in the bile into the bowel. This makes it difficult to interpret planar images or single-photon emission computed tomography (SPECT) images of the upper abdomen.[39]

These difficulties led to the development of ^{111}In diethylenetriaminopentaacetic acid-linked octreotide (^{111}In-DTPA-D-Phe^1-octreotide), also known as [^{111}In]pentetreotide or OctreoScan.[39] ^{111}In is relatively cheap and more freely available than Na^{123}I. DTPA-D-Phe-octreotide may be labelled with ^{111}In in any nuclear medicine department using a simple single-step procedure. ^{111}In has a longer physical half-life than ^{123}I (2.8 days versus 13.2 h) which improves scintigraphy 24 and 48 h after injection. [^{111}In]pentetreotide has a longer residence in the circulation than [^{123}I-Tyr^3]octreotide (33% versus 15% of administered dose in the circulation 10 min after injection) which may improve uptake of the ra-

diolabel by the somatostatin receptor-bearing lesion to be imaged. Reduced hepatobiliary metabolism of [^{111}In]pentetreotide makes this agent more suitable for imaging hepatic metastases and intra-abdominal disease.[39,40]

As tumour to background ratios of [^{111}In]pentetreotide are highest in animals 24 h after injection, when interference from blood pool radiation is minimal, this time is deemed most appropriate for the acquisition of scintigraphic images in patients.[39,40]

[^{111}In]pentetreotide studies

[^{111}In]pentetreotide imaging has been investigated in all tumour types known to express somatostatin receptors.[40] In keeping with the established *in vitro* data and with previous studies using [^{123}I-Tyr^3]octreotide, [^{111}In]pentetreotide has proved to be an effective radiopharmaceutical agent in the detection and localization of hSSTR-expressing tumours in man.[40] The effectiveness of [^{111}In]pentetreotide scintigraphy has been established in the management of GEP tumours including carcinoid tumours. The radiolabel often localizes primary GEP tumours that are undetectable by other methods, including abdominal ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI), arteriography and venous sampling. [^{111}In]pentetreotide may also detect otherwise unsuspected metastatic deposits. The detection of both primary and metastatic deposits at a single sitting not only contributes to patient comfort but has led to changes in management decisions in a significant proportion of cases. The technique may prove valuable in predicting whether or not a tumour, or the syndromes induced by hormone secretion from the tumour, will respond to octreotide therapy.[40–44] [^{111}In]pentetreotide is now licenced throughout Europe for the diagnostic evaluation of patients with GEP tumours.

We have undertaken a number of studies in patients with both neuroendocrine and non-endocrine solid tumours, which demonstrate both the efficacy and limitations of [^{111}In]pentetreotide scinitigraphy in oncology.

Small-cell lung cancer

We evaluated the efficacy of [^{111}In]pentetreotide scintigraphic imaging in staging 13 patients with SCLC before any treatment. Following standard staging investigations, six patients were found to have limited disease while seven had extensive disease. Of the seven patients with extensive disease, four had liver metastases, four bony involvement, one a single large brain metastasis and one an adrenal metastasis. Scintigraphic imaging with [^{111}In]pentetreotide led to the detection of all primary sites of disease (Figure 1). This included a patient whose primary tumour, detected at bronchoscopy, was not visualized with chest X-ray or CT of the thorax. In the seven patients with extensive disease, patchy uptake within the liver, consistent with metastatic disease, was observed in three out of four cases (Figure 2) and skeletal disease was detected in two out of four patients. None of the other known sites of metastatic disease were seen. In one patient a previously undetected cerebellar metastasis was found, which had not been suspected following routine staging. This was later confirmed with a CT brain scan.

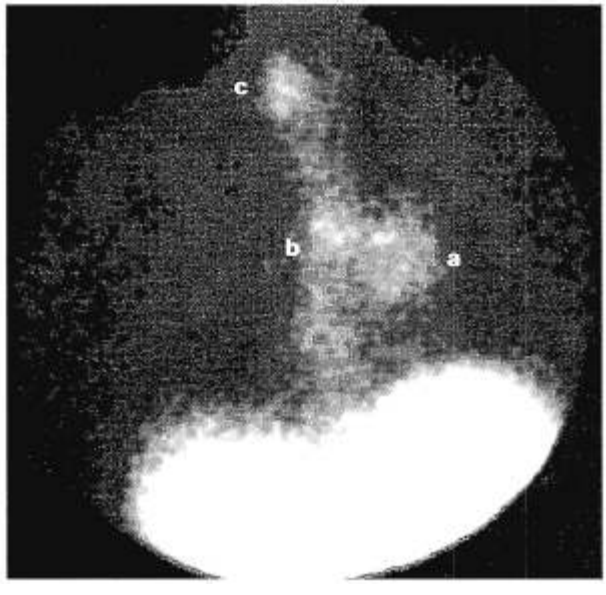

Figure 1. A large primary tumour is seen in the left lung field in the region of the hilum (a). Pathological uptake is also seen throughout the mediastinum, particularly adjacent to the hilum (b) and to the right of the trachea (c). Single-photon emission computed tomography (SPECT) imaging further localized the disease, demonstrating not only mediastinal adenopathy but also pathological accumulation of the radiolabel in the sternum and thoracic spine (not shown).

Therefore, [^{111}In]pentetreotide correctly staged nine out of 13 patients (69%), and detected five out of 10 known metastases and one previously un-

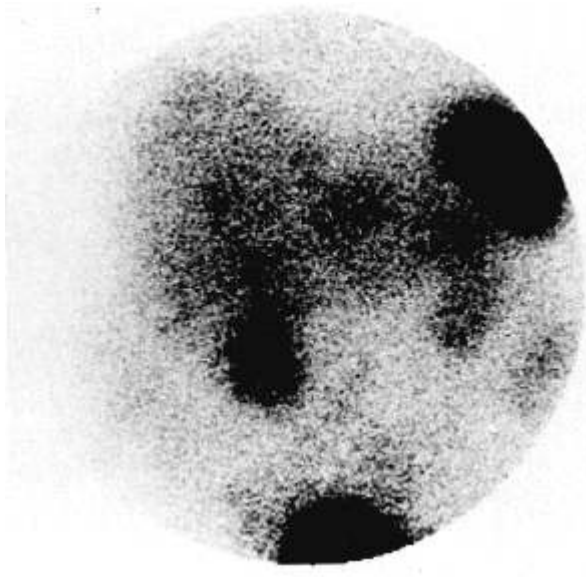

Figure 2. An anterior view of the abdomen showing patchy uptake of radiolabel throughout the liver. Physiological uptake is seen in the kidneys, spleen and bladder.

known disease site (56%). Disease was downstaged in four out of seven patients with extensive disease and upstaged in one patient with limited disease. Of the eight patients found to have metastases at the completion of all investigations, [^{111}In]pentetreotide detected secondaries in four or 50%.

We subsequently assessed a further 10 patients with SCLC. Seven of these were evaluated either during or immediately after the first cycle of chemotherapy. [^{111}In]pentetreotide failed to localize the primary tumour in one patient and detected metastases in only one of six patients with extensive disease. Of the remaining three patients, one was imaged after two cycles of treatment and another at relapse. In both cases, all sites of disease were detected. The third patient, imaged for what was thought to be non-SCLC, was found to have SCLC on histological evaluation of the resected specimen after surgery. Both standard and [^{111}In]pentetreotide imaging suggested limited disease.[45]

It is not clear why the metastases were not visualized in all patients with extensive disease. Non-specific uptake of the radiolabel seen in the spleen, kidneys and urinary tract, liver and gastrointestinal tract, pituitary and thyroid gland may have obscured visualization of metastases to these areas. However, the lack of uptake of radiolabel by bone and brain deposits cannot be explained in this way. There are a number of possibilities. In a proportion of cases the metastatic disease may represent a dedifferentiated clone of the primary SCLC not expressing hSSTR. Local factors may also have affected individual patients, either by downregulating hSSTR expression or, if high local levels of endogenous somatostatin were being produced, by blocking the receptor site, thus inhibiting visualization of the disease. In image-negative metastatic disease the SCLC cells themselves may not be expressing specific hSSTR. Rather, it may be that the primary tumour is being visualized due to uptake of the radiolabel by the local inflammatory response, since activated immune cells are known to express hSSTR[10,21], and/or by hSSTR which may be found in high concentrations on peritumoural veins.[13] If this is so, then those tumours where the metastases are seen may represent the true proportion of metastatic SCLC expressing high-affinity hSSTR, that is, 50% of the patients with extensive disease evaluated in the prechemotherapy study. This is in keeping with the known *in vitro* data.[3,46] Further studies have confirmed our findings.[47,48]

Of particular interest are the results of imaging SCLC patients following chemotherapy (Figure 3). Four patients imaged prior to treatment, two with limited disease and two with extensive disease, were re-evaluated with [^{111}In]pentetreotide. A further patient with extensive disease who was imaged with [^{111}In]pentetreotide after completion of his first cycle of chemotherapy was also assessed after completion of treatment. [^{111}In]pentetreotide scintigraphy revealed an area of pathological uptake in the region of the original disease in two patients thought to be in complete remission with chest X-ray and CT scan. In one of these patients a bronchoscopy failed to reveal any tumour. However, an MRI scan subsequently demonstrated an abnormality away from the bronchus suggestive of residual disease. The patient relapsed at this site. Therefore the technique appears to allow a more accurate assessment of prognosis for the individual patient following completion of chemotherapy and may aid subsequent management decisions. Use of this imaging modality may be of particular importance in the evaluation of the response by hSSTR-positive SCLC to novel forms of treatment.[49]

In summary, [^{111}In]pentetreotide scintigraphy may be a useful complementary tool in the radiological diagnostic evaluation of patients with SCLC, and may have a role to play in identifying those patients most likely to respond to somatostatin analogue therapy. Of great significance in this regard is the efficacy of this agent in detecting residual SCLC disease, suggesting that treated SCLC tumours continue to express hSSTR. This lays the groundwork for an evaluation of the use of

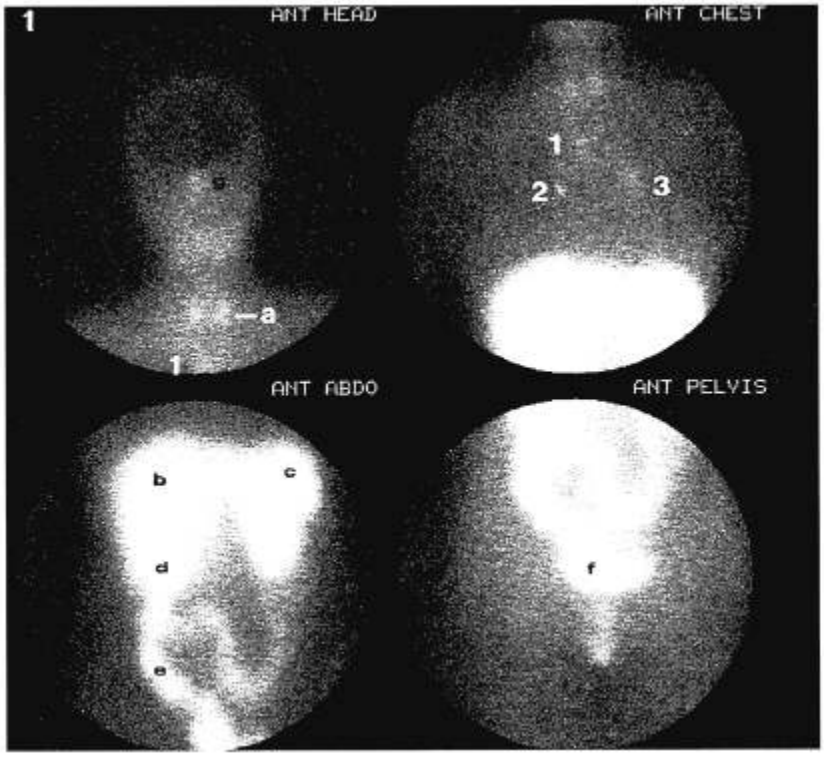

Figure 3. Anterior planar images of the head and neck, thorax, abdomen and pelvis of a patient after two cycles of chemotherapy for small-cell lung carcinoma. Physiological uptake of the radiolabel is seen in the thyroid (a), liver (b), spleen (c), kidneys (d), bowel (e), bladder (f) and pituitary (g). Pathological accumulation is seen in the mediastinum (1), the right hilum (2) and the left hilum (3).

somatostatin analogues as therapeutic agents in the treatment of patients with chemotherapeutically debulked SCLC disease.[49]

Extrapulmonary small-cell carcinomas

Extrapulmonary small-cell carcinomas of the gastrointestinal tract and pancreas are rare aggressive tumours associated with a poor prognosis. Like SCLC they express neuroendocrine features and respond to chemotherapy. We have reported two cases of extrapulmonary small-cell carcinomas imaged with [^{111}In]pentetreotide (Table 1). The first patient developed her tumour on a background of multiple endocrine neoplasia type 1. Imaging with [^{111}In]pentetreotide localized the gastrinoma and all carcinoma sites detected by standard staging procedures at a single sitting. Treatment with doxorubicin, cyclophosphamide and etoposide resulted in a partial remission. [^{111}In]pentetreotide imaging after chemotherapy detected all residual sites of disease. The second patient presented with a gastric cardia tumour extending submucosally into the lower oesophagus. [^{111}In]pentetreotide imaging failed to localize the tumour. Therefore it appears that extrapulmonary small-cell carcinomas may express hSSTR, allowing imaging with [^{111}In]pentetreotide before and after chemotherapy, demonstrating the efficacy of this technique in monitoring tumour response to treatment.[45,50]

Table 1. Summary of lung and extrapulmonary small-cell carcinoma (n = 25) imaging data.

	Sites of disease (no.)	
	Standard imaging	[^{111}In]Pentetreotide
Primary	24	23*
Liver/adrenals	11	6
Bone	7	4
Brain	1	1†

[^{111}In]Pentetreotide imaging detected an intrathoracic primary small-cell lung cancer not seen on computerized tomography scan* and an otherwise unsuspected cerebellar metastasis†. However, known, radiologically detected metastases were not visualised in seven out of 15 patients. [^{111}In]Pentetreotide imaging failed to detect sites of disease in two patients.

Non-small-cell lung cancer

Of 23 patients imaged with non-SCLC, 20 had the procedure performed as part of the preoperative assessment. [^{111}In]pentetreotide detected the primary tumour in all patients, correctly staging

the disease in 17 patients. Of the three patients incorrectly staged, two were as the result of false-positive uptake in benign lesions. Pathological accumulation of the radiolabel, interpreted as non-SCLC metastatic disease, was seen in a thyroid nodule in one patient and in the mediastinum in another. Postsurgical evaluation of the thyroid nodule revealed a colloid cyst. Histological review of the lymph nodes in the patient with mediastinal uptake revealed granulomatous disease, recently reported to express hSSTR.[51] In the third case the tumour appeared smaller on [^{111}In]pentetreotide imaging than on CT scanning and at surgery. On the other hand, disease spread was seen with [^{111}In]pentetreotide imaging in one case that was not initially suspected. In a further patient a small primary squamous cell cancer not visualized on chest X-ray or CT scan but found at bronchoscopy was localized with SPECT scintigraphy.

Three patients were imaged with known disseminated disease. The metastatic sites were visualized in all cases (Figure 4a and 4b). Two reported studies have confirmed the efficacy of [^{111}In]pentetreotide imaging in primary non-SCLC, with detection of the pulmonary lesion in 40 out of 40 and 10 out of 13 patients, respectively.[47,48] However, mediastinal and distant metastases were frequently missed in patients with known metastatic disease.

The finding of uptake in the non-SCLC tumours in these studies is unexpected, as the analysis of xenografts grown from non-SCLC cell lines and freshly resected tumour specimens, using cell membrane preparations and autoradiography, had failed to reveal hSSTR.[3] We evaluated membrane preparations of freshly frozen non-SCLC tumour specimens resected from three patients, two of whom had had their tumours visualized with [^{111}In]pentetreotide prior to surgery. In all three samples we detected the presence of high-affinity hSSTR. A histological assessment of the samples before the binding assay showed them to be composed of tumour cells and necrotic tissue, stroma and/or inflammatory cells. Therefore we concluded that the hSSTR may have been on tissues other than the cancer cells.[49] The strongest evidence for the presence of specific hSSTR in non-SCLC is the demonstration by Fujita *et al.*[52] of hSSTR1 and hSSTR2 messenger RNA in non-SCLC cell lines.

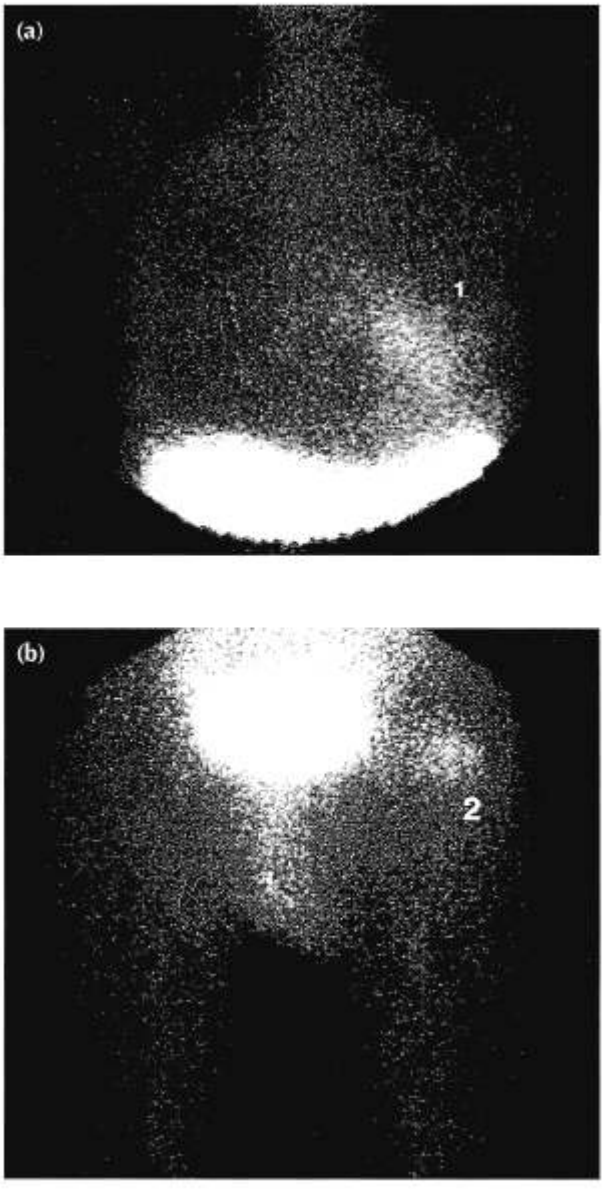

Figure 4. (a) Anterior planar image of the thorax of a man with non-small-cell lung cancer showing pathological accumulation of the radiolabel in the left lung consistent with a tumour extending from the hilum (1); (b) a lesion present in the left hip of the same patient (2).

Bronchial carcinoid disease

We recently reported the successful localization of the primary tumour in two patients with bronchial carcinoid disease (Figure 5).[53] In one of these, membrane preparations from the resected specimen were analysed for hSSTR and a single class of high-affinity hSSTR was identified.[49]

Medullary thyroid carcinoma

In a recent study, we reported the successful localization of recurrent/metastatic medullary thyroid carcinoma in four out of five patients, using ^{111}In-

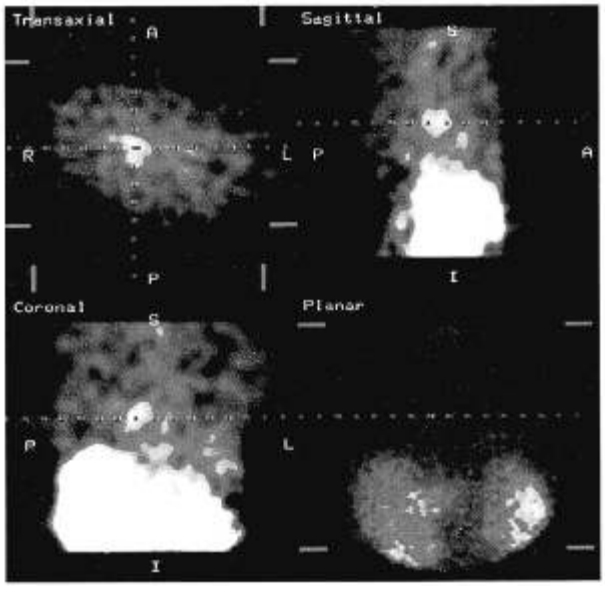

Figure 5. Single-photon emission computed tomography (SPECT) image of a patient with a bronchial carcinoid tumour not localized with planar imaging. The tumour was found to express high-affinity somatostatin receptors when evaluated following surgery.

labelled anticarcinoembryonic antigen monoclonal antibody fragments.[54] We subsequently reassessed four of these patients with [^{111}In]pentetreotide imaging. In all four patients metastatic disease was localized, including mediastinal disease in the patient who had had a negative scan in the previous study (O'Byrne *et al.*, unpublished data, 1993). Further studies have demonstrated that tumour sites may be localized in the majority of patients with medullary thyroid carcinoma.[55–57] However, the technique is insensitive in detecting liver metastases and intrathyroidal tumours due to physiological uptake of the radiolabel in these sites. Furthermore, false-positive results may be obtained due to the localization of other pathological processes that express hSSTR. The visualization of medullary thyroid carcinoma *in vivo* correlates with the presence of hSSTR *in vitro*. Serum calcitonin : carcinoembryonic antigen ratios in patients whose tumours are detected during scintigraphy are higher,[55–57] suggesting that hSSTR are present on more differentiated medullary thyroid carcinomas. Finally, [^{111}In]pentetreotide imaging may have a particular use in the identification of patients with medullary thyroid carcinoma who have multiple endocrine neoplasia type IIB syndrome in whom the detection of associated phaeochromocytomas has been reported.[55–57]

Results of somatostatin analogue imaging in other tumour types

Pituitary adenomas

Membrane binding assays, autoradiography and *in situ* hybridization, have been able to demonstrate hSSTR on the vast majority of somatotroph adenoma samples and cell lines *in vitro*. There is a close correlation between preoperative suppression of growth hormone with octreotide and the subsequent detection of somatostatin receptors on surgically resected specimens from these patients.[5,11,12,40] A significant proportion of nonfunctioning pituitary tumours have been found to express hSSTR. Again, it is the hSSTR-positive subgroup of patients who are likely to respond to octreotide treatment. In a study of four patients, long-term high-dose octreotide treatment resulted in a significant reduction in gonadotrophin levels in two of the four and an improvement in the visual field defects in three. However, a substantial reduction in tumour size was not seen. [^{111}In]pentetreotide imaging may localize these tumours *in vivo*.[40,58] It is interesting that thyroid stimulating hormone-producing adenomas have also been detected *in vivo*.[40] Nevertheless, there are a number of drawbacks to [^{111}In]pentetreotide pituitary imaging. First, the normal pituitary expresses hSSTR and may be visualized. Second, pituitary metastases from hSSTR-positive malignancies such as SCLC, lymphomas and parasellar meningiomas may be imaged, reducing the differential diagnostic capacity of [^{111}In]pentetreotide.[40,58]

Breast cancer

In vitro studies suggest that a significant proportion of breast tumours express hSSTR.[32] A recent study reported the localization of primary breast tumours in 39 out of 52 patients (75%) imaged with [^{111}In]pentetreotide. Following surgery, *in vitro* autoradiography of 30 of these tumours with [^{125}I-Tyr^3]octreotide confirmed that 28 were hSSTR-positive. Invasive ductal cancer was significantly more likely to express hSSTR *in vivo* than invasive lobular cancer ($p < 0.05$). Likewise, T2 tumours were more likely to be imaged than T1 lesions ($p < 0.05$). Nonpalpable axillary lymph nodes were seen in four out of 13 patients with subsequently confirmed metastases. After a mean follow-up period of 2.5 years radiolabelled somatostatin analogue scintigraphy in 28 out of 37 patients with an original

in vivo hSSTR-positive tumour revealed areas of pathological accumulation of the radiolabel in eight patients, two of whom had confirmed metastatic disease. The technique is therefore a sensitive method of detecting hSSTR-positive breast tumours, localizing otherwise unsuspected metastatic sites of disease in a proportion of patients. Given the recent encouraging antiproliferative effects of somatostatin analogues on hSSTR-positive breast cancer lines *in vitro* and *in vivo* as well as the promising results of a number of clinical trials, [^{111}In]pentetreotide scintigraphy may be found useful in the selection of patients for treatment with somatostatin analogues.[59]

Lymphomas

Given the knowledge that cells and neoplasms of lymphoid origin express hSSTR,[10,21] recent studies have focused on the use of [^{111}In]pentetreotide in the pretreatment and follow-up evaluation of patients with Hodgkin's and non-Hodgkin's lymphomas. The results to date have been encouraging. Because total body scanning is performed, [^{111}In]pentetreotide may be able to detect clinically non-suspicious lesions earlier. Neither radiotherapy nor chemotherapy influence the sensitivity of this imaging. When the first scans reveal hSSTR-positive disease, residual disease after treatment is also hSSTR-positive. Therefore the radiolabel may be used to monitor response to therapy as for SCLC and extrapulmonary small-cell carcinoma. Furthermore, [^{111}In]pentetreotide may be able to distinguish between benign and malignant tissue, particularly in the presence of a residual mass after therapy, which is not possible using ultrasound, CT or MRI.[40,60–62] Therefore it appears that [^{111}In]pentetreotide scintigraphy may become a complementary technique in the radiological diagnostic evaluation and follow up of patients with malignant lymphoma.

Neuroblastomas and phaeochromocytomas

Recent evidence suggests that approximately 75% of phaeochromocytomas and over 50% of neuroblastomas express hSSTR. In keeping with these findings, octreotide has been shown to significantly reduce catecholamine levels in patients with chromaffin cell tumours,[63] and to inhibit cyclic AMP accumulation and clonal proliferation of hSSTR-positive neuroblastoma cell lines.[15] Phaeochromocytomas have been visualized using [^{111}In]pentetreotide. Unfortunately, due to high uptake in the kidney (the principal route of radiolabel excretion), visualization of primary adrenal phaeochromocytomas with [^{111}In]pentetreotide scintigraphy may be impeded.[39,40] Nonetheless, recent work has indicated a potential use for the radiolabel in this condition.[64] [^{111}In]pentetreotide scintigraphy was compared with meta-iodobenzylguanidine imaging in patients with malignant phaeochromocytoma. The uptake of meta-iodobenzylguanidine was more intense than that of [^{111}In]pentetreotide. However, while meta-iodobenzylguanidine imaged significantly more sites of disease, a number of foci were seen only with octreotide imaging. It was concluded that [^{111}In]pentetreotide imaging may be useful in identifying sites of metastatic malignant phaeochromocytoma, particularly in meta-iodobenzylguanidine image-negative tumours.[40,64] In keeping with the *in vitro* data, [^{111}In]pentetreotide imaging is also effective in detecting neuroblastoma, localizing disease sites in up to 89% of cases studied.[40]

Ectopic Cushing's syndrome

hSSTR scintigraphy has been evaluated in patients with Cushing's syndrome secondary to ectopic adrenocorticotrophic hormone- or corticotrophin-releasing hormone. In two studies the primary tumour was located in nine out of 11 patients. Normal scans were obtained in eight patients with corticotrophin-secreting pituitary adenomas and one with an adrenal tumour. These results suggest that hSSTR imaging can be included as a diagnostic step for patients with suspected ectopic adrenocorticotropic or corticotrophin-releasing hormone-secreting tumours and their metastases.[65,66].

Miscellaneous

In vitro data suggest that all meningiomas and a proportion of other well-differentiated central nervous system tumours express somatostatin receptors.[5,11,12,40] Meningiomas (100%) and astrocytomas (66%) have been successfully localized with radiolabelled somatostatin analogues.[40,67,68] Indeed, Maini *et al.*[67] have demonstrated that [^{111}In]pentetreotide can be used to discriminate between meningioma and acoustic neuroma and concluded that [^{111}In]pentetreotide imaging is a safe and rapid test that can increase the specificity of traditional neuroimaging procedures.

In accord with results using [^{123}I-Tyr^3]octreotide, [^{111}In]pentetreotide has proved effective in detecting neuroendocrine tumours of the head and neck, including carcinoid of the larynx, Merkel cell carcinoma and paragangliomas. As described for GEP tumours, SCLC and lymphomas, [^{111}In]pentetreotide scintigraphy not only localizes clinically suspected lesions but also detects multicentricity and distant metastases. In this context, and with paragangliomas in general, [^{111}In]pentetreotide imaging could be used as a screening test to be followed by more conventional imaging with CT, MRI or ultrasound of the sites at which abnormalities are found. Further work has confirmed that radiolabelled somatostatin analogue imaging is a simple and sensitive method for the *in vivo* localization of Merkel cell tumours and has an equal or even greater sensitivity than CT or ultrasound.[40,69,70]

Approximately 72% of renal cell carcinomas express somatostatin receptors *in vitro*.[71] Because renal cell cancers are also highly angiogenic, the angiogenesis-inhibiting somatostatin analogues may be useful in the management of these tumours. In accord with *in vitro* data, [^{111}In]pentetreotide imaging has detected renal cell cancer lesions in 43% of patients assessed. As with other tumours, the radiolabel may make it possible to predict those tumours that are likely to respond to somatostatin analogue therapy.[72]

Future directions

Novel radiolabelled somatostatin analogues

The successful application of [^{111}In]pentetreotide imaging in oncology has led to research into novel radiolabelled somatostatin analogues. These efforts have concentrated on the development of a radiolabel capable of detecting receptor subtypes not readily visualized with [^{111}In]pentetreotide and on making somatostatin receptor imaging safer and cheaper.

One of the products of this research is [^{111}In-DTPA-D-Phe^1]RC-160. Compared to [^{111}In]pentetreotide the new radiolabel shows a higher ratio of blood/background to tumour activity and therefore has no advantage over [^{111}In]pentetreotide in the visualization of tumours that bind both analogues. However, recent reports have suggested that hSSTR subtypes present on breast, ovary, exocrine pancreas, prostate and colon cancer will differentially bind RC-160 but not octreotide. In these tumours [^{111}In-DTPA-D-Phe^1]RC-160 may be of value as a radiopharmaceutical agent for imaging hSSTR-positive tumours that do not bind octreotide.[73]

A further novel analogue is [DFO]octreotide (SDZ 216-927), which consists of desferrioxamine B coupled to octreotide via a succinyl linker. This conjugate can be labelled with ^{67}Ga for scintigraphy or ^{68}Ga for positron emission tomography (PET) scanning. In rats bearing an hSSTR-positive pancreatic tumour and injected with 20 MBq [^{67}Ga-DFO]octreotide, the accumulation of the radiolabel after 1 h was 0.38 ± 0.08% injected dose/g, and the tumour : non-tumour ratios for blood, muscle, liver and intestine were 2.5, 7.4, 1.9 and 1.6, respectively. PET studies with [^{68}Ga-DFO]octreotide recorded a very rapid accumulation at the tumour and a subsequent residence half-life of approximately 6 h, suggesting that this agent may be used to diagnose hSSTR-positive tumours.[74]

Finally, attempts have been made to couple octreotide with technetium-99m which is safer to handle and significantly cheaper than ^{111}In. The new derivative of octreotide, SDZ 219-387, readily chelates technetium-99m under mild labelling conditions in good yields. Unfortunately, the radioligand is highly lipophilic and is excreted mainly through the hepatobiliary system. As a consequence, [^{99m}Tc]SDZ 219-387 exhibits increased background activity and is therefore inappropriate for the visualization of somatostatin receptor-positive tumours and/or their metastases in the abdomen.[75]

Peroperative localization of hSSTR-positive tumours

The use of a probe designed to detect γ-ray emitting radionuclides bound to a specific molecule of a tumour cell may provide an accurate technique for localizing primary tumours and their metastases at surgery. Surgical probes have been developed to detect both [^{125}I-Tyr^3]octreotide and [^{111}In]pentetreotide bound to hSSTR-bearing tumours during an operation with encouraging results in medullary carcinoma of the thyroid, midgut carcinoid tumours and endocrine pancreatic tumours. Further studies are required to validate the encouraging preliminary results and to assess the impact of this technique on the duration of symptom control and survival.[76–79]

Radiotherapeutics

The possibility of using a radiolabelled chelated somatostatin analogue as a radiotherapeutic agent in treating somatostatin receptor-positive SCLC tumours is an exciting prospect for the future. As somatostatin analogues are based on sequences of host-circulating hormone they rarely induce immunization. The accumulation of [^{111}In]pentetreotide in gastrointestinal APUDomas is between 0.0123 and 0.2% of the administered dose per gram of tumour tissue. The rapid clearance of the radiolabel from the blood, the relatively low accumulation in the liver (1.9 and 2.2% of the dose administered after 4 and 24 h, respectively) resulting in a relatively low rate of excretion into the gastrointestinal tract and, finally, predominantly renal clearance are advantageous. However, the level of renal accumulation and the relatively long renal effective half-life will limit the maximally applicable radiation dose. Investigations into procedures which would lower the renal accumulation of the radiolabel are ongoing.[40]

Conclusion

In conclusion, radiolabelled somatostatin analogue imaging is the first in what promises to be a long line of radiolabelled peptides which will allow the detection of specific receptor-bearing lesions in patients. The imaging of all disease sites at a single sitting, thereby making further investigations unnecessary, the localization of otherwise unexpected metastatic deposits and the detection of residual disease not found by other means suggest that [^{111}In]pentetreotide may be a useful adjunct in the diagnostic evaluation of patients with hSSTR tumours. Moreover, somatostatin analogue scintigraphy may be useful in the selection of patients for somatostatin analogue therapy, either alone or in combination with cytotoxic agents.

References

1. Reichlin S. Somatostatin (part 1). *N Engl J Med* 1983; **309**: 1495–1501.
2. Reichlin S. Somatostatin (part 2). *N Engl J Med* 1983; **309**: 1556–1563.
3. O'Byrne KJ, Carney DN. Somatostatin and the lung. *Lung Cancer* 1993; **10**: 151–172.
4. Mascardo RN, Sherline P. Somatostatin inhibits rapid centrosomal separation and cell proliferation induced by epidermal growth factor. *Endocrinology* 1992; **111**: 1394–1396.
5. Reubi JC, Kvols L, Krenning E, *et al.* Distribution of somatostatin receptors in normal and tumour tissue. *Metabolism* 1990; **39** (suppl 2): 78–81.
6. Yamada Y, Post SR, Wang K, *et al.* Cloning and functional characterisation of a family of human and mouse somatostatin receptors expressed in brain, gastrointestinal tract, and kidney. *Proc Natl Acad Sci USA* 1992; **89**: 251–255.
7. Yamada Y, Reisine T, Law SF, *et al.* Somatostatin receptors, an expanding gene family: cloning and functional characteristics of human SSTR3, a protein coupled to adenylyl cyclase. *Mol Endocrinol* 1992; **6**: 2136–2142.
8. Yamada Y, Kagimoto S, Kuboto A, *et al.* Cloning, functional expression and pharmacological characteristics of a fourth (hSSTR4) and a fifth (hSSTR5) human somatostatin receptor subtype. *Biochem Biophys Res Commun* 1993; **195**: 844–852.
9. Rohrer L, Raulf F, Bruns C, *et al.* Cloning and characterization of a fourth human somatostatin receptor. *Proc Natl Acad Sci USA* 1993; **90**: 4196–4200.
10. van Hagen PM, Krenning EP, Kwekkeboom DJ, *et al.* Somatostatin and the immune and haemapoetic system: a review. *Eur J Clin Invest* 1994; **24**: 91–99.
11. Reubi JC, Laissue J, Krenning E, *et al.* Somatostatin receptors in human cancer: incidence, characteristics, functional correlates and clinical implications. *J Steroid Biochem Mol Biol* 1992; **43**: 27–35.
12. Reubi JC, Schaer JC, Waser B, *et al.* Expression and localisation of somatostatin receptor SSTR1, SSTR2, SSTR3 messenger RNAs in primary human tumours using *in situ* hybridisation. *Cancer Res* 1994; **54**: 3455–3459.
13. Reubi JC, Horisberger U, Laissue J. High density of somatostatin receptors in veins surrounding human cancer tissue: role in tumor–host interaction. *Int J Cancer* 1994; **56**: 681–688.
14. Foekens JA, Portengen H, van Putten WLJ, *et al.* Prognostic value of receptors for insulin-like growth factor, somatostatin, and epidermal growth factor in human breast cancer. *Cancer Res* 1989; **49**: 7002–7009.
15. O'Dorisio MS, Chen F, O'Dorisio TM, *et al.* Characterisation of somatostatin receptors on human neuroblastoma tumors. *Cell Growth Differ* 1994; **5**: 1–8.
16. Egan SE, Weinberg RA. The pathway to signal achievement. *Nature* 1993; **365**: 781–783.
17. Pan MG, Florio T, Stork PJS. G protein activation of a hormone-stimulated phosphatase in human tumor cells. *Science* 1992; **256**: 1215–1217.
18. Buscail L, Delesque N, Esteve JP, *et al.* Stimulation of tyrosine phosphatase and inhibition of cell proliferation by somatostatin receptor subtypes SSTR1 and SSTR2. *Proc Natl Acad Sci USA* 1994; **91**: 2315–2319.
19. Patel YC, Greenwood MT, Warzynska A, *et al.* All 5 cloned human somatostatin receptors (hSSTR1-5) are functionally coupled to adenylyl cyclase. *Biochem Biophys Res Commun* 1994; **198**: 605–612.
20. Qin Y, Ertl T, Groot K, *et al.* Somatostatin analog RC-160 inhibits growth of CFPAC-1 human pancreatic cancer cells *in vitro* and intracellular production of cyclic adenosine monophosphate. *Int J Cancer* 1995;

60: 694–700.
21. Ilondo MM, de Meyts P, Bouchelouche P. Human growth hormone increases cytosolic free calcium in cultured human IM-9 lymphocytes: a novel mechanism of growth hormone transmembrane signalling. *Biochem Biophys Res Commun* 1994; **202**: 391–397.
22. Pollack MN, Polychronakos C, Guyda H. Somatostatin analogue SMS 201-995 reduces serum IGF-1 levels in patients with neoplasms potentially dependent on IGF-1. *Anticancer Res* 1989; **9**: 889–892.
23. Woltering EA, Barrie R, O'Dorisio TM, *et al.* Somatostatin analogues inhibit angiogenesis in the chick chorioallantoic membrane. *J Surg Res* 1991; **50**: 245–251.
24. Gastpar H, Zoltobrocki M, Weissgerber PW. The inhibition of cell stickiness by somatostatin. *Res Exp Med (Berl)* 1983; **182**: 1–6.
25. Schally AV. Hypothalamic hormones: from neuroendocrinology to cancer therapy. *Anti-Cancer Drugs* 1994; **5**: 115–130.
26. Sandler LM, Burrin JM, Williams G, *et al.* Effective long-term treatment of acromegaly with a long-acting somatostatin analogue (SMS 201-99). *Clin Endocrinol (Oxf)* 1987; **26**: 85–95.
27. Saltz L, Trochanowski B, Buckley M, *et al.* Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer* 1993; **72**: 244–248.
28. Kvols L, Reubi JC. Metastatic carcinoid tumors and the malignant carcinoid syndrome. *Acta Oncol* 1993; **32**: 197–201.
29. Anthony L, Johnson D, Hande K, *et al.* Somatostatin analogue phase I trials in neuroendocrine neoplasms. *Acta Oncol* 1993; **32**: 217–223.
30. Klijn JGM, Hoff AM, Planting AST, *et al.* Treatment of patients with metastatic pancreatic and gastrointestinal tumours with a somatostatin analogue Sandostatin: a phase II study including endocrine effects. *Br J Cancer* 1990; **62**: 627–630.
31. Parmar H, Charlton CDA, Phillips RH, *et al.* Therapeutic response to somatostatin analogue, BIM 23014, in metastatic prostatic cancer. *Clin Exp Metastasis* 1992; **10**: 3–11.
32. Prevost G, Israel L. Somatostatin and somatostatin analogues in human breast cancer. *Recent Results Cancer Res* 1993; **129**: 63–70.
33. Rosenberg L, Barkun AN, Denis MH, *et al.* Low dose octreotide and tamoxifen in the treatment of adenocarcinoma of the pancreas. *Cancer* 1995; **75**: 23–28.
34. Romani R, Morris DL. SMS 201.995 (Sandostatin) enhances *in-vitro* effects of 5-fluorouracil in colorectal cancer. *Eur J Surg Oncol* 1995; **21**: 27–32.
35. Krenning EP, Bakker WH, Breeman WAP, *et al.* Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. *Lancet* 1989; **i**: 242–244.
36. Lamberts SWJ, Bakker WH, Reubi JC, *et al.* Somatostatin-receptor imaging in the localisation of endocrine tumors. *N Engl J Med* 1990; **323**: 1246–1249.
37. Lamberts SWJ, Hofland LJ, van Koetsveld PM, *et al.* Parallel *in vivo* and *in vitro* detection of functional somatostatin receptors in human endocrine pancreatic tumors: consequences with regard to diagnosis, localisation and therapy. *J Clin Endocrinol Metab* 1990; **71**: 566–574.
38. Kwekkeboom DJ, Krenning EP, Bakker WH, *et al.* Radioiodinated somatostatin analog scintigraphy in small-cell lung cancer. *J Nucl Med* 1991; **32**: 1845–1848.
39. Krenning EP, Bakker WH, Kooij PP, *et al.* Somatostatin receptor scintigraphy with Indium-111-DTPA-D-Phe-1-octreotide in man: metabolism, dosimetry and comparison with iodine-123-Tyr-3-octreotide. *J Nucl Med* 1992; **33**: 652–658.
40. Krenning EP, Kwekkeboom JD, Bakker WH, *et al.* Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phe^1]- and [^{123}I-Tyr^3]-octreotide: the Rotterdam experience with more than 1,000 patients. *Eur J Nucl Med* 1993; **20**: 716–731.
41. Kwekkeboom DJ, Krenning EP, Bakker WH, *et al.* Somatostatin analogue scintigraphy in carcinoid tumours. *Eur J Nucl Med* 1993; **20**: 283–292.
42. Hammond PJ, Arka A, Peters AM, *et al.* Localisation of metastatic gastroenteropancreatic tumours by somatostatin receptor scintigraphy with ^{111}In-DTPA-D-Phe^1-octreotide. *Q J Med* 1994; **87**: 83–88.
43. King CM, Reznek RH, Bomanji RH, *et al.* Imaging neuroendocrine tumours with radiolabelled somatostatin analogues and X-ray computed tomography: a comparative study. *Clin Radiol* 1993; **48**: 386–391.
44. Zimmer T, Ziegler K, Bader M, *et al.* Localisation of neuroendocrine tumours of the upper gastrointestinal tract. *Gut* 1994; **35**: 471–475.
45. O'Byrne KJ, Ennis JT, Freyne PJ, *et al.* Imaging of small cell tumours with the radiolabelled somatostatin analogue, ^{111}In-pentetreotide [abstract 1229]. *Proc Am Soc Clin Oncol* 1994; **13**: 364.
46. O'Byrne KJ, Halmos G, Pinski J, *et al.* Somatostatin receptor expression in lung cancer. *Eur J Cancer* 1994; **30A**: 1682–1687.
47. Kwekkeboom DJ, Kho GS, Lamberts SW, *et al.* The value of octreotide scintigraphy in patients with lung cancer. *Eur J Nucl Med* 1994; **21**: 1106–1113.
48. Kirsch CM, von Pawel J, Grau I, *et al.* Indium-111 pentetreotide in the diagnostic work up of patients with bronchogenic carcinoma. *Eur J Nucl Med* 1994; **21**: 1318–1325.
49. O'Byrne KJ, Ennis JT, Freyne PJ, *et al.* Scintigraphic imaging of small cell lung cancer patients with ^{111}In-pentetreotide, a radiolabelled octapeptide analogue of somatostatin. *Br J Cancer* 1994; **69**: 762–766.
50. O'Byrne KJ, Goggins MG, McDonald GS, *et al.* A metastatic neuroendocrine anaplastic small cell tumor with multiple endocrine neoplasia type 1 syndrome: assessment of disease status and response to doxorubicin, cyclophosphamide, etoposide chemotherapy through scintigraphic imaging with ^{111}In-pentetreotide. *Cancer* 1994; **74**: 2374–2378.
51. van Hagen PM, Krenning EP, Reubi JC, *et al.* Somatostatin analogue scintigraphy in granulomatous disease. *Eur J Nucl Med* 1994; **21**: 497–502.
52. Fujita T, Yamaji Y, Sato M, *et al.* Gene Expression of somatostatin receptor subtypes, SSTR1 and SSTR2, in human lung cancer cell lines. *Life Sci* 1994; **55**: 1797–1806.
53. O'Byrne KJ, O'Hare NJ, Freyne PJ, *et al.* Imaging of bronchial carcinoid tumours with indium-111 pentetreotide. *Thorax* 1994; **49**: 284–286.
54. O'Byrne KJ, Hamilton D, Robinson I, *et al.* Imaging

of medullary carcinoma of the thyroid using ^{111}In-labelled anti-CEA monoclonal antibody fragments. *Nucl Med Commun* 1992; **13**: 142–148.
55. Kwekkeboom DJ, Reubi JC, Lamberts SWJ, *et al.* *In vivo* somatostatin receptor imaging in medullary thyroid carcinoma. *J Clin Endocrinol Metab* 1993; **76**: 1413–1417.
56. Dorr U, Frank-Raue K, Raue F, *et al.* The potential value of somatostatin receptor scintigraphy in medullary thyroid carcinoma. *Nucl Med Commun* 1993; **14**: 439–445.
57. Krausz Y, Ish-Shalom S, Dejong RB, *et al.* Somatostatin receptor imaging of medullary thyroid carcinoma. *Clin Nucl Med* 1994; **19**: 416–421.
58. de Bruin TWA, Kwekkeboom DJ, van't Verlaat JW, *et al.* Clinically nonfunctioning pituitary adenoma and octreotide response to long term high dose treatment, and studies *in vitro*. *J Endocrinol Metab* 1992; **75**: 1310–1317.
59. van Eijck CH, Krenning EP, Bootsma A, *et al.* Somatostatin-receptor scintigraphy in primary breast cancer. *Lancet* 1994; **343**: 640–643.
60. Reubi JC, Waser B, van Hagen M, *et al.* *In vitro* and *in vivo* detection of somatostatin receptors in human malignant lymphomas. *Int J Cancer* 1992; **50**: 895–900.
61. van Hagen PM, Krenning EP, Reubi JC, *et al.* Somatostatin analogue scintigraphy of malignant lymphomas. *Br J Haematol* 1993; **83**: 75–79.
62. Bong SB, VanderLaan JG, Louwes H, *et al.* Clinical experience with somatostatin receptor imaging in lymphoma. *Semin Oncol* 1994; **21** (suppl 13): 46–50.
63. Invitti C, de Martin I, Bolla GB, *et al.* Effect of octreotide on catecholamine plasma levels in patients with chromaffin cell tumors. *Horm Res* 1993; **40**: 156–160.
64. Tenenbaum F, Lumbroso J, Schlumberger M, *et al.* Comparison of radiolabeled octreotide and metaiodobenzylguanidine (MIBG) scintigraphy in malignant pheochromocytoma. *J Nucl Med* 1995; **36**: 1–6.
65. de Herder WW, Krenning EP, Malchoff CD, *et al.* Somatostatin receptor scintigraphy: its value in tumor localisation in patients with Cushing's syndrome caused by ectopic corticotropin or corticotropin-releasing hormone secretion. *Am J Med* 1994; **96**: 305–312.
66. Weiss M, Yellin A, Husza'r M, *et al.* Localisation of adrenocorticotropic hormone-secreting bronchial carcinoid tumor by somatostatin receptor scintigraphy. *Ann Intern Med* 1994; **121**: 198–199.
67. Maini CL, Tofani A, Scuito R, *et al.* Somatostatin receptors in meningiomas: a scintigraphic study using ^{111}In-DTPA-D-Phe-1-octreotide. *Nucl Med Commun* 1993; **14**: 550–558.
68. Hildebrandt G, Scheidhauer K, Luyken C, *et al.* High sensitivity of the *in vivo* detection of somatostatin receptors by ^{111}Indium (DTPA-octreotide)-scintigraphy in meningiomas patients. *Acta Neurochir Wien* 1994; **126**: 63–71.
69. Kau RJ, Wagner-Manslau C, Saumweber DM, *et al.* Detection of somatostatin receptors in tumors in the area of the head and neck and their clinical importance. *Laryngorhinootologie* 1994; **73**: 21–26.
70. Kwekkeboom DJ, Hoff AM, Lamberts SWJ, *et al.* Somatostatin analogue scintigraphy: a simple and sensitive method for the *in vivo* visualisation of Merkel cell tumours and their metastases. *Arch Dermatol* 1992; **128**: 818–821.
71. Reubi JC, Kvols L. Somatostatin receptors in human renal cell carcinomas. *Cancer Res* 1992; **52**: 6074–6078.
72. Flamen P, Bossuyt A, Degreve J, *et al.* Imaging of renal cell cancer with radiolabelled octreotide. *Nucl Med Commun* 1993; **14**: 873–877.
73. Breeman WA, Hofland LJ, van der Pluijm M, *et al.* A new radiolabelled somatostatin analogue [^{111}In-DTPA-D-Phe^1]RC-160: preparation, biological activity, receptor scintigraphy in rats and comparison with [^{111}In-DTPA-D-Phe^1]octreotide. *Eur J Nucl Med* 1994; **21**: 328–335.
74. Smith-Jones PM, Stolz B, Bruns C, *et al.* Gallium-67/gallium 68-[DFO]-octreotide: a potential radiopharmaceutical for imaging of somatostatin receptor positive tumors: synthesis and radiolabelling *in vitro* and preliminary *in vivo* studies. *J Nucl Med* 1994; **35**: 317–325.
75. Maina T, Stolz B, Albert R, *et al.* Synthesis, radiochemistry and biological evaluation of a new somatostatin analogue (SDZ 219-387) labelled with technetium-99m. *Eur J Nucl Med* 1994; **21**: 437–444.
76. Schirmer WJ, O'Dorisio TM, Schirmer TP, *et al.* Intraoperative localisation of neuroendocrine tumours with [^{125}I-Tyr^3]-octreotide and a hand held gamma detecting probe. *Surgery* 1993; **114**: 745–751.
77. Waddington WA, Kettle AG, Heddle RM, *et al.* Intraoperative localisation of recurrent medullary carcinoma of the thyroid using indium-111 pentetreotide and a nuclear surgical probe. *Eur J Nucl Med* 1994; **21**: 363–364.
78. Ahlman H, Wangberg B, Tisell LE, *et al.* Clinical efficacy of octreotide scintigraphy in patients with midgut carcinoid tumours and evaluation of intraoperative scintillation detection. *Br J Surg* 1994; **81**: 1144–1149.
79. Ahlman H, Tisell LE, Wangberg B, *et al.* Somatostatin receptor imaging in patients with neuroendocrine tumors: preoperative and postoperative scintigraphy and intraoperative use of a scintillation detector. *Semin Oncol* 1994; **21** (suppl 13): 21–28.