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REVIEW ARTICLE **CME**

Radiolabelled Somatostatin Analogues for Single-photon Emission Scintigraphy

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ABSTRACT

One of the areas where nuclear medicine has proved effective has been in the imaging of somatostatin receptor expressing tumours. These can be overexpressed in a number of tumours, but are most commonly seen in a family of tumours called neuroendocrine tumours. The ability to visualise a particular tumour site depends on the affinity of the radiopeptide for the somatostatin receptors expressed by that tumour. The most widely used such peptide is Indium-111 (^{111}In)-pentetreotide, which is commercially available in many countries. It is possible to change the peptide chain to affect affinities to tumours, but no other ^{111}Indium-labelled agent has become more widely used, partly due to costs. More recent work has concentrated on technetium-99m (^{99m}Tc)–labelled tracers including ^{99m}Technetium-depreotide used for lung cancer imaging and ^{99m}Technetium-EDDA/HYNIC-octreotate, which combines optimal tumour affinity and imaging characteristics.

Key Words: *Neoplasms; Indium radioisotopes; Neuroendocrine tumors; Octreotide; Pentetic acid; Receptors, somatostatin*

中文摘要

單光子發射閃爍照相法的放射標記生長抑素類似物

E Nowosinska、JR Buscombe

核醫學被證實為有效的一個應用是對腫瘤組織生長抑素受體的成像。這種受體在許多腫瘤會過度表達，但這種情況發生在神經內分泌腫瘤尤其普遍。至於是否可以觀察到一個特定的腫瘤位置，則視乎放射標記的多曲肽對於該腫瘤組織生長抑素受體的親和力。由於腫瘤顯像劑^{111}Indium-pentetreotide在多個國家的市場上都可買到，所以被廣泛使用。事實上，可以更改肽鏈來改變標記物對其他腫瘤的親和力，可是因為成本關係，沒有其他^{111}Indium標記物普及應用。最近有研究集中在^{99m}Tc標記放射性示踪劑，包括針對肺癌成像的^{99m}Technetium-depreotide和^{99m}Technetium-EDDA/HYNIC-octreotate，後者結合了最佳的腫瘤的親和力和影像特性。

INTRODUCTION

Somatostatin is a small cyclic neuropeptide that acts as a neurotransmitter in the brain and gut where it inhibits the release of hormones, growth factors and cytokines. It also suppresses cell proliferation.[1] Somatostatin circulates in the blood in two biologically active forms: SST-14 consisting of 14 amino acids, and SST-28 consisting of 28 amino acids. It acts through

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membrane-bound receptors that are widely distributed throughout the body. There are five subtypes of the human somatostatin receptors (SSTRs) which have been characterised (SSTR subtypes 1-5)[2-4] and natural somatostatin binds with similar affinity to all of them. Natural somatostain has a short half-life and is rapidly degraded by enzymatic action. Therefore somatostatin analogues that mimic somatostatin effects but are resistant to enzyme degradation have been synthesised. Among these, octreotide and lanreotide are the currently used analogues in clinical practice. These are cyclic octapeptides, which have longer half-lives (1.5-2 hours) than natural somatostatin.

These analogues demonstrate some differences in the binding affinities to all five receptor subtypes. For example, octreotide exhibits a very low affinity for SSTR subtypes 1 and 4, but binds with high affinity to subtype 2 (predominantly) and subtype 5, and with a moderate affinity to subtype 3. Lanreotide expresses a relatively high affinity to somatostatin subtype 5 receptors.[5] Thus, it seems that small changes in the sequences of these peptides have a great impact on their performance (Table).

Although SSTRs are present in normal tissues, they were also expressed in high concentration in small cell lung cancer, breast cancer, lymphoma, and neuroendocrine tumours (NETs).[6]

The NETs are a heterogenous group of slow-growing tumours. The most common types include carcinoids, and other pancreatic endocrine tumours. Whilst others (melanomas, pheochromocytomas, and medullary thyroid carcinomas) may also be regarded as NETs, though they are not normally considered to be in this group. NETs may present with a wide variety of functional or non-functional endocrine syndromes, they may be familial and they are associated with other tumours.

Of the five major SSTR subtypes, numbers 2 and 5 are the most commonly expressed in NETs. There is, however, considerable variation in SSTR subtype concentrations among the different tumour types, and among tumours of the same type.[7]

The high density of peptide receptors demonstrated on NETs as well as their metastases have been used for both diagnosis and therapy of these tumours with radionuclide techniques.

DIAGNOSIS OF NEUROENDOCRINE TUMOURS

Somatostatin receptor scintigraphy (SRS)

SRS is a sensitive and specific technique to demonstrate in vivo the presence and abundance of SSTR.[8] The main factors that determine the ability of SRS in detecting a lesion are its size, location, receptor density, and the target to background ratio.[9] A range of radiolabelled peptides have been used for somatostatin imaging.

^{111}Indium-DTPA-DPhe-1-octreotide (^{111}In-pentetreotide)

^{111}In-pentetreotide imaging is considered to be the scintigraphic method of choice for NET localisation. The internalisation process of ^{111}In-pentetreotide may assist in successful scintigraphy.[10] It facilitates retention of the radiopeptide in receptor expressing tumours, whereas their relatively small size facilitates rapid clearance from the blood.[11] A major advantage of ^{111}In-pentetreotide is its ability to highlight sites of NET in areas where computed tomography (CT) and magnetic resonance imaging (MRI) may be unhelpful, such as the liver, in and around the pancreas, and metastatic lesions outside the abdomen and chest.[12]

The efficacy of SRS using ^{111}In-pentetreotide in patients with pancreatic NETs and carcinoid was evaluated in a European multicentre trial in 1995[13] (Figures 1 to 3). The highest detection rate was for glucagonoma (100%), VIPomas (88%), gastrinomas (73%), and carcinoids (87%). However, insulinoma was detected in only 46% of cases due to low expression of SSTR subtype 2 in insulin-secreting tumours and their small size (below the

Table. Affinity profiles (IC50, NM) for human somatostatin receptor (SSTR) subtypes 1-5.

Peptides	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
SS-28	5.2	2.7	7.7	5.6	4.0
[^{111}In-DTPA] Octreotide	>10,000	22	182	>1000	237
[^{111}In DOTA,Tyr3] Octreotide DOTATOC	>10,000	11	389	>10,000	114
[^{111}In DOTA,Tyr3] Octreotate DOTATATE	>10,000	1.5	>1000	453	547
[^{111}In -DOTA] Lanreotide DOTALAN	>10,000	23	290	>10,000	16

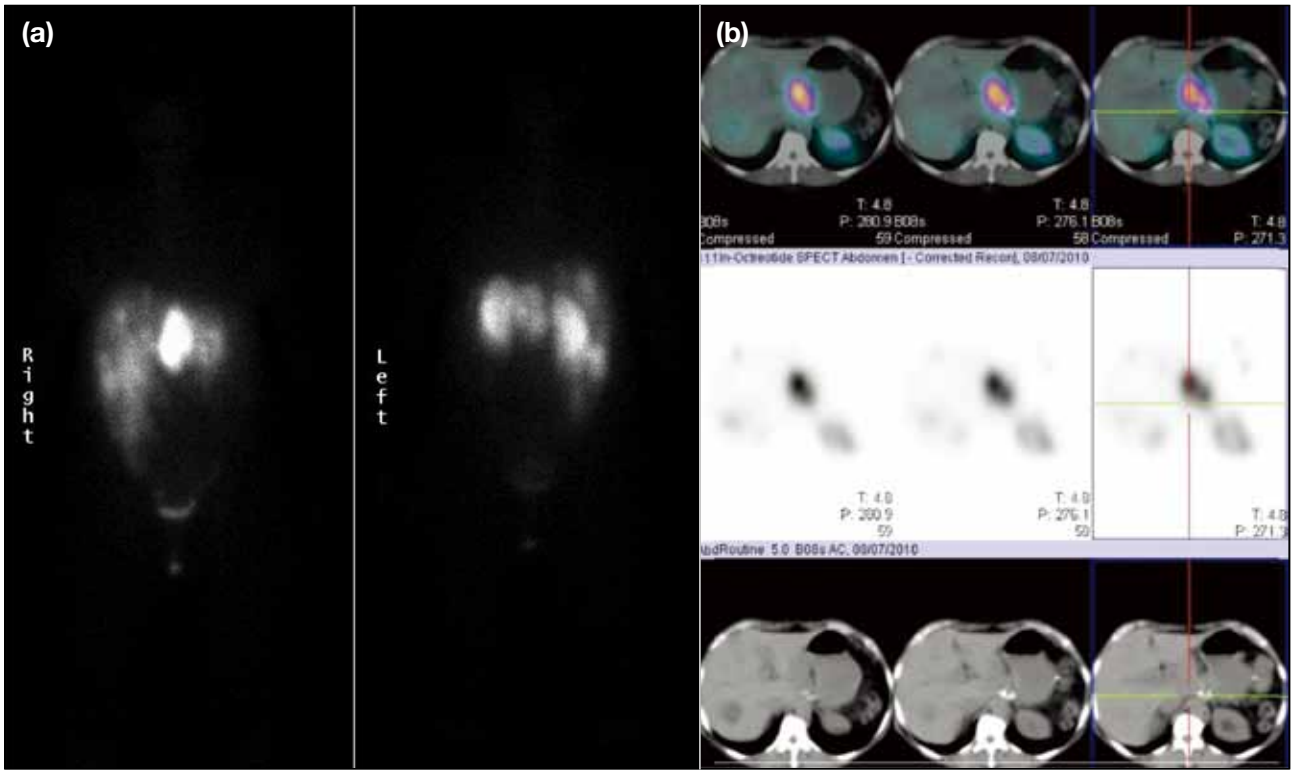

Figure 1. (a) A patient with known metastatic pancreatic neuroendocrine tumour showing the octreotide avid lesions in the liver and in the mid abdomen on the whole-body ^{111}In pentetreotide images. (b) The single-photon emission computed tomography–computed tomography (SPECT-CT) ^{111}In-pentetreotide images show several liver metastases and pancreatic mass (note: fused images in top row, ^{111}In-pentetreotide images in middle row and CT bottom row).

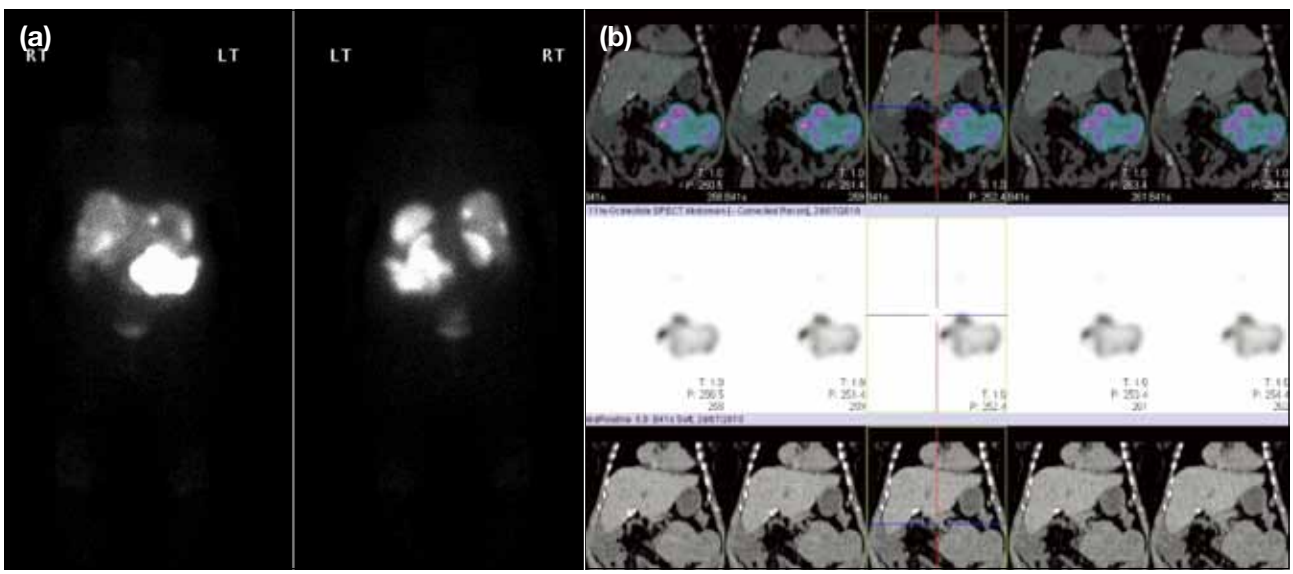

Figure 2. (a) A patient with known metastaic midgut neuroendocrine tumour showing multiple foci of increased tracer uptake within the liver and mid abdomen on the whole-body ^{111}In-pentetreotide images. (b) The single-photon emission computed tomography–computed tomography (SPECT-CT) images show a large mesenteric mass just anterior to the aorta (note: fused images in top row, ^{111}In-pentetreotide images in middle row and CT bottom row).

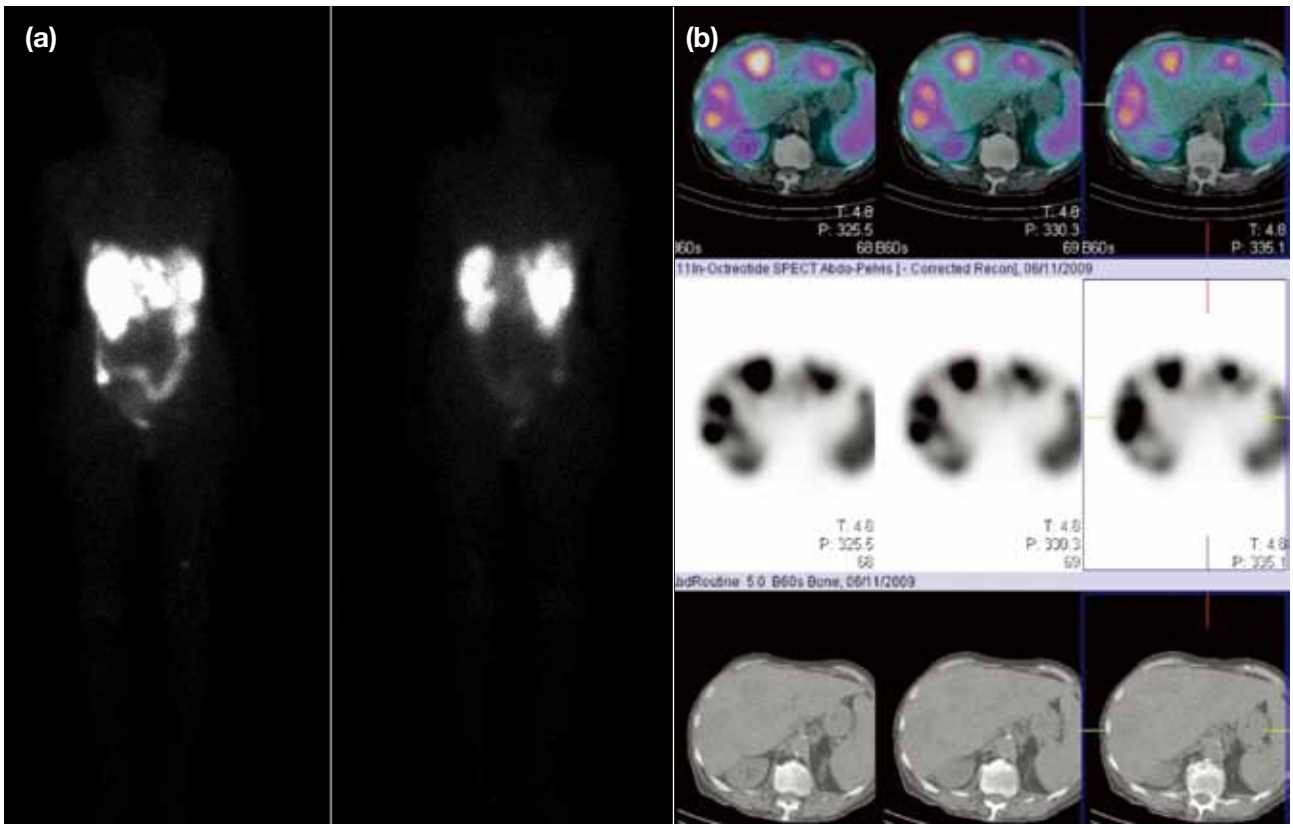

Figure 3. (a) A patient with a large-volume metastatic neuroendocrine tumour in the liver with unknown primary whole-body ^{111}In-pentetreotide images. (b) The site and distribution of the liver metastases are more clearly demonstrated by the single-photon emission computed tomography–computed tomography (SPECT-CT) [note: fused images in the top row, ^{111}In-pentetreotide images in middle row and CT images bottom row].

resolution limit of single-photon imaging). Malignant and metastatic insulinomas may be more easily detected by ^{111}In-pentetreotide than a single primary tumour.[13]

Kaltsas at al[14] in their study confirmed that ^{111}In-pentetreotide was an imaging modality of choice in the initial evaluation of gastroenteropancreatic neuroendocrine and islet cell tumours, which exhibited a sensitivity of 67 to 100%. It can also identify clinically unsuspected lesions and optimise the overall staging of these tumours.[14]

^{111}Indium-DOTA-DPhe–Tyr3-octreotide (DOTATOC)

One section of the MAURITIUS (Multicentre Analysis of a Universal Receptor Imaging and Treatment Initiative, a European Study) trial directly compared ^{111}In-DTPA-DPhe-1-octreotide and ^{111}In-DOTA-DPhe–Tyr3-octreotide scintigraphy. The study revealed discrepancies in radionuclide imaging characteristics, including more clearly defined tumour uptake and detection of the lesions with reduced background, in a third of the patients imaged with ^{111}In-DOTA-DPhe–Tyr3-octreotide. On the molecular level, these differences were related to the higher affinity of ^{111}In-DOTA-DPhe–Tyr3-octreotide for SSTR subtype 2.[15]

^{111}Indium-DOTA-LANREOTIDE (DOTA-LAN)

^{111}In-DOTALAN is another type of ^{111}In-labelled somatostatin analogue which displays high binding affinity to SSTR subtypes 2 and 5 and lower binding affinity to subtype 1. In addition, it also binds significantly to receptor subtypes 3 and 4 which can result in high background and bone marrow activity. This was confirmed when ^{111}In-pentetreotide was noted to detect more sites of NET than ^{111}In-DOTALAN in a direct comparison.[15]

^{99m}Technetium-labelled peptides

^{111}In has several disadvantages, including a long half-life (T1/2=67 h), suboptimal gamma energy (resulting in low injectable activity), and a high radiation burden. Therefore technetium-99m (^{99m}Tc)–labelled somatostatin analogues have been developed utilising the optimal 6-hour half-life and gamma emissions of

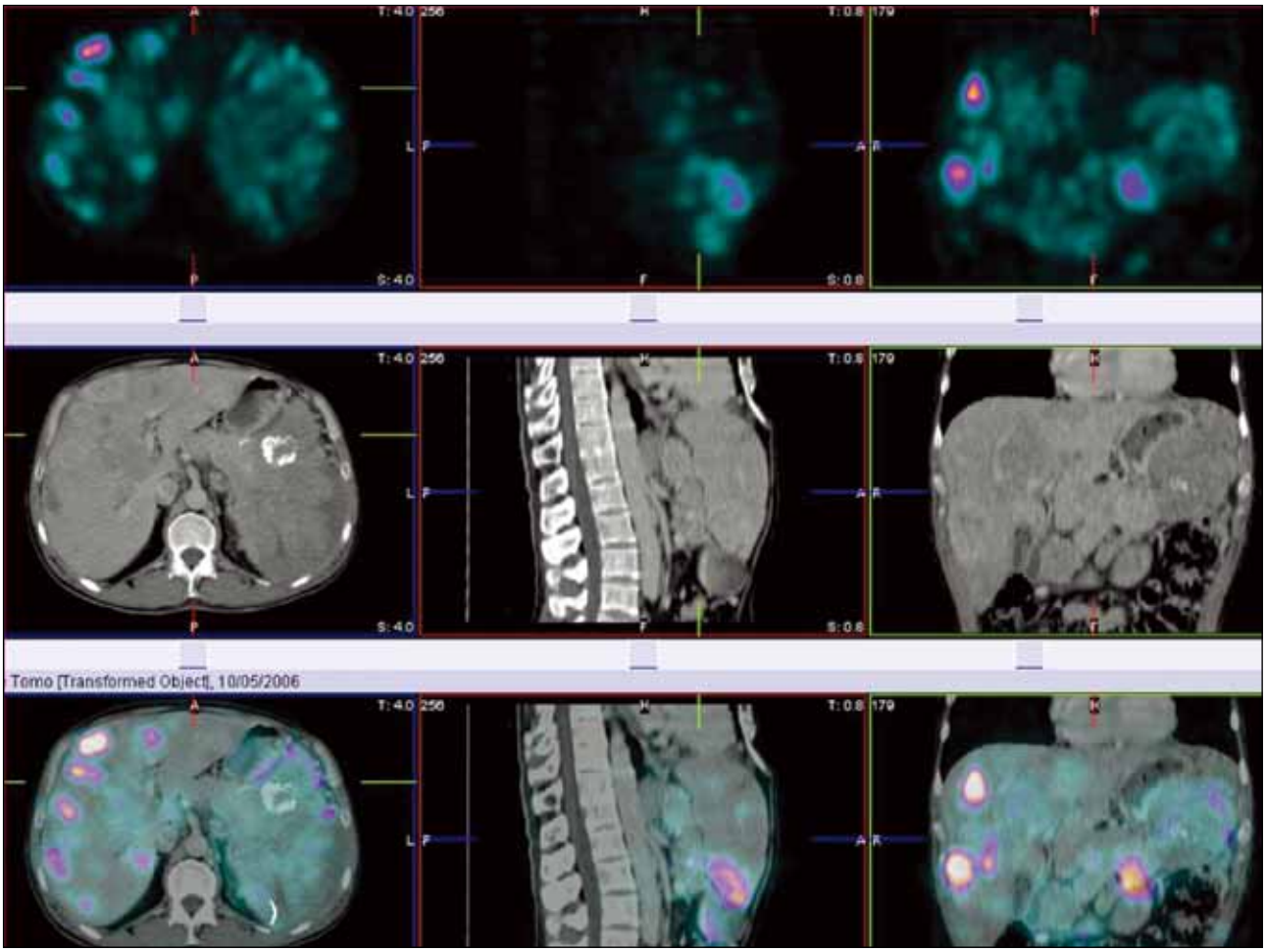

Figure 4. A patient with pancreatic neuroendocrine tumour showing good uptake of ^{99m}Tc-EDDA/HYNIC-octreotate images in multiple liver metastases (in the top row) compared with computed tomographic images (in the middle row) and fused images (in the bottom row). Images courtesy of Dr Cwikla, Warsaw, Poland.

^{99m}Tc, namely ^{99m}Tc EDDA/HYNIC-octreotate and Tc-99m-EDDA/HYNIC-TOC, EDDA/HYNIC being a nicotinic acid derivative which is the ligand between the peptide chain and the ^{99m}Tc. These products were designed to improve availability, cost and image quality of SSTR scintigraphy, as well as a means to reduce the radiation burden to the patient.[16]

^{99m}Technetium-EDDA/HYNIC-octreotate

^{99m}Tc-EDDA/HYNIC-octreotate is a ^{99m}Tc-labelled somatostatin analogue which is currently being used to visualise SSTR-expressing tumours. A recent study comparing ^{111}In-pentetreotide with ^{99m}Tc-EDDA/HYNIC-octreotate scans showed better image quality and detection of more metastases with the latter. The authors endorsed ^{99m}Tc-EDDA/HYNIC-octreotate as an excellent alternative to ^{111}In-pentereotide imaging for the detection and staging of the patients with carcinoid tumours.[17] Though this product has been available in Eastern Europe for about 5 years, there are no clear data to indicate that this technique is any more sensitive than ^{111}In-pentetreotide, though the image quality was better (Figure 4).

^{99m}Technetium-depreotide

This product was developed to have a wider affinity for a range of tumour types than demonstrated by ^{111}In-pentetreotide. Although this product can be used for imaging a range of NETs, it was especially suited to visualising tumours of fore-gut origin (bronchial and thymic carcinoids) but less satisfactory for midgut tumours,[18] for which its sensitivity was only 50%. However, it has found a niche market in the identification of non–small-cell lung cancer, where formal clinical trials showed it had an accuracy of 90% for finding lung cancer.[19] Nevertheless, the method has been overtaken by positron emission tomography and is probably little used despite being cheaper and more

convenient.

Using radiolabelled somatostatins

Somatostain analogue single-photon scintigraphy was considered by organisations such as the European Neuroendocrine Tumour Society to have a limited role in the diagnosis of primary tumours, due to the lack of evidence, whereas histology was regarded as more important.[20] It may nevertheless have a role in finding the presence and site of a tumour in patients with raised plasma markers such as chromogranin-B but no obvious lesions on CT or MRI, though in this situation too the evidence is scarce.[20] Less controversially, it is used as a complementary test for staging and re-staging of NETs. A good example of this was the use of single-photon emission computed tomography–CT (Figures 3 and 4). The third type was to identify which patients could be treated by non-radioactive and radioactive somatostatin analogues.[20]

CONCLUSIONS

SSTR-targeting peptides are widely used for the imaging and therapy in NETs. The introduction of new receptor-specific radiolabelled peptides has improved diagnostic capacity, localisation, staging, and selection of treatment in patients with NETs. Whilst experience from many centres suggests that ^{111}In-pentetreotide does not yet have sufficiently robust evidence about its accuracy, nor can newer somatostatin analogues (e.g. ^{99m}Tc-HYNIC/EDDA-octreotate) be considered agents for routine use, until such data are available.

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