

Review

Treatment of advanced neuroendocrine tumours with the radiolabelled somatostatin analogue octreotide

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ABSTRACT

Neuroendocrine tumours (NET) have a particular tendency to express functional receptors and/or uptake mechanisms. Radionuclides, such as ¹¹¹In-pentetreotide, a somatostatin analogue, which bind to somatostatin receptors, present an imaging modality that has been used for both the diagnosis and staging of NET. Scintigraphy with ¹¹¹In-pentetreotide can identify lesions beyond the diagnostic sensitivity of conventional imaging modalities. In addition, NET that demonstrate positive uptake to a diagnostic ¹¹¹In-pentetreotide can, in theory, be treated with these radionuclides, thus presenting a novel and evolving therapeutic modality in addition to other traditional therapeutic approaches. Although experience with ⁹⁰Y-DOTA-D-Phe¹-Tyr³-octreotide therapy is still limited, preliminary studies have demonstrated useful activity in a variety of NET with limited side-effects. Large phase II clinical trials using ⁹⁰Y-DOTA-D-Phe¹-Tyr³-octreotide therapy are still on-going and the results are expected to be presented soon. In order to improve the response rates obtained, newer somatostatin analogues are being developed and the combination with other β -emitting particles in addition to ⁹⁰Y is being considered.

Key words: neuroendocrine, tumours, radionuclides

INTRODUCTION

Neuroendocrine tumours (NET) constitute a heterogeneous group of tumours which originate from the diffuse neuroendocrine system (DNES) and are programmed to adopt a specific neuroendocrine phenotype¹. The system includes endocrine glands, such as the pituitary, the parathyroids and adrenal glands

as well as endocrine islets within glandular tissue (thyroid or pancreatic) and cells disseminated between exocrine cells, such as endocrine cells of the digestive and respiratory tracts^{2,3}. Although NET may vary in clinical presentation, location and specific histology, they share common features which are detected by refined morphological techniques for endocrine granules, histochemical techniques for secretory peptides or amines and electron microscopy³. Some NET may occasionally exert a very aggressive behavior and become highly malignant (poorly-differentiated NET), but the great majority tend to be relatively slow growing (well-differentiated NET) and retain many multipotent differentiation capacities^{1,3}. Such features

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include the possession of neuroamine uptake mechanisms and/or specific receptors at the cell membrane, such as somatostatin receptors, which can be of great value in identifying and localizing these tumours as well as in their therapy.

¹¹¹IN-PENTETREOTIDE IN THE DIAGNOSIS OF NEUROENDOCRINE TUMOURS

Radionuclides represent a diagnostic modality where radiolabelled peptide analogues, based on their ability to bind to suitable ligands, have been utilized for the identification and localization of NET⁴. The use of radionuclides presents an imaging modality based on *physiological* characteristics (the presence of functioning receptors and uptake mechanisms) rather than on purely anatomical alterations⁵. This imaging modality has been extensively used for the diagnosis and treatment of NET as the great majority of them express somatostatin receptors and therefore become an ideal target for somatostatin derived radionuclides^{4,5}.

Somatostatin is a 14 aminoacids-peptide hormone that is present in the hypothalamus, the cerebral cortex, the brainstem, the gastrointestinal system and the pancreas, whereas somatostatin receptors have been identified on many cells of neuroendocrine origin^{6,7}. Somatostatin is mainly an inhibitory peptide that has a very short half-life, approximately 2 minutes, which makes it unsuitable for routine clinical use^{7,8}. Introduction of D-amino acids and shortening of the molecule to the bioactive core sequence resulted in the eight amino acids-containing somatostatin analogues^{1,6,7}. Octreotide (Novartis, Basel, Switzerland) is the first somatostatin analogue to be used in clinical practice while considerable experience has also been obtained with lanreotide (Ipsen, Paris, France) and more recently vapreotide (Figure 1)⁹. These compounds can be conjugated with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7, 10-tetraacetic acid) as a way of coupling somatostatin analogues with various radionuclides^{5,8}. Out of the five subtypes of somatostatin receptors that have been described, somatostatin receptor type 2 is the one most frequently found in NET^{5,8}. Octreotide exerts its highest affinity for somatostatin receptors type 2, 3 and 5 and thus scintigraphy with octreotide reflects the visualization of octreotide-binding somatostatin receptors^{7,8}. In general, "well-differentiated" NET usually express soma-

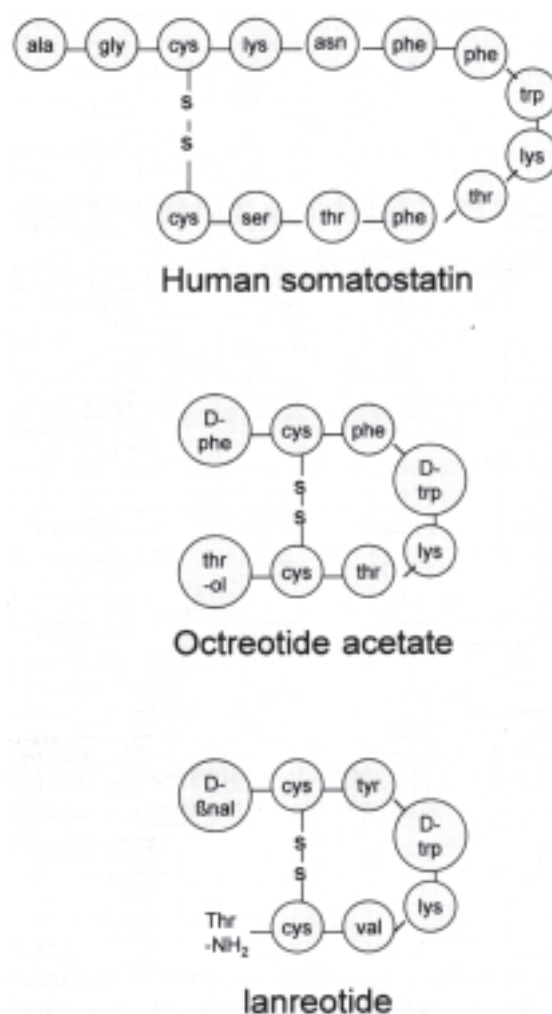


Figure 1. Structure of human somatostatin - 14 and its long acting analogues which are currently used in clinical practice

tostatin receptors which are generally absent from "poorly-differentiated" tumours^{2,9}.

Covalently linking ethylene-triamine-penta-acetic acid (DTPA) with octreotide results in DTPA-octreotide (pentetreotide); this tracer was initially labelled with ¹²³I, but is more clinically effective with ¹¹¹In¹⁰. Scintigraphy with ¹¹¹In-pentetreotide has been shown to have a detection rate of 67-91% for all NET but is of low specificity as uptake is also demonstrable in many other tumours, granulomas and autoimmune diseases^{4,7,11}. (Table 1 shows the particular sensitivity of ¹¹¹In-pentetreotide in the identification and localization of various NET). The fact that abdominal single photon emission computed tomography (SPECT) was not routinely performed in some of the original

Table 1. ¹¹¹In-pentetreotide imaging results in a variety of neuroendocrine tumours

Tumour	Percent tumours with ¹¹¹ In-pentetreotide uptake
Carcinoid	96%
Pheochromocytoma	86%
Medullary thyroid carcinoma	71%
Paranglioma	94%
Insulinoma	61%
Glucagonoma	100%
Gastrinoma	100%

Adopted from Wiseman and Kvols¹¹

studies may explain the differences in the detection ability reported between several studies^{4,8,11,12}. Scintigraphy with ¹¹¹In-pentetreotide is used for the diagnosis and staging of the tumours as well as identifying the patients who may be suitable for treatment with radiolabelled octreotide^{1,4,7}. The detection of an unsuspected lesion in a patient with *known* metastatic spread usually has little impact on management. In contrast, the detection of such a lesion in patients with a single known lesion or without any known lesion is important in that it may affect the selection of curative surgery, which remains the treatment of choice in patients with NET⁸. However, there are no clinical or biochemical predictors of a positive scan, and there is no correlation of a positive scan with the anatomical site of the origin of the tumour^{4,12}. In spite of the efforts in developing more specific radioligands, at present ¹¹¹In-pentetreotide remains the radiopharmaceutical of first choice for the imaging of NET¹⁰. The injected activity in adults is 110-220 MBq of ¹¹¹In-pentetreotide; approximately 80% of i.v. administered radiolabelled ¹¹¹In-pentetreotide is eliminated via the urinary system¹⁰.

BASIC CONCEPTS OF APPLYING RADIOPHARMACEUTICAL THERAPY IN NEUROENDOCRINE TUMOURS

Many tumours are highly radiosensitive, but delivering an adequate dose to the tumour can result in damage to the surrounding healthy tissue. Coupling a radioisotope to a molecule which would specifically bind to tumour cells could, in theory, deliver an effective radiation dose to the tumour without damage to non-tumour tissues, potentially limiting adverse effects^{8,11,12}. The success of the therapeutic strategy depends upon the amount of radioligand which can be concentrated within tumour cells and the rates of internalization, degradation and recycling of both ligand and receptor^{8,11}. Targeted radiotherapy will be effective in tumour treatment if all or nearly all tumour cells have the target antigen, receptor or chemical structure for the radioisotope for the carrier molecule to bind^{11,13}. Tumour heterogeneity will cause incomplete responses at best unless the radiation delivered can kill the nearby tumor cells that are target-negative^{8,11}. Thus, the radioisotope physical properties are important for targeting radiation to the target positive tumour cells but also for the target negative cells as their death will depend on the crossfire from the radioisotope localized on or in the target-positive tumour cells^{11,13}. This non-targeted radiation will also contribute to the radiation dose being absorbed by the surrounding normal cells¹³. The selection of the best radioisotope to use for target radiotherapy depends on the type of radiation emitted, the emission energies, the distance over which the energy is deposited and the physical half-life of the radioisotope (Table 2)^{8,11}.

Radioiodine for treatment of thyroid disorders has been the best example of a radionuclide targeting

Table 2. β -Emitting Radionuclides for Targeted Radiotherapy

Radionuclide	Gamma Emission (kev)	Physical Half-Life ($T_{1/2}$, days)	Beta Emission X90 (mm in water)
¹⁵³ Sm	103	1.93	1.01
⁹⁰ Y	-	2.67	5.34
¹⁸⁶ Re	137	3.78	1.8
¹⁷⁷ Lu	113,208	6.68	-
¹³¹ I	365,637	8.04	0.83
³² P	-	14.28	3.61
⁸⁹ Sr	-	50.52	-

Adopted from Wiseman and Kvols¹¹

agent with a high target-to-nontarget ratio, rapid clearance of the unbound radioisotope and a long residence time in the target¹¹. With the introduction of ¹³¹I-labelled metaiodobenzylguanidine (MIBG), the field of radionuclide treatment has been extended to a wide range of NET^{11,12,14}. Metaiodobenzylguanidine is taken up actively by cell membranes and then by neurosecretory granules in the cytoplasm of cells that express amino-uptake mechanisms; more than 90% of pheochromocytomas and paragangliomas, 70% of carcinoids and around 35% of medullary thyroid carcinomas concentrate MIBG^{2,12,15}. Based on a positive scintigraphy with ¹²³I-MIBG, treatment with ¹³¹I-MIBG has produced overall objective tumor responses ranging between 7.5-35% in a variety of NET (higher response rates have been obtained in patients with chromaffin cell tumours)^{2,12,15}. As scintigraphy with ¹¹¹In-pentetreotide is more sensitive than scintigraphy with ¹²³I-MIBG in identifying various types of NET^{4,12}, it is expected that treatment with radiolabelled somatostatin analogues will probably be applicable to a larger population of patients with NET as well as locate the same lesions identified by ¹³¹I-MIBG^{4,12}.

RADIOPHARMACEUTICAL THERAPY WITH ¹¹¹IN OCTREOTIDE

¹¹¹In emits mainly γ -radiation, which passes through tissue relatively easily and can be imaged using a γ -scanner⁵. In addition, ¹¹¹In also emits Auger and conversion electrons having particle ranges of 0.02 to 10 μ m and 200 to 500 μ m respectively and can therefore be used to investigate its antiproliferative effect in malignant tumours^{8,11}. The short ranged Auger electrons are expected to exert an effect on tumour cell proliferation as the radiotoxicity of Auger electrons is very high if their target, the DNA of the cell, is within the particle range^{8,16}. Following initial experiments in rats where a tumouricidal effect of the radiopharmaceutical was established, the treatment was approved for phase I study in humans^{8,13}. Following dosimetry and pharmacokinetic data derived from animal studies, ¹¹¹In-octreotide was given in humans with at least 2-week intervals between administrations and a total of 8 administrations was aimed at⁸. Potential hematological, biochemical and endocrine side-effects were examined and patients were scanned 3 and 7 days after each administration of the radiotherapeutic dose. The percentage uptake of the administered dose in

total body and in the most prominent tumour was calculated⁸. With administered doses of 6000 to 7000 MBq, critical organs were shown to be the kidney and the spleen. Thirty end stage patients with NET were treated; twenty-one of these patients received a cumulative dose of 20 GBq [¹¹¹InDTPA] octreotide⁸. Seven patients who were treated with a total dose of less than 20GBq had to stop therapy prematurely due to the extension of their disease despite treatment with ¹¹¹In-DTPA-octreotide⁸. From the 21 patients who received adequate doses of ¹¹¹In-DTPA-octreotide (all had progressive disease), 6 showed an antiproliferative effect demonstrated as shrinkage of the tumour. In addition, in another 8 patients treatment with ¹¹¹In-DTPA-octreotide resulted in stabilization of their disease (Figure 2)⁸. However, in spite of these moderately encouraging preliminary results, the radionuclides used in receptor scintigraphy, such as ¹¹¹In, are in general not as suitable for radiotherapy as potent B-emitters, such as yttrium 90 (⁹⁰Y)^{8,11-13}.

RADIOPHARMACEUTICAL THERAPY WITH ⁹⁰Y OCTREOTIDE

Radionuclides emitting B-radiation have greater therapeutic potential since the particles they emit have sufficient energy to cause cell damage without penetrating very far into surrounding tissue^{5,8,11}. A high-energy B-emitter attached to a somatostatin receptor analogue could potentially deliver a lethal dose of radiation to a somatostatin receptor-positive tumour with minimal damage to healthy tissue. The same somatostatin analogue (Tyr³-octreotide) used for diagnosis has been coupled to a bifunctional chelating agent (DOTA) for the complexing of ⁹⁰Y, a pure energetic β -emitter well suited for internal radiotherapy^{2,8,11-13}. In contrast to ⁹⁰Y-DTPA-octreotide, ⁹⁰Y-DOTA-D-Phe¹-Tyr³-octreotide, (⁹⁰Y-SMT487, *OctreoTher*TM), shows no dissociation from the DOTA chelated peptide in serum and can deliver tumouricidal doses of radiation by targeting somatostatin receptor positive tumours who have demonstrated uptake on a diagnostic ¹¹¹In-pentetreotide scan (*Octreoscan*)^{8,13}. SMT487 binds with high affinity to somatostatin receptors (subtypes 2 and 3) and retains both its binding properties and physiological function when labelled with ⁹⁰Y¹⁷. *OctreoTher* induced significant tumour regression in nude mice bearing human pancreatic carcinoma cells and prolonged survival^{8,17}. These

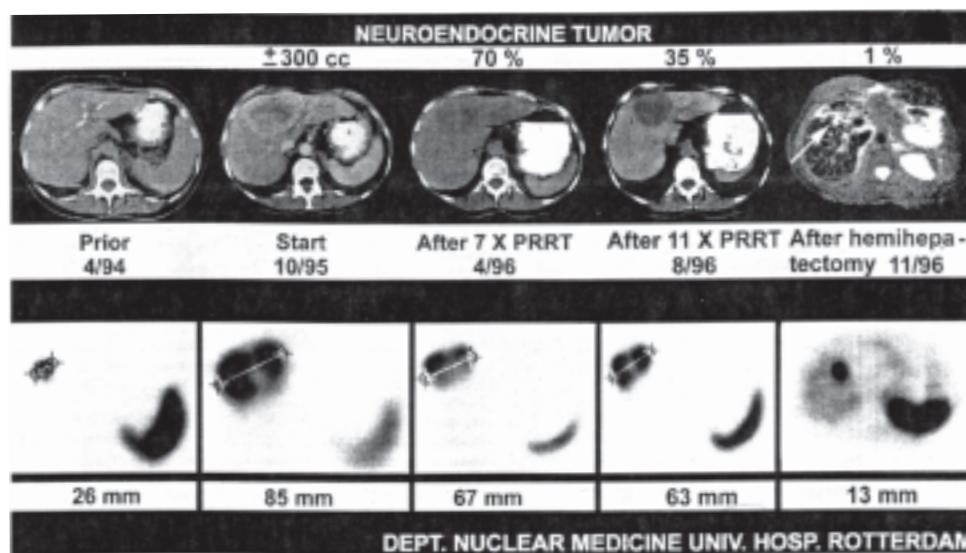


Figure 2. Effects of radiotherapy with [$^{111}\text{In-DTPA}$]octreotide in a patient with a hepatic metastasis of a neuroendocrine tumour treated according to the described protocol. The upper panel shows transversal CT scans, except on 11/96 (MRI), and the lower panel illustrates transversal slices of [$^{111}\text{In-DTPA}$]octreotide SPECT images. The decline in tumour size (300cc) was 30% after seven treatment courses and 65% after 11 courses. After the effect of 11 treatment-courses, the option of hemi-hepatectomy became feasible and this procedure was carried out, leaving *in situ* a lesion of 9mm diameter (MRI) at the cutting-edge (Reproduced with permission from *Ann Oncol*, 10 (Suppl 2): S23-S29, 1999).

good preclinical results led to phase I clinical trials mainly with *OctreoTher* and various other ^{90}Y -labelled somatostatin analogues¹⁷. Phase I clinical trials conducted in patients with NET established that after an intravenous infusion, plasma radioactivity disposition of *OctreoTher* was multiphasic (terminal $t_{1/2}$ approximately 8.6h); unbound radioactivity was excreted in urine¹⁷. By 24hrs, post-dose plasma radioactivity was <1% of the injected dose while *OctreoTher* was not significantly taken up by erythrocytes. A correlation between creatinine clearance and total body radioactivity clearance was observed reflecting that the kidney is the principal drug elimination organ. It was therefore suggested that *OctreoTher* is not recommended in subjects whose creatinine clearance is less than 40ml/min^{8,17}. Radioactivity exposure was mainly, besides the kidneys, to the spleen, urinary bladder wall and tumours. The relative biodistribution and pharmacokinetic profile of *OctreoTher* was not altered by changes in the absolute peptide dose over the range of 50-500 mcg while concomitant administration of amino acids reduced renal radioactivity uptake without altering tumour uptake in a phase I study¹⁷. Cationic amino acids appear to be responsible for the “blocking” of renal tubule uptake of proteins or peptides¹⁸. This is because the membranes of renal tu-

bules contain negatively charged sites to which positively charged residues of peptides or proteins are thought to bind^{8,17,18}. An inhibition of this binding site may explain the effects by administering the positively charged amino acid lysine (both D- and L-lysine) on the re-uptake of *OctreoTher*. A variety of other maneuvers have been attempted, so far without success, in further lowering the renal uptake of *OctreoTher*^{8,17}.

In another similar preliminary study of 20 patients with a variety of tumours, Paganelli *et al.* reported results for an escalating dosage using *OctreoTher*¹⁹. Treatment was initiated with 1.1 GBq per cycle (3 cycles per patient), increasing by 0.4 GBq increments. The maximum tolerated dose was not stated but dosimetric estimations showed that the highest doses were delivered to kidneys ($3.3 \pm 2.2\text{mGy/MBq}$) and spleen ($7.6 \pm 6.3\text{MBq/MBq}$). Only one patient showed grade II renal toxicity and five had hematological toxicity of the same grade. For higher activities renal or splenic toxicities could be prevented by intravenous administration of D-lysine: the objective response rate (complete + partial responses) was 20%^{2,19}. Phase I clinical trials results support the safety and tolerability of the dose selected for further study. A Novartis-sponsored

phase II study involving centers in the USA, Europe and Australia is currently on-going to test the efficacy of *OctreoTher* in patients with a variety of disseminated NET and the results will soon be published^{10,17}. While in general *OctreoTher* is a non- γ emitter, the β -particles can cause localised release of γ -activity from affected cells ("bremsstrahlung"), and we have found that some imaging of the effectiveness of therapy is possible (Figure 3). A fixed-dose regimen of 120 mCi/cycle x 3 cycles administered with concomitant amino acid infusion has been chosen for the study^{10,17}. Until the results of this study are published, treatment with radiolabelled somatostatin analogues will remain an attractive alternative therapeutic option to current available therapeutic modalities.

Currently, there is very little experience in using ⁹⁰Y-DOTATOC, a compound which appears to be identical to *OctreoTher*, for the treatment of metastatic NET compared to that of ¹³¹I-MIBG^{20,21}. ⁹⁰Y-DOTATOC is a peptide vector DOTA-D-Phe1-Tyr³-Octreotide (DOTATOC; DOTA: 1,4,7,10-tetra-azacyclododecane-N, N',N'',N'''-tetraacetic acid), stably labelled with yttrium-90^{20,21}. Out of ten patients with somatostatin receptor-positive metastatic NET treated with ⁹⁰Y-DOTATOC, the 6 patients who received multiple doses reported improvement in tumour growth, hormonal secretion and symptoms, with minimal side-effects, while the others showed stable disease, suggesting that ⁹⁰Y-DOTATOC is a potentially valuable therapy for somatostatin receptor-positive tumours (Figure 4)²¹. In total, 24 patients have been treated with ⁹⁰Y-DOTATOC and received <7,400 MBq/m²²¹. This dose corresponds to 200mCi/m², and some of the administered cycles were in the presence

of concomitant amino acid infusion. Only 4 patients who received doses >360 mCi without concomitant amino acid infusion developed renal toxicity; thus, all doses equal to or below 360 mCi administered with concomitant amino acid infusion appear to have been tolerated safely²¹.

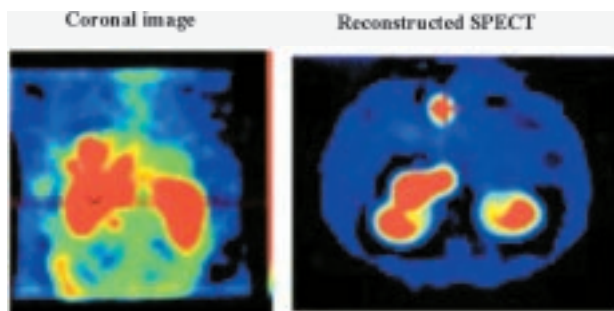


Figure 3. SPECT image obtained at 24 hours following ⁹⁰Y-octreotide (*OctreoTher*) in a patient with a malignant insulinoma demonstrating a liver metastasis.

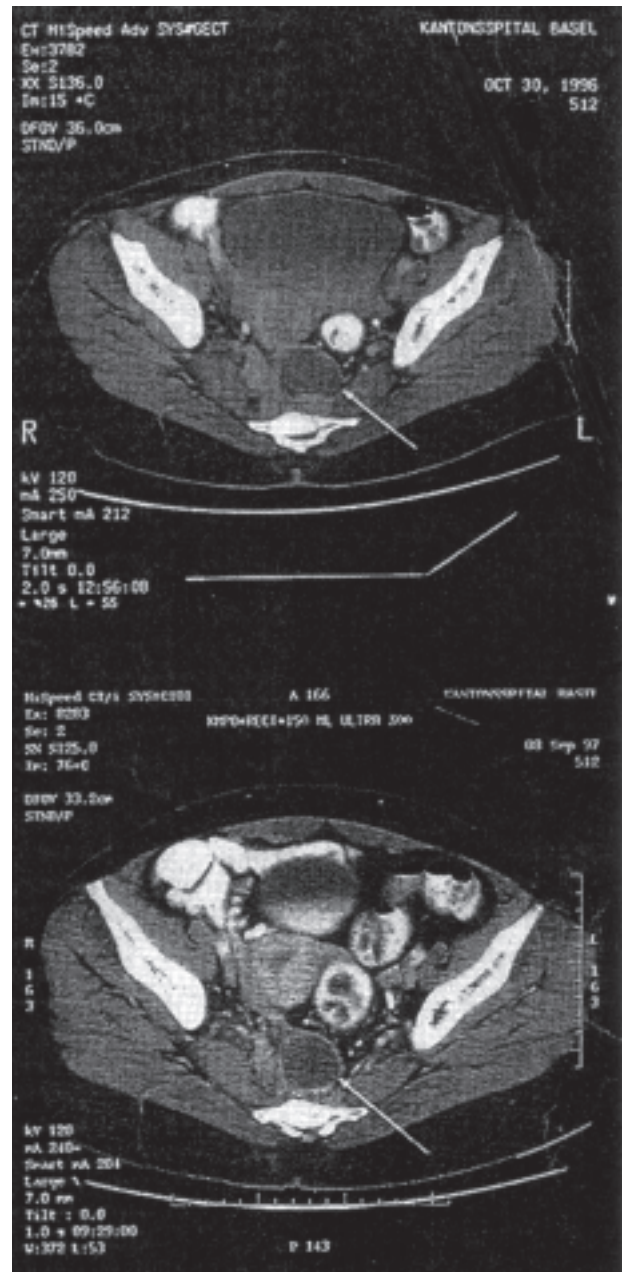


Figure 4. Contrast enhanced transaxial computed tomograph images before (top) and after treatment with [⁹⁰Y-DOTATOC] (bottom) in the second patient. (Reproduced with permission from *Lancet*, 351:418,1998).

Studies comparing the detection ability of ^{123}I -MIBG and *Octreoscan* have consistently shown that *Octreoscan* is more sensitive than ^{123}I -MIBG and it will also probably locate the same lesions identified by ^{131}I -MIBG^{4,12}. Thus, therapy with either *OctreoTher* or ^{90}Y -DOTATOC will probably be applicable to a larger population of patients with NET than therapy with ^{131}I -MIBG^{4,12,19,20}. In addition, in occasional patients mainly with hepatic metastases, who show complementary uptake with ^{123}I -MIBG to non-octreotide avid lesions, concomitant use of ^{131}I -MIBG and *OctreoTher* or ^{90}Y -DOTATOC may be another therapeutic option^{4,12}. As shown from data derived from patients treated with ^{131}I -MIBG, the main predictor of the outcome of therapy with either *OctreoTher* or ^{90}Y -DOTATOC is principally the extent of the disease and the total tumour load^{2,15}.

In order to overcome the limitations of administering tumouricidal doses of radiotherapy to non-octreotide avid lesions and the lack of uptake to certain areas of the tumours due to tumour heterogeneity several β -emitters, in addition to ^{90}Y , such as ^{153}Sm , ^{177}Lu and ^{186}Re are being considered for therapy when linked to somatostatin analogues (Table 2)¹¹. It has been suggested that for octreotide avid tumours radionuclear therapy with the combination of ^{177}Lu and ^{90}Y will probably be more efficacious than treatment with ^{90}Y alone. In addition, other somatostatin analogues are in development and are expected to show superior imaging and therapeutic properties compared to octreotide.

FUTURE PROSPECTS

It is likely that 'internal radiotherapy' for the treatment of NET will develop considerably within the next few years. Until now, indications with ^{131}I -MIBG have been limited to palliative treatment of malignant chromaffin cell and carcinoid tumours, most often at an advanced disease stage. Therapeutic efficiency has been improved by increasing the injected activity, particularly in patients with limited tumour burden. The recent application of ^{90}Y -labelled somatostatin analogues represents a major advantage as these radionuclides can be taken up by a wider number of NET¹². To be fully efficient, these radionuclides should probably be injected into patients with small tumour targets (not more than 1-2cm in diameter). For large macroscopic targets, internal radiotherapy is clearly inefficient be-

cause of low and particularly heterogeneous tumour uptake. Although combination therapy with both ^{131}I -MIBG and *OctreoTher* remains an attractive theoretical option for tumours that demonstrate diagnostic uptake, the only currently established solution is to perform as complete a surgical resection as possible subsequent to injection of diagnostic activity to ensure good uptake of the radiopharmaceutical by tumour targets. If injections are repeated regularly, it is likely that the disease can at least be stabilized for a period of several years if not cured. Finally, it may be hoped that the efficacy of internal radiotherapy will be improved by co-administration of chemotherapeutic drugs whose radiosensitising properties may be synergistic with that of irradiation².

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