Differences in Biodistribution Between ^{99m}Tc -Depreotide, ^{111}In -DTPA-Octreotide, and ^{177}Lu -DOTA-Tyr³-Octreotate in a Small Cell Lung Cancer Animal Model

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ABSTRACT

Aim: ^{177}Lu -DOTA-Tyr³-octreotate is a candidate radiopharmaceutical for the therapy of somatostatin receptor (sstr)-positive small cell lung cancer (SCLC). Scintigraphy of lung tumors is made with 2 alternative somatostatin analogs, ^{111}In -DTPA-octreotide or ^{99m}Tc -depreotide. The aim of this study was to compare the biodistribution of these 3 radiopharmaceuticals in SCLC xenografted to nude mice. **Methods:** Nude mice, bearing tumors from the human SCLC cell line NCI-H69, were intravenously injected with 10 MBq (2.4 μg) ^{99m}Tc -depreotide and 2 MBq (0.5 μg) ^{111}In -DTPA-octreotide simultaneously. The activity concentration (%IA/g) was measured in tumor and normal tissue at 2, 4, and 24 hours postinjection (hpi). The results were compared with earlier published biodistribution data of 3 MBq (0.7 μg) ^{177}Lu -DOTA-Tyr³-octreotate in the same animal model. **Results:** The activity concentration of ^{111}In -DTPA-octreotide in tumor was higher than the activity concentration of ^{99m}Tc -depreotide at 2–24 hpi, $p < 0.05$. The highest tumor uptake at 24 hpi was, however, found for ^{177}Lu -DOTA-Tyr³-octreotate. The activity concentration of ^{99m}Tc -depreotide was significantly higher in the heart, lungs, liver, the salivary glands, spleen, and bone marrow than for ^{111}In -DTPA-octreotide at 2–24 hpi. Saturation of the somatostatin receptors may have influenced the uptake in tumor andsstr-positive normal tissues. **Conclusion:** The low tumor-to-lung and tumor-to-liver activity concentration ratios for ^{99m}Tc -depreotide could result in a lower detection rate of SCLC with this compound versus ^{111}In -DTPA-octreotide. ^{177}Lu -DOTA-Tyr³-octreotate gave the highest tumor-activity concentration, and has, thus, the best properties for therapy.

Key words: biodistribution; radiolabeled somatostatin analogs; small cell lung cancer; nude mice

INTRODUCTION

It is well known that some tumor cells express somatostatin receptors (sstr) on their cell membrane. Five different human sstr subtypes have

been cloned, sstr1–5.¹ Owing to the short biological half-life of native somatostatin, synthetic analogs have been produced. Radionuclide therapy using the somatostatin analog Tyr³-octreotate labeled with ^{177}Lu has led to effective therapeutic responses ofsstr2-positive neuroendocrine tumors, both in animal and patient studies.^{2,3} Likewise, the treatment ofsstr2-positive small cell lung cancer (SCLC) xenografted to nude mice with ^{177}Lu -DOTA-Tyr³-octreotate was successful.⁴

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Several studies on somatostatin-receptor scintigraphy (SRS) with ^{111}In -DTPA-octreotide (OctreoScan[®]) have been performed on patients with SCLC.^{5–7} These studies showed that the method was effective in detecting primary tumors, but were of limited value for distant metastases. The new $^{99\text{m}}\text{Tc}$ -labeled somatostatin analog depreotide (NeoTect[™], NeoSpect[™]) is used for scintigraphy on the suspicion of malignant lung tumors, both SCLC and non-SCLC.^{8–10} $^{99\text{m}}\text{Tc}$ -depreotide allows for a 1-day imaging protocol and offers low radiation exposure and high image quality.^{8–10} Both $^{99\text{m}}\text{Tc}$ and ^{111}In have physical properties suitable for a diagnostic purpose, but $^{99\text{m}}\text{Tc}$ is more ideal for imaging, more readily available, and more cost-efficient with the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator.

Depreotide is a synthetic linear tetrapeptide, attached to one of the residues of a cyclic hexapeptide, while octreotide and Tyr³-octreotate are both octapeptides. All 3 analogs contain an amino-acid sequence similar to that of native somatostatin. The different chemical structure of the peptides will affect the affinity to the differentsstr subtypes and the biodistribution. Furthermore, the affinity and biodistribution are also affected, to some extent, by the choice of chelate and radionuclide.¹¹

Because $^{99\text{m}}\text{Tc}$ -depreotide, ^{111}In -DTPA-octreotide, and ^{177}Lu -DOTA-Tyr³-octreotate all have been used in different receptor-binding studies in patients and/or animals with SCLC, the aim of this study was to compare the biodistribution of these 3 radiopharmaceuticals in the same animal model: nude mice bearing tumors from the human SCLC cell line NCI-H69. The physical properties for the 3 radionuclides $^{99\text{m}}\text{Tc}$, ^{111}In , and ^{177}Lu are shown in Table 1.

MATERIALS AND METHODS

Radiopharmaceuticals

The radiolabeling was performed according to instructions given by the manufacturers. $^{111}\text{InCl}_3$ and DTPA-octreotide were obtained as parts of the OctreoScan[®] kit (Mallickrodt Tyco Healthcare; Stockholm, Sweden), and depreotide was purchased as NeoSpect[™] (Amersham Health AB; Solna, Sweden) and was reconstituted with $^{99\text{m}}\text{TcO}_4$ in a phosphate-buffered saline (PBS) solution. The peptide-bound fractions of $^{99\text{m}}\text{Tc}$ and ^{111}In were higher than 97% and 99%, respectively, as demonstrated by instant thin-layer chromatography (ITLC-SG, Gelman; Ann Arbor, MI) with 0.1 M sodium citrate (pH, 5.0; VWR International AB; Stockholm, Sweden) as the mobile phase.

Animals

Female nude mice BALB/c (Iffa Credo, Charles River Laboratories; Les Oncins, France), 4 weeks of age, were each subcutaneously (s.c.) injected in the neck with 2×10^7 tumor cells from the human SCLC cell line NCI-H69 (ATCC HTB-119, American Type Culture Collection; Manassas, VA). Tumors were allowed to grow for 5 weeks, reaching the size of approximately 10 mm in diameter. This study was approved by the Ethical Committee for Animal Research in Göteborg, Sweden.

Each of the 12 mice was simultaneously injected into the tail vein with 2 MBq ^{111}In -DTPA octreotide (0.5 μg) and 10 MBq $^{99\text{m}}\text{Tc}$ -depreotide (2.4 μg). The mice were sacrificed at 2, 4, and 24 hours postinjection (hpi), $n = 3$ –5. Tumor tissue, blood, thigh muscle, the adrenals,

Table 1. The Physical Properties of $^{99\text{m}}\text{Tc}$, ^{111}In , and ^{177}Lu

Isotope	Half-life ^a	Gamma radiation energy ^a	Beta radiation, max energy ^a
$^{99\text{m}}\text{Tc}$	6.0 hours	140 keV (89%)	—
^{111}In	2.8 days	171 keV (90%) 245 keV (94%)	—
^{177}Lu	6.7 days	113 keV (6%) 208 keV (11%)	498 keV (79%) 177 keV (12%) 385 keV (9%)

^aData from Chu et al., The Lund/LBNL Nuclear Data Search, Version 2.0, 1999, LBNL, Berkeley, California, and the Department of Physics, Lund University, Lund, Sweden.

Only the most abundant gamma and beta radiation is presented.

heart, lungs, small intestine, kidneys, salivary glands, pancreas, liver and fat from the mesentery, spleen, and bone marrow (from both femora) were collected and weighed.

Activity Measurements

The activity in the syringes was measured with a well-type ionization chamber (CRC-15R, Capintec, Inc.; Ramsey, NJ). The activity in the tissue samples was measured with a gamma counter (Wallac 1480 WIZARD® 3", Wallac Oy; Turku, Finland). The efficiency of the gamma counter was determined relative to the efficiency of the ionization chamber, and corrections for detector background, dead time loss, and volume effect were made. In the gamma counter, the samples were first measured for ^{99m}Tc in the 140-keV energy gamma peak (window range, 127–154 keV). Because there was contribution from Compton photons from the 171-keV and 245-keV gamma radiation of ^{111}In in the ^{99m}Tc energy window, the counts from ^{111}In in the ^{99m}Tc -window were subtracted. This contribution was measured 5 days later when the ^{99m}Tc activity was assumed to be negligible. Correction for radioactive decay between the 2 measurement time points was made. The ^{111}In activity was measured in the window for the summation peak at 416 keV (window range, 376–456 keV).

The activity concentration at the time t , $C_{\text{tissue}}(t)$, was then calculated as the percent of injected activity per gram of tissue (%IA/g):

$$C_{\text{tissue}}(t) = \frac{A_{\text{tissue}}(t) / m_{\text{tissue}}}{A_{\text{injected}}} * 100 \quad (1)$$

where $A_{\text{tissue}}(t)$ is the activity in the sample, m_{tissue} the mass of the sample, and A_{injected} the activity injected into the mouse. Correction was made for radioactive decay between injection and dissection time.

Tissue₁-to-tissue₂ activity concentration ratios were defined as:

$$T_1/T_2(t) = \frac{C_{\text{tissue } 1}(t)}{C_{\text{tissue } 2}(t)} \quad (2)$$

All results were expressed as mean $\pm$ the standard error of the mean. The two-tailed, paired Student's t test was used to compare activity concentrations ($p < 0.05$ was considered statistically significant). The results at 24 hpi were also com-

pared to earlier published biodistribution data of 3 MBq (0.7 μg) ^{177}Lu -DOTA-Tyr³-octreotate in the same animal model.¹²

RESULTS

Table 2 shows the activity concentration of ^{99m}Tc -depreotide and ^{111}In -DTPA-octreotide in tumor and normal tissue at 2, 4, and 24 hours postinjection (hpi). Earlier published data of the activity concentration at 24 hpi of ^{177}Lu -DOTA-Tyr³-octreotate¹² are included in Table 2 for comparison.

In tumor tissue, the activity concentration of ^{111}In -DTPA-octreotide was higher than the activity concentration of ^{99m}Tc -depreotide at 2, 4, and 24 hpi ($p < 0.05$ for all time points). For both ^{111}In -DTPA-octreotide and ^{99m}Tc -depreotide, the activity concentration in the tumor decreased from 2 to 24 hpi. In most normal tissues, both the ^{99m}Tc -depreotide and ^{111}In -DTPA-octreotide activity concentration decreased rapidly with time. The exceptions were the ^{99m}Tc -depreotide activity concentration in the kidneys, which increased from 2 hpi to 24 hpi, and the ^{99m}Tc -depreotide activity concentration in the liver, which was almost constant from 2–24 hpi. The activity concentration of ^{99m}Tc -depreotide was significantly higher in the blood, heart, lungs, liver, salivary glands, spleen, and bone marrow at 2 and 4 hpi than the activity concentration of ^{111}In -DTPA-octreotide ($p < 0.05$). At 24 hpi, the activity concentration of ^{99m}Tc -depreotide was significantly higher than for ^{111}In -DTPA-octreotide in all normal tissues ($p < 0.05$), except for blood and mesenteric fat.

The highest tumor uptake at 24 hpi was found for ^{177}Lu -DOTA-Tyr³-octreotate. In addition, ^{177}Lu -DOTA-Tyr³-octreotate resulted in the highest activity concentration in bone marrow at 24 hpi. The ^{177}Lu -DOTA-Tyr³-octreotate activity concentration at 24 hpi in the lungs, pancreas, and adrenals was in the same range as the ^{99m}Tc -depreotide activity concentration, and significantly higher than the ^{111}In -DTPA-octreotide activity concentration. In the kidneys, ^{177}Lu -DOTA-Tyr³-octreotate resulted in the lowest activity concentration. The bone-marrow-to-blood activity concentration ratio (Bm/B) was 3.1 ± 0.6 , 55 ± 10 , and 150 ± 70 at 24 hpi for ^{111}In -DTPA-octreotide, ^{99m}Tc -depreotide, and ^{177}Lu -DOTA-Tyr³-octreotate, respectively.

Table 2. The Activity Concentration C_{tissue} (%IA/g), Corrected for Radioactive Decay, in Tumor and Normal Tissues at 2, 4, and 24 Hours after Simultaneous Intravenous Injection in SCLC-Bearing Nude Mice of 10 MBq (2.4 μg) $^{99\text{m}}\text{Tc}$ -Depreotide, and 2 MBq (0.5 μg) ^{111}In -DTPA-Octreotide

Tissue	$^{99\text{m}}\text{Tc}$ -depreotide			^{111}In -DTPA-octreotide			^{177}Lu -octreotate
	2 hpi	4 hpi	24 hpi	2 hpi	4 hpi	24 hpi	24 hpi
Blood	0.58 $\pm$ 0.03	0.12 $\pm$ 0.03	0.01 $\pm$ 0.003	0.12 $\pm$ 0.01	0.03 $\pm$ 0.0004	0.01 $\pm$ 0.0006	0.01 $\pm$ 0.001
Heart	0.45 $\pm$ 0.03	0.18 $\pm$ 0.01	0.11 $\pm$ 0.02	0.09 $\pm$ 0.01	0.04 $\pm$ 0.002	0.02 $\pm$ 0.01	0.03 $\pm$ 0.002
Lungs	1.7 $\pm$ 0.1	1.0 $\pm$ 0.1	0.65 $\pm$ 0.12	0.52 $\pm$ 0.04	0.33 $\pm$ 0.004	0.21 $\pm$ 0.07	0.60 $\pm$ 0.11
SG	0.47 $\pm$ 0.07	0.31 $\pm$ 0.01	0.20 $\pm$ 0.02	0.10 $\pm$ 0.02	0.06 $\pm$ 0.0008	0.02 $\pm$ 0.004	0.04 $\pm$ 0.01
Liver	5.7 $\pm$ 0.4	7.1 $\pm$ 0.6	5.4 $\pm$ 0.5	0.34 $\pm$ 0.02	0.29 $\pm$ 0.02	0.14 $\pm$ 0.01	0.10 $\pm$ 0.01
SI	0.70 $\pm$ 0.22	0.32 $\pm$ 0.02	0.17 $\pm$ 0.02	0.43 $\pm$ 0.19	0.11 $\pm$ 0.01	0.05 $\pm$ 0.01	0.15 $\pm$ 0.02
Fat	1.3 $\pm$ 0.2	0.82 $\pm$ 0.29	0.59 $\pm$ 0.18	0.55 $\pm$ 0.04	0.20 $\pm$ 0.10	0.14 $\pm$ 0.07	0.19 $\pm$ 0.07
Pancreas	0.96 $\pm$ 0.07	0.62 $\pm$ 0.03	0.48 $\pm$ 0.06	0.55 $\pm$ 0.17	0.41 $\pm$ 0.02	0.16 $\pm$ 0.02	0.40 $\pm$ 0.04
Spleen	1.5 $\pm$ 0.3	1.5 $\pm$ 0.1	0.93 $\pm$ 0.12	0.17 $\pm$ 0.01	0.13 $\pm$ 0.004	0.07 $\pm$ 0.01	0.12 $\pm$ 0.02
Muscle	0.17 $\pm$ 0.02	0.09 $\pm$ 0.02	0.05 $\pm$ 0.01	0.10 $\pm$ 0.06	0.02 $\pm$ 0.002	0.01 $\pm$ 0.002	0.01 $\pm$ 0.001
Kidneys	26 $\pm$ 8	38 $\pm$ 11	99 $\pm$ 8	29 $\pm$ 2	30 $\pm$ 4	7.3 $\pm$ 2.6	2.2 $\pm$ 0.3
Adrenals	0.84 $\pm$ 0.13	0.67 $\pm$ 0.07	0.42 $\pm$ 0.06	0.38 $\pm$ 0.21	0.54 $\pm$ 0.40	0.07 $\pm$ 0.01	0.34 $\pm$ 0.06
BM	0.78 $\pm$ 0.08	0.63 $\pm$ 0.08	0.38 $\pm$ 0.07	0.09 $\pm$ 0.01	0.05 $\pm$ 0.01	0.04 $\pm$ 0.02	1.0 $\pm$ 0.4
Tumor	2.0 $\pm$ 0.3	1.5 $\pm$ 0.1	0.64 $\pm$ 0.37	3.1 $\pm$ 0.3	2.5 $\pm$ 0.2	1.5 $\pm$ 0.4	3.7 $\pm$ 1.0

hpi, hours post injection; SG, salivary glands; SI, small intestine; BM, bone marrow; SCLC, small cell lung cancer.

In addition, earlier published data of 3 MBq (0.7 μg) ^{177}Lu -DOTA-Tyr³-octreotate in the same animal model (see Reference 12). Data are expressed as mean $\pm$ standard error of the mean ($n = 3-6$).

Tumor-to-bone-marrow activity concentration ratio (T/Bm), tumor-to-liver activity concentration ratio (T/Li), and tumor-to-lung activity concentration ratio (T/Lu) were higher for ^{111}In -DTPA-octreotide than for $^{99\text{m}}\text{Tc}$ -depreotide at all time points ($p < 0.05$). Tumor-to-kidney activity concentration ratios (T/Ki) were similar for both radionuclides at 2 and 4 hpi, but at 24 hpi T/Ki was higher for ^{111}In -DTPA-octreotide ($p < 0.05$). At 24 hpi, T/Li and T/Ki was highest for ^{177}Lu -DOTA-Tyr³-octreotate, but T/Bm was highest for ^{111}In -DTPA-octreotide, and T/Lu was in the same range for ^{177}Lu -DOTA-Tyr³-octreotate and ^{111}In -DTPA-octreotide.

DISCUSSION

For tumor tissue, the ^{111}In -DTPA-octreotide activity concentration was higher than for $^{99\text{m}}\text{Tc}$ -depreotide. At 24 hpi, the tumor-to-normal-tissue activity concentration ratios of ^{111}In -DTPA-octreotide for most tissues were higher than at 2-4 hpi. For $^{99\text{m}}\text{Tc}$ -depreotide, the tumor-to-normal-tissue activity concentration ratios did not increase with time. This fact, together with the longer half-life of ^{111}In , is a reason for carrying out scintigraphy later with ^{111}In -DTPA-octreotide, 24-48 hours postinjection (hpi), compared to 2-4 hpi for $^{99\text{m}}\text{Tc}$ -depreotide. The uptake of $^{99\text{m}}\text{Tc}$ -depreotide in normal tissue was higher than for ^{111}In -DTPA-octreotide, both in this study and in a comparison between $^{99\text{m}}\text{Tc}$ -depreotide and ^{111}In -DTPA-octreotide scintigraphy in 43 patients with neuroendocrine tumors other than SCLC.¹³ However, because of the higher administered activity and shorter physical half-life of $^{99\text{m}}\text{Tc}$, the effective dose per routine examination is in the same range for both radiopharmaceuticals.^{10,14}

The high liver uptake of $^{99\text{m}}\text{Tc}$ -depreotide can be a problem for the visualization of abdominal tumors or liver metastases, if the same results were obtained in humans. The activity concentration of ^{111}In -DTPA-octreotide in the liver was significantly lower. The published clinical study showed that ^{111}In -DTPA-octreotide was more sensitive than $^{99\text{m}}\text{Tc}$ -depreotide, especially to detect liver metastases.¹³ In our study, the activity concentration of $^{99\text{m}}\text{Tc}$ -depreotide in tumor and lung tissues was similar at 2-24 hpi (T/Lu was close to 1), which must be a problem for the detection of lung tumors. Clinical studies have, however, shown both high sensitivity and specificity of $^{99\text{m}}\text{Tc}$ -depreotide single-photon emission computed tomography (SPECT) for lung tu-

mors,^{8–10} (i.e., the tumor-to-lung activity concentration ratio in humans was high enough to visualize tumors in the lungs). However, the vast majority of the studies have been done on non-small cell lung cancer (N-SCLC),^{8–10} and the detection rate of SCLC may differ from that of N-SCLC.

There may have been saturation of sstr for all 3 radiopharmaceuticals in this study, as the total amount of peptide injected in each mouse was high. The recommended human dose of depreotide (47 μ g) is 5 times the human dose of octreotide (10 μ g), which was the reason to inject 5 times higher the amount of depreotide than octreotide in this study. Saturation can reduce the uptake in both tumor and sstr-positive normal tissues. In a study by Bernhardt et al.¹⁵ the uptake of ¹¹¹In-DTPA-octreotide in the human midgut carcinoid GOT1, xenografted to nude mice, was maximal for injected amounts up to 1 μ g DTPA-octreotide. Human SCLC expresses, in general, a lower density of sstr than carcinoids,¹ and, hence, the saturation will start at lower amounts of octreotide. Furthermore, as DOTA-Tyr³-octreotate has a higher affinity to sstr2 than DTPA-octreotide,¹¹ the saturation probably occurs with even lower amounts of DOTA-Tyr³-octreotate.

In this study, ¹⁷⁷Lu-DOTA-Tyr³-octreotate resulted in the highest tumor activity concentration, followed by ¹¹¹In-DTPA-octreotide and ^{99m}Tc-depreotide. This may, partly, be explained by different sstr2 affinity (IC_{50} = 1.5, 12, and 6.1 nM, respectively, for the unlabeled peptides^{10,11}), and the cell line NCI-H69 mainly expresses sstr2.¹⁶ ¹⁷⁷Lu-DOTA-Tyr³-octreotate also resulted in the lowest kidney activity concentration, a very important parameter, as the kidneys are the main risk organ in somatostatin receptor-mediated radionuclide therapy.¹⁷ In the pancreas, spleen, adrenals, lungs, and small intestine, the activity concentration of ^{99m}Tc-depreotide was significantly higher than that of ¹¹¹In-DTPA-octreotide at 24 hpi, despite a possible higher saturation for ^{99m}Tc-depreotide versus ¹¹¹In-DTPA-octreotide. Studies have identified sstr expression in all of these tissues in humans.¹ Compared to DOTA-Tyr³-octreotate, which binds to sstr2 with the highest affinity and also to sstr4 and sstr5 with lower affinity, DTPA-octreotide and depreotide have binding affinity to sstr2, sstr3 and sstr5.^{10,11}

Biodistribution studies of ^{99m}Tc-depreotide have earlier been made on rabbits, rats, and monkeys.¹⁰ The biodistribution in these 3 animal types was similar to the results obtained in our

study on mice (i.e., there was rapid clearance of ^{99m}Tc-depreotide from the blood pool and the uptake occurred mainly in the kidneys, liver, and gastrointestinal tract, with excretion of the radionuclide by the kidneys). ^{99m}Tc-depreotide was also detected in the bone marrow, but the uptake was not quantified.¹⁰ No previous measurements have, to our knowledge, been performed of the activity concentration of ¹¹¹In-DTPA-octreotide or ^{99m}Tc-depreotide in bone marrow in animals.

Measurement of ¹¹¹In-DTPA-octreotide in 1 patient resulted in bone-marrow-to-blood activity concentration ratio (Bm/B) of 1.7 at 24 hpi.¹⁸ In our animal model, Bm/B was 3.1 ± 0.6 for ¹¹¹In-DTPA-octreotide and significantly higher for the other 2 radiopharmaceuticals. It is known that nonpeptide-bound ¹⁷⁷Lu results in high bone marrow uptake.¹² The amount of ¹⁷⁷Lu ions could be reduced by the addition of DTPA before injection, and results in ¹⁷⁷Lu-DTPA with a rapid renal clearance¹⁹ and, thus, minimal bone marrow uptake.

¹⁷⁷Lu is a suitable radionuclide for therapy because of its physical properties. In addition, the biological half-life of ¹⁷⁷Lu-DOTA-Tyr³-octreotate in the SCLC tumor was approximately 4 days, compared to 2–3 days for most of the normal tissues,¹² which is a favorable situation for therapy, because the tumor-to-normal-tissue activity concentration ratios will then increase with time.

CONCLUSIONS

The ¹¹¹In-DTPA-octreotide activity concentration in tumor tissue was higher, but the uptake in normal tissue was lower, compared to ^{99m}Tc-depreotide. Low tumor-to-lung and tumor-to-liver activity concentration ratios for ^{99m}Tc-depreotide could lead to a lower tumor detection rate for this compound versus ¹¹¹In-DTPA-octreotide. The highest tumor uptake and lowest kidney uptake in this SCLC animal model was found for ¹⁷⁷Lu-DOTA-Tyr³-octreotate, which also is the radiopharmaceutical with the best physical properties for therapy.

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REFERENCES

1. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. *Endocr Rev* 2003;24:389.
2. Kwekkeboom DJ, Bakker WH, Kam BL, et al. Treatment of patients with gastro-entero-pancreatic (GEP) tumors with the novel radiolabeled somatostatin analog [¹⁷⁷Lu-DOTA(0), Tyr³]octreotate. *Eur J Nucl Med Mol Imaging* 2003;30:417.
3. Breeman WA, Mearadji A, Capello A, et al. Antitumor effect and increased survival after treatment with [¹⁷⁷Lu-DOTA(0), Tyr³]octreotate in a rat liver micro-metastases model. *Int J Cancer* 2003;104:376.
4. Schmitt A, Bernhardt P, Nilsson O, et al. Radiation therapy of small cell lung cancer with ¹⁷⁷Lu-DOTA-Tyr³-octreotate in an animal model. *J Nucl Med* 2004; 45:1542.
5. Reisinger I, Bohuslavitzki, KH, Brenner W, et al. Somatostatin receptor scintigraphy in small cell lung cancer: Results of a multicenter study. *J Nucl Med* 1998; 39:224.
6. Berenger N, Moretti JL, Boaziz C, et al. Somatostatin receptor imaging in small cell lung cancer. *Eur J Cancer* 1996;32A:1429.
7. Hochstenbag MM, Heidendal GA, Wouters EF, et al. In-111 octreotide imaging in staging of small cell lung cancer. *Clin Nucl Med* 1997;22:811.
8. Blum J, Handmaker H, Lister, James J, et al. A multicenter trial with a somatostatin analog (^{99m}Tc depreotide in the evaluation of solitary pulmonary nodules. *Chest* 2000;117:1232.
9. Grewal RK, Dadparvar S, Yu JQ, et al. Efficacy of Tc-99m depreotide scintigraphy in the evaluation of solitary pulmonary nodules. *Cancer J* 2002;8:400.
10. EMEA CPMP/2065/00: European Medicines Agency, 2000.
11. Reubi JC, Schar JC, Wasar B, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *Eur J Nucl Med* 2000;27:273.
12. Schmitt A, Bernhardt P, Nilsson O, et al. Biodistribution and dosimetry of ¹⁷⁷Lu-labeled [DOTA(0), Tyr³]octreotate in male nude mice with human small cell lung cancer. *Cancer Biother Radiopharm* 2003;18:593.
13. Lebtahi R, Le Chloirec J, Houzard C, et al. Detection of neuroendocrine tumors: ^{99m}Tc-P829 scintigraphy compared with ¹¹¹In-pentetreotide scintigraphy. *J Nucl Med* 2002;43:889.
14. ICRP Publication 80: International Commission on Radiological Protection, 1998.
15. Bernhardt P, Kölby L, Johansen V, et al. Biodistribution of ¹¹¹In-DTPA-D-Phe1-octreotide in tumor-bearing nude mice: Influence of amount injected and route of administration. *Nucl Med Biol* 2003;30:253.
16. Taylor JE, Theveniau MA, Bachirzadeh R, et al. Detection of somatostatin receptor subtype 2 (SSTR2) in established tumors and tumor cell lines: Evidence for SSTR2 heterogeneity. *Peptides* 1994;15:1229.
17. De Jong M, Valkema R, Jamar F, et al. Somatostatin receptor-targeted radionuclide therapy of tumors: Pre-clinical and clinical findings. *Semin Nucl Med* 2002; 32:133.
18. Forssell-Aronsson E, Fjälling M, Nilsson O, et al. Indium-111 activity concentration in tissue samples after intravenous injection of indium-111-DTPA-D-Phe1-octreotide. *J Nucl Med* 1995;36:7.
19. Breeman WA, van der Wansem K, Bernard BF, et al. The addition of DTPA to [¹⁷⁷Lu-DOTA(0), Tyr³]octreotate prior to administration reduces rat skeleton uptake of radioactivity. *Eur J Nucl Med Mol Imaging* 2003;30:312.