Radiotherapy with a Radiolabeled Somatostatin Analogue, [^{111}In-DTPA-D-Phe^1]-Octreotide

A Case History

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INTRODUCTION

In 1987, we started octreotide receptor scintigraphy in humans. After a few years of using the radioiodinated [Tyr^3]-octreotide,[1] we switched to [^{111}In-DTPA-D-Phe^1]-octreotide, which has many advantages over the radioiodinated compound.[2,3] Patients with various forms of cancer, both classically known as neuroendocrine and nonendocrine, have been investigated.[4]

The application of these new peptide-receptor agents in scintigraphy, and of many others that will become available in the near future, such as substance P and bombesin or their derivatives, might evoke a combination of optimism and pessimism. After all, the presence of receptors determines the possibility of detecting the abnormality or tumor by peptide receptor scintigraphy (PRS). Thus, the classical concept of false positives and false negatives really is not applicable to visualization by means of PRS.[5] This technique primarily allows an interpretation with regard to receptor presence and not to anatomical abnormalities, as is the case with CT, ultrasound, and MRI. Only at a second stage, after showing the localization of an abnormal density of receptors, one might conclude the presence of an anatomical abnormality expressing the peptide receptors, for example, a primary pancreatic islet cell tumor expressing somatostatin receptors. However, when PRS does not demonstrate (a) lesion(s), suggesting that a tumor or (several of the) metastases do not express (anymore) a certain peptide receptor, this also might be of paramount importance with regard to therapeutic advice to the patient. Dedifferentiation of a tumor is accompanied by loss of a given peptide receptor, and this information influences the oncologist's therapeutic decisions. An example is the choice between the use of somatostatin analogues or cytostatic drugs in patients with neuroendocrine tumors that are well differentiated or have become anaplastic, respectively.[6,7] With future (radio)therapy using (radio)labeled peptide(-derivatives), the presence (in the individual patient!) of several undifferentiated metastases, that do not bind a given (radio)ligand as opposed to the well-differentiated metastases, necessitates (an)

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additional application(s) of a (radio)ligand with appropriate binding characteristics for the undifferentiated tumors, possibly by injection of a "cocktail" of (radiolabeled) ligands. Thus, mapping of the presence (including the localization of the tumors and of the distribution) of peptide receptors on all metastases in the individual patient by PRS may become an attractive, noninvasive, harmless, easy-to-perform tool for an individual therapeutic approach of the cancer patient.

In this report, we present a patient with an inoperable, metastasized glucagonoma in whom peptide receptor radiotherapy (PRRT) with Auger and conversion electrons emitting [^{111}In-DTPA-D-Phe^1]-octreotide affects the growth of the tumor and the circulating glucagon levels. Because of their more appropriate physical characteristics, future nuclear radiotherapy is directed to the use of α- or β-particles emitting radionuclide-labeled peptides.

SELECTION OF RADIONUCLIDE FOR RADIOTHERAPY WITH THE RADIOLABELED SOMATOSTATIN ANALOGUE [DTPA-D-Phe^1]-OCTREOTIDE

For radiotherapeutic applications, several radionuclides have been proposed and investigated to be coupled to [DTPA-D-Phe^1]-octreotide. Radiolabeled [DTPA-D-Phe^1]-octreotide has an appropriate distribution profile in humans for this purpose. At the moment, theoretically suitable β-emitting radionuclides are not available in pure form or show a dissociation from the chelated peptide in serum. Therefore, we decided to investigate the antiproliferative effect of the Auger and conversion electrons of [^{111}In- DTPA-D-Phe^1]-octreotide. FIGURE 1 and TABLES 1 and 2 illustrate the origin and the main physical characteristics of these electrons, respectively.

MATERIAL AND METHODS

[DTPA-D-Phe^1]-octreotide and $^{111}InCl_3$ (370 MBq/mL in HCL, pH = 1.5–1.9) were obtained from Mallinckrodt Medical BV (Petten, the Netherlands). [DTPA-D-Phe^1]-octreotide was labeled with ^{111}In as has been described elsewhere.[2] Doses ranged from 1590 MBq to 4810 MBq ^{111}In, which were coupled with amounts of [DTPA-D-Phe^1]-octreotide ranging from 10 to 120 μg. The protocol of [^{111}In- DTPA-D-Phe^1]-octreotide scintigraphy has been described previously.[4] Radiotherapy with [^{111}In- DTPA-D-Phe^1]-octreotide was applied after informed consent by the patient and approval by the medical ethics committee of our institution.

CASE

The patient is a 55-year-old female, who underwent two abdominal tumor operations in 1988 and 1989, including partial pancreatectomy, splenectomy, and dissection of paraaortal lymph nodes. At the second operation, liver metastases were not present. Histology showed a neuroendocrine tumor with positive immunohistochemistry for glucagon, pancreatic polypeptide, somatostatin, calcitonin, ACTH, gastrin, and carcinoembryonic antigen (CEA). The patient had been referred to our hospital because of the demonstration of somatostatin receptors on the recurrent metastases according to octreotide scintigraphy. The patient never experienced signs or symptoms of a hormone-producing neuroendocrine tumor. Only elevated serum levels of glucagon were found. Because of the excellent clinical condition of the patient at the

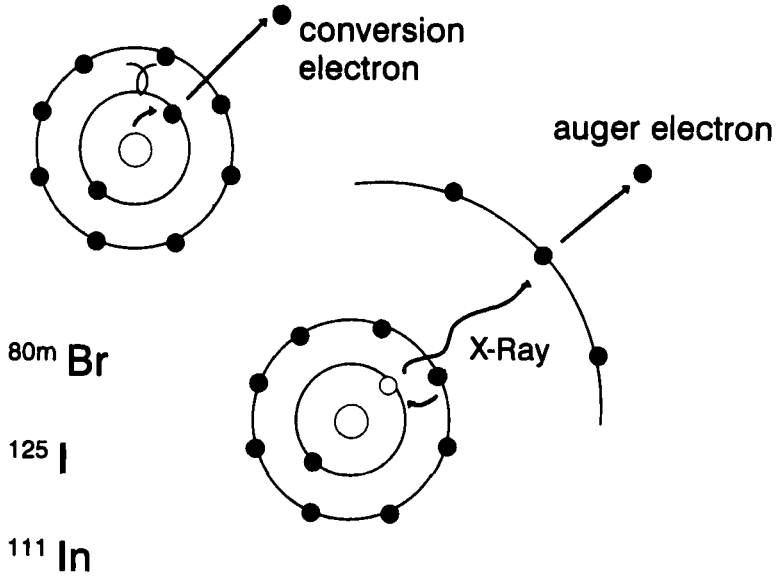


FIGURE 1. Schematic representation of gamma-ray emission ("internal conversion") leading to the ejection of conversion electrons (nuclear photons transfer their energy to orbital electrons, which are then ejected from the atom, thereby leaving an electron vacancy (indicated with the small open circle)) and Auger electrons (the latter by X-ray photon interaction with a loosely bound outer electron). The maximum particle range of conversion and Auger electrons emitted by ^{111}In is indicated in TABLE 1.

TABLE 1. Physical Characteristics of the Radionuclide ^{111}In ($t_{½}$ = 2.83 d)

Emission type	E[a] (keV)	R[b] (μm)
Gamma-photons	171–245	
Conversion electrons	144–245	200–550
Auger electrons	0.5–25	.02–10

[a] E, energy.
[b] R, particle range.

TABLE 2. Energies and Yields of Conversion and Auger Electrons of ^{111}In

	E (keV)	Yield (percent)
Conversion	145–170	10
Conversion	218–245	6
Auger	19–25	16
Auger	2.6–3.6	102
Auger	0.5	191

time of referral, it was decided not to treat her with cytostatics. Treatment with increasing doses of octreotide was started. Eventually therapy with interferon-α was started. Inasmuch as no antiproliferative effect was observed during this medical treatment, it was decided to investigate the effect of therapeutic doses of [^{111}In-DTPA-D-Phe^1]-octreotide. Neither acute nor long-term side effects, including effects on renal, pituitary, and bone marrow functions, were observed up to half a year after the last administration of a radiotherapeutic dose of [^{111}In- DTPA-D-Phe^1]-octreotide (data not shown). FIGURE 2 illustrates the time schedules of treatments applied to this patient and their effects on tumor size and both glucagon and γ-glutamyl transferase serum levels. FIGURES 3–5 show examples of CT scans related to time and of [^{111}In-DTPA-D-Phe^1]-octreotide scintigrams. It is evident that both the tumor load, and glucagon and γ-glutamyl transferase levels react beneficially to radiotherapy. The decrease in glucagon levels is only transient. In accordance with the decline in γ-glutamyl transferase levels, the CT scan of the liver shows a clear decrease in the size of liver metastases.

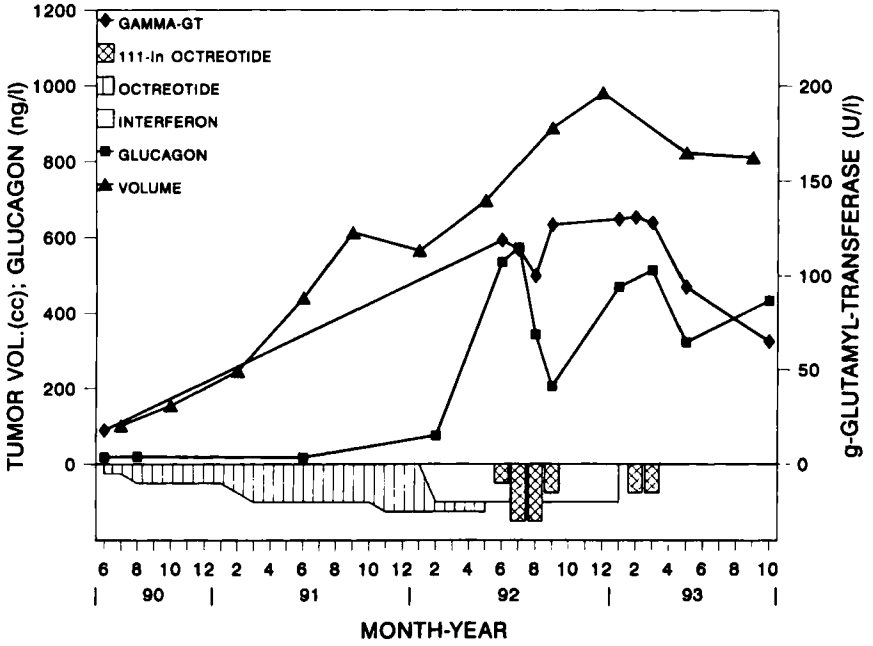


FIGURE 2. Results of various treatments, including radiotherapy with [^{111}In-DTPA-D-Phe^1]-octreotide, in a patient with a metastasized inoperable glucagonoma. From 6/1990 to 5/1992, increasing doses of (not radiolabeled) octreotide (300 to 1500 μg/day) were used. From 2/1992 to 1/1993, interferon-α (3×10^6 units three times/week) was used. Because of persistent increase in size of tumor volume during this medical treatment, [^{111}In-DTPA-D-Phe^1]-octreotide was administered from 6 to 9/1992 (in 5 doses, total 15,022 MBq), and in 2/1993 (2664 MBq) and 3/1993 (2590 MBq). The use of octreotide had been stopped before this radiotherapy. Tumor volume is volume of all abdominal tumors in cc, according to volume measurements of tumors found with whole abdominal CT scanning; glucagon and γ-glutamyl transferase are serum levels.

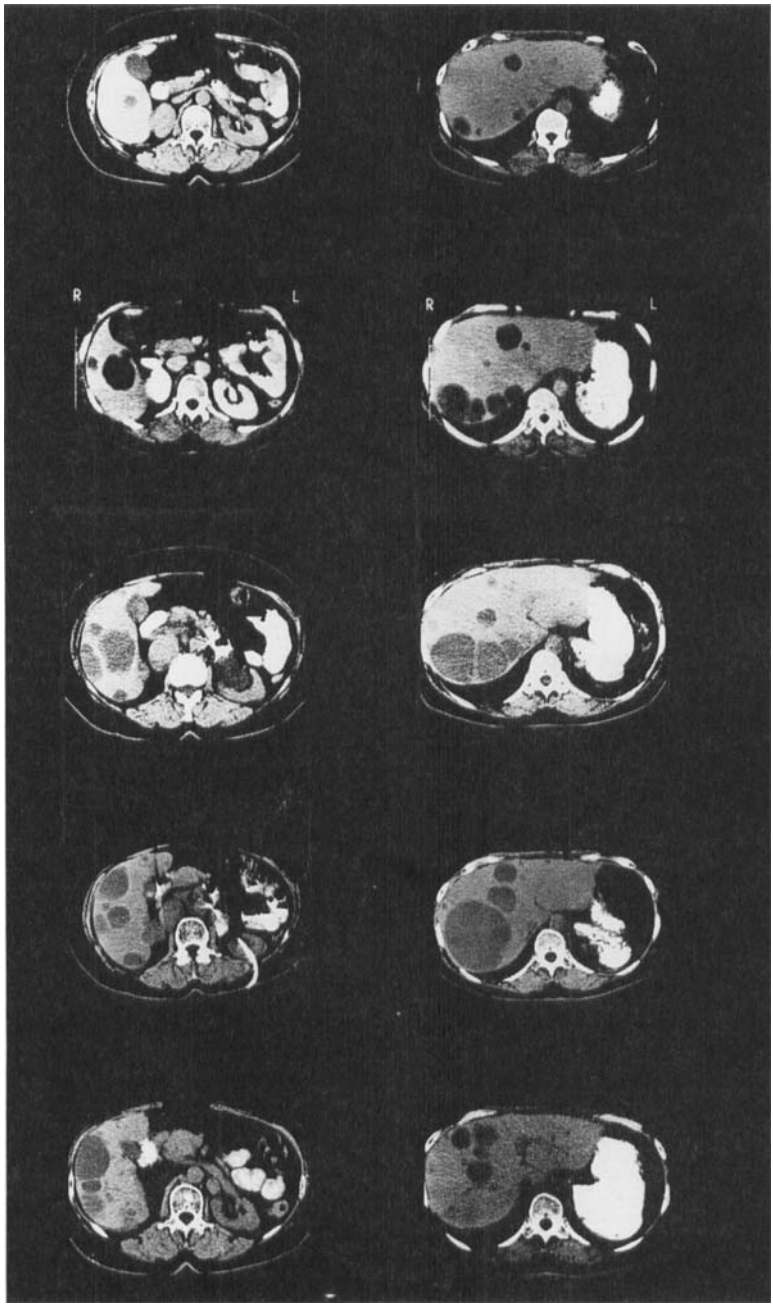


FIGURE 3. CT scanning of the here-reported case with metastasized inoperable glucagonoma; views are from two levels of the liver and related to time: row 1 = 23 July 1990; row 2 = 3 June 1991; row 3 = 4 May 1992; row 4 = 17 December 1992; and row 5 = 30 August 1993.

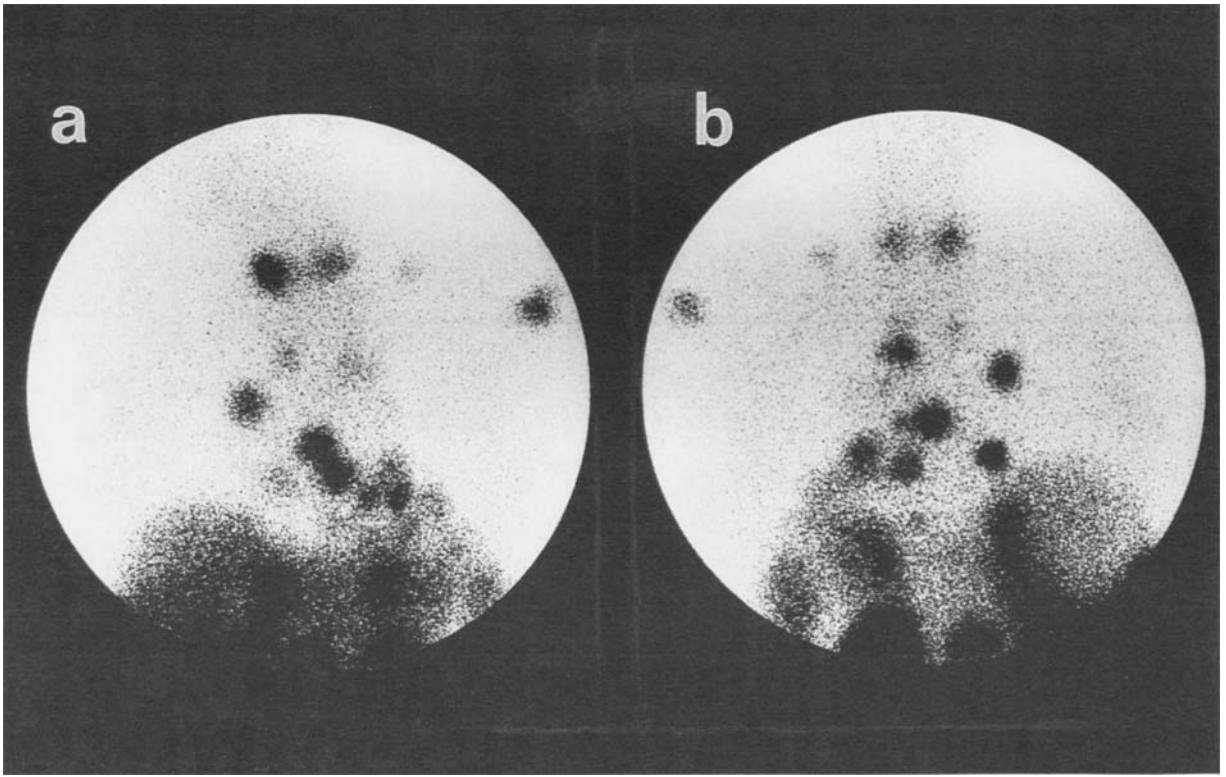
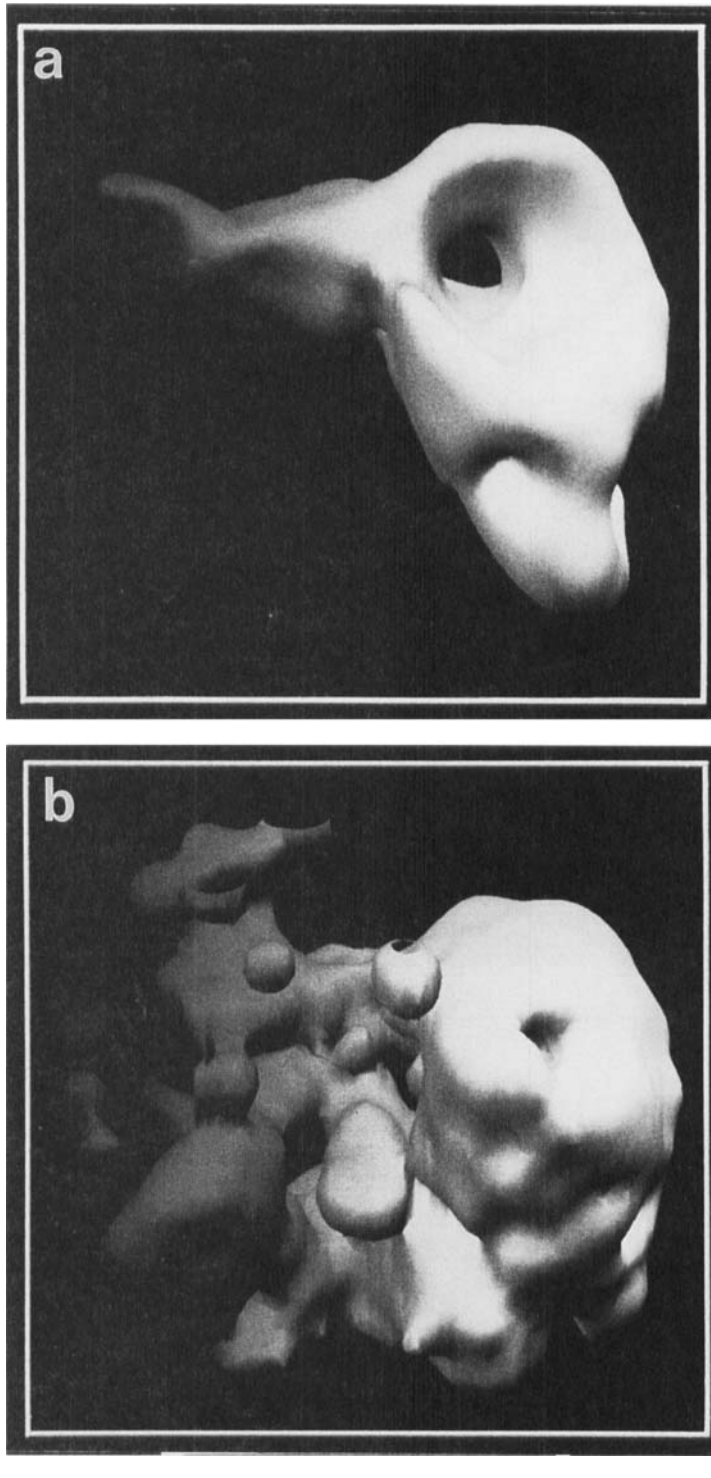


FIGURE 4. Planar [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy of the here-reported case with metastasized inoperable glucagonoma. Images a and b are anterior and posterior thoracic-abdominal views, respectively. Note the many "hot" spots at the various sites, representing metastases of the glucagonoma.


a
b

DOSIMETRY OF [^{111}In- DTPA-D-Phe^1]-OCTREOTIDE ACCUMULATION

Accumulation of [^{111}In- DTPA-D-Phe^1]-octreotide in the organs with significant uptake, that is, liver and kidneys, and one selected abdominal tumor (mass = 300 g) were calculated as described before.[3] Because of the high radiotherapeutic doses of [^{111}In- DTPA-D-Phe^1]-octreotide that were given, it was possible to scan the patient over a long period. An example of the course of the radioactivity is given in FIGURE 6. The amount of radioactivity in the liver and the tumor showed a slow decrease (biological half-life >700 h), whereas the radioactivity in the kidney has a biological half-life of about 270 hours. A total of 20 GBq (550 mCi) [^{111}In- DTPA-D-Phe^1]-octreotide was given intravenously in seven administrations (FIG. 2).Because of the fact that the patient had a nephrostomy drain on the left side, only 35% of the produced urine entered the bladder. The urine was not collected for measurements of radioactivity. For these reasons, the dose to the urinary bladder was estimated using the results described previously.[3] The thus estimated dose to the urinary bladder wall was 1.3 Gy. Using the MIRDOSE2 program, the calculated doses on the liver and kidneys were 2.4 and 5 Gy, respectively.[3] As the tumor had about the same mass as the kidneys (on the basis of the CT scans), and the radiation dose to the tumor was, for more than 95%, caused by the radioactivity in the tumor, the S-factor for the kidneys was used for the calculation of the dose on the tumor. The estimated apparent radiation dose to the tumor was 13 Gy.

DISCUSSION

Scintigraphy with [^{111}In-DTPA-D-Phe^1]-octreotide of the glucagonoma in our patient showed an intense accumulation of radioactivity in the tumor, indicating the expression of a high number of octreotide receptors. Despite the presence of octreotide receptors on the metastases, growth of the tumors continued during octreotide treatment, although a modest antiproliferative effect at an octreotide dose of 1500 μg/day could not be excluded in retrospect. Also during treatment with the combination of a high dose of octreotide and interferon-α, tumor volume continued to increase. Only after a cumulative dose of 20 GBq [^{111}In-DTPA-D-Phe^1]-octreotide, a decrease in total tumor volume in the abdomen of about 20% was observed. Furthermore, after both episodes (in 1992 and 1993) of [^{111}In-DTPA-D-Phe^1]-octreotide radiotherapy a (transient) decline in glucagon and γ-glutamyl transferase serum levels was observed. Possibly, these changes in serum markers can be regarded as signs of an antiproliferative effect of the high doses of [^{111}In-DTPA-D-Phe^1]-octreotide. Such an effect might be comparable to the decline in thyroglobulin levels, which is frequently observed after successful treatment with radioactive iodine for thyroid cancer. It is unlikely that the peptide of [^{111}In-DTPA-D-Phe^1]-octreotide itself in-

FIGURE 5. Three-dimensional representation of the upper abdomen (posterior views) of the here-reported case with metastasized inoperable glucagonoma after injection with ^{99m}Tc-colloid (a) and [^{111}In-DTPA-D-Phe^1]-octreotide (b). These scintigrams were carried out before the second period of radiotherapy with [^{111}In-DTPA-D-Phe^1]-octreotide. Note the large "cold" area in the upper part of the right lobe of the liver on the colloid scan and the presence of radioactivity in this area on the [^{111}In-DTPA-D-Phe^1]-octreotide scan. This difference is explained by the presence of somatostatin receptor expressing tumor tissue. Furthermore, the [^{111}In-DTPA-D-Phe^1]-octreotide image shows many hot spots at various sites, representing metastases of the glucagonoma.

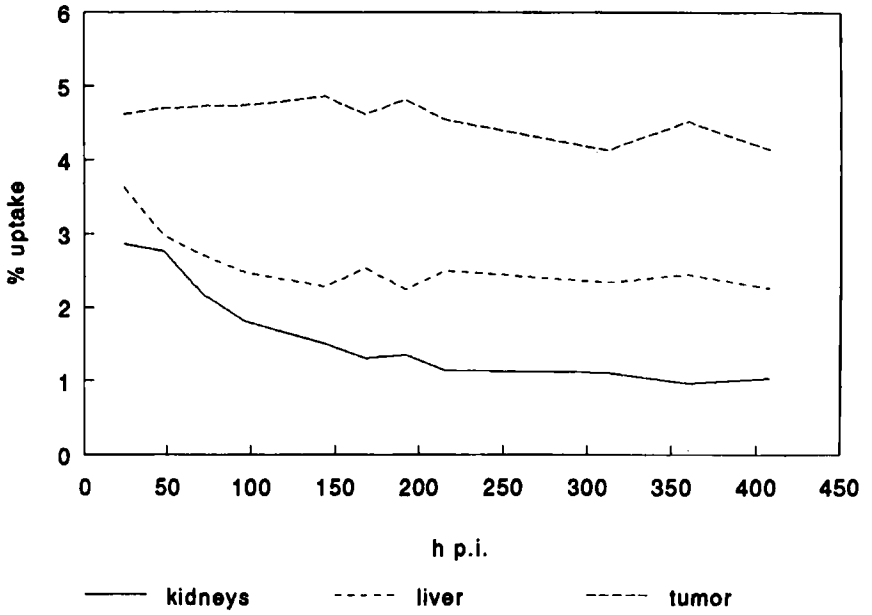


FIGURE 6. The percentage uptake in the kidneys, liver, and abdominal tumor area after a treatment dose of [^{111}In-DTPA-D-Phe^1]-octreotide as function of time after injection.

duced this effect, because of the interval of several weeks between administration of radioligand and the collection of the serum sample for glucagon measurement.

Intense and homogeneous distribution of somatostatin receptors on most glucagonomas is demonstrated by [^{111}In-DTPA-D-Phe^1]-octreotide autoradiography (not shown). Of course this is advantageous for PRRT with [^{111}In-DTPA-D-Phe^1]-octreotide and might partly explain its effect in this case. The apparent radiation dose to the tumor (13 Gy) is calculated according to conventional dosimetry. The application of conventional dosimetry is validated by the fact that the range of several of the ionizing particles emitted is much longer than the average tumor cell diameter. Because of the fact that ^{111}In is also an Auger-electron emitter (range 0.02–10 μm), the actual radiation dose may be much higher when the ^{111}In-labeled pharmaceutical is internalized into the cell (TABLES 1 and 2). The estimated apparent radiation dose to the tumor (assuming a tumor volume on the basis of the CT scan) with the performed radiotherapy with [^{111}In-DTPA-D-Phe^1]-octreotide is relatively low. It is tempting to speculate that the observed response to this radiotherapy (because of the abundance of Auger electrons with a very short particle range) indicates that the [^{111}In-DTPA-D-Phe^1]-octreotide is internalized into the tumor cell. *In vitro* tests will have to confirm this hypothesis. If [^{111}In-DTPA-D-Phe^1]-octreotide is not internalized, but only binds to its receptors at the plasma membrane with the observed long residence time, then it may be concluded that the contribution of the conversion electrons (with their longer particle range than the Auger electrons) to the radiotherapeutic effect of [^{111}In-DTPA-D-Phe^1]-octreotide is more important.

However, in general, ^{111}In is not the most appropriate radionuclide for this objective, inasmuch as it lacks the preferable, higher energies of α- and β-particles.

It is to be expected that the radiotherapeutic use of radionuclides with those higher energies, coupled to small peptides, leads to higher radiation doses and more appropriate particle ranges. Also tumors with an inhomogeneous distribution of peptide receptors may then respond in a favorable way to this kind of treatment. ^{161}Tb is one of the radionuclides, which is a candidate, because it emits β-particles and is able to bind to the chelator DTPA without dissociation in blood.

Both PRS and PRRT with radiolabeled peptides(-derivatives), like hormones and growth factors, are at the moment in their infancy. Nevertheless, the body distribution of small radiolabeled peptides in humans and the results of scintigraphy with [^{111}In-DTPA-D-Phe^1]-octreotide are promising for PRS and PRRT. PRS might not only become a diagnostic localizing tool for most cancer types and their metastases, but it will also form the basis for PRRT with radiolabeled peptides. In general, the kidneys are the most critical organs for radiotherapy with radiolabeled peptides. Investigations are being performed to lower the renal accumulation of radioactivity by interrupting the tubular reabsorption of these radioligands by (1) infusion of amino acids (mainly lysine and arginine) and (2) transient ATP lowering in renal tubular cells.[8,9] Nevertheless, the tolerable radiation dose of the kidneys seems already to be relatively high.[10,11] Furthermore, by decreasing the renal accumulation of radioactivity, the cumulative dose of radiolabeled peptides for PRRT can be increased, thereby optimizing the ultimate radiation dose to the tumor(s). It is hoped that the latter can also be reached in the future by inducing an up-regulation of the receptor density. In conclusion, it is to be expected that the arsenal of treatment modalities in oncology in the near future will be extended by PRRT, using radiolabeled peptides(derivatives), which are more or less derived from native substances. This contrasts to the larger mouse monoclonal antibodies,[10,11] of which the application leads to a higher background radiation and also the forming of human anti-mouse antibodies if administered repeatedly.[12]

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