Inhomogeneous Localization of Radioactivity in the Human Kidney After Injection of \([^{111}\text{In-DTPA}]\text{Octreotide}\)

Marion de Jong, PhD 1; Roelf Valkema, MD 1; Arthur van Gameren 1; Hester van Boven, MD 2; Axel Bex, MD 2; Eric Pieter van de Weyer, MD 3; Jan Dirk Burggraaf, MD 3; Meike Körner, MD 4; Jean-Claude Reubi, MD 4; and Eric P. Krenning, MD 1

1 Department of Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands; 2 Netherlands Cancer Institute, Amsterdam, The Netherlands; 3 Spaarne Hospital, Heemstede, The Netherlands; and 4 Division of Cell Biology and Experimental Cancer Research, Institute of Pathology, University of Bern, Bern, Switzerland

In peptide receptor radionuclide therapy (PRRT) using somatostatin analogs labeled with β-emitters, the radiosensitive kidney is the dose-limiting organ, because of high uptake and retention of the radionuclides after glomerular filtration. Dosimetry calculations are mostly based on the MIRD scheme, assuming homogeneous renal radioactivity distribution. The aim of this study was to reveal the radioactivity distribution in the normal human kidney after intravenous injection of \([^{111}\text{In-diethylenetriaminepentaacetic acid (DTPA)]\text{Octreotide}}\). Methods: Three patients received intravenous injection of \([^{111}\text{In-DTPA]Octreotide}}\) before nephrectomy because of renal cancer. Distribution of radioactivity in the human kidney was investigated using SPECT scanning before and ex vivo autoradiography of the kidney after surgery. Results: Radioactivity was localized predominantly in the cortex of the kidney. In the cortex, radioactivity was not distributed homogeneously but formed a striped pattern, with most of the radioactivity centered in the inner cortical zone. Conclusion: These findings show that average dose calculations using the MIRD scheme, assuming homogeneous renal radioactivity distribution, are inadequate to estimate the radiation dose to various parts of the kidney after PRRT. Different effects due to inhomogeneity can be expected from PRRT using radionuclides emitting particles with short particle ranges, for example, Auger electron emitters, α-emitters, and low-energy β-emitters.

Key Words: radionuclide therapy; radiopharmaceuticals; renal; kidney; octreotide; peptide receptor radionuclide therapy


On their plasma membranes, cells express receptor proteins with high affinity for regulatory peptides, such as somatostatin. Changes in the density of these receptors during disease (e.g., overexpression in many tumors) provide the basis for new imaging and radionuclide therapy methods. The peptide analogues most successfully applied for visualization of receptor-positive tumors are radiolabeled somatostatin analogues. Scintigraphy with \([^{111}\text{In-diethylenetriaminepentaacetic acid (DTPA)]-Octreotide (Octroscan; Mallinckrodt, Inc.)}\) has proven to be sensitive and specific for localizing somatostatin receptor-positive tumors and their metastases (1). Continuing research is aimed at developing a therapeutic analog taking advantage of the specificity of the receptor binding and the localized radiation dose from the radionuclide linked to the peptide. Because indium (\([^{111}\text{In}\]) emits 2 long-range γ-rays, it is not optimal for therapeutic use. Instead, \([^{90}\text{Y-dodecanetetraacetic acid (DOTA)-Tyr3-Octreotide}}\), with the high-energy β-emitter \([^{90}\text{Y}\] (mean energy, 0.93 MeV; half-life, 64 h) strongly linked in the DOTA-cage, has been developed and is now clinically being evaluated for an optimized peptide receptor radionuclide therapy (PRRT) (2–8). \([^{90}\text{Y-DOTA-Tyr3-Octreotide}}\) lacks γ-emission itself or a γ-ray–emitting diagnostic analog. \([^{177}\text{Lu}}\) (T1/2, 6.7 d) emits, besides β-particles (mean energy, 0.13 MeV), γ-rays suitable for imaging (113 keV at 6% per decay and 208 keV at 10% per decay). Together with a slightly altered somatostatin analog, octreotate, in which the amino acid threoninol at the C-terminal side of the octapeptide has been replaced by threonine, \([^{177}\text{Lu-DOTA-Tyr3-Octreotide}}\) forms a superior therapeutic compound with considerably enhanced uptake in receptor-positive tumors (9–11).

In most radionuclide therapies, bone marrow toxicity is dose limiting. In PRRT, bone marrow is also at risk, but after PRRT using somatostatin analogs labeled with β-emit-
ters, such as $^{90}\text{Y}$ and $^{177}\text{Lu}$, the radiosensitive kidney is the
dose-limiting organ because of high uptake and retention of
radionuclides in the kidney after glomerular
filtration.

Clinical PRRT studies aim at a maximum renal radiation
dose of 23–27 Gy, because this dose is expected to produce
clinically significant nephrotoxicity in 5%–50% of the sub-
jects by 5 y of follow-up, based on experience with frac-
tionated external-beam radiation therapies (72). Dosimetry
calculations are based on the MIRD scheme, providing a
generalized phantom with which the doses to all internal
organs can be calculated from the organ residence times for
the considered radionuclide, assuming homogeneous radio-
activity distribution over the kidney. The radiation dose that
can be delivered safely to the kidneys during PRRT remains
to be established, however. Also, the exact mechanism of
renal uptake and localization of radioactivity, whether ho-
mogeneous over the kidney or confined to certain areas,
after radiolabeled somatostatin analog injection in patients
is not known.

The aim of this study was to reveal the radioactivity
distribution in the human kidney after intravenous injection
with $[^{111}\text{In-DTPA}]$octreotide, using ex vivo autoradiogra-
phy. $[^{111}\text{In-DTPA}]$octreotide is a practical model peptide for
the larger group of radiolabeled somatostatin analogs cur-
rently being used for PRRT.

**MATERIALS AND METHODS**

Three men with single primary renal tumors received 220 MBq
of $[^{111}\text{In-DTPA}]$octreotide intravenously 96 h (patient 1, aged
54 y), 72 h (patient 2, aged 65 y), or 48 h (patient 3, aged 70 y)
before nephrectomy. None of the patients used Sandostatin (No-
vartis) subcutaneously or intramuscularly. All patients gave in-
formed consent to participate in the study. $^{111}\text{InCl}_3$, and $[^{111}\text{DTPA}]$oc-
treotide were from Mallinckrodt Medical BV, and labeling was
performed in accordance with the package insert. Twenty-four
hours after injection, planar scintigraphy and SPECT were per-
formed. During surgery, renal tissue was obtained for ex vivo
autoradiography. The pieces of radioactive kidney for autoradi-
ography were taken from the nonneoplastic part of the organ. From
patients 1 and 2, complete renal lobes (consisting of a medullary
pyramid and the overlying cortex) were obtained. From patient 3,
part of a renal lobe was obtained. The tissue was frozen on
ethanol/dry ice and processed further for autoradiography. The
tissue was embedded in TissueTek (Sakura) and processed for
cryosectioning. Tissue sections (10 μm) were mounted on glass
slides. Several slides were used to make autoradiographs, and the
adjacent sections were hematoxylin–eosin stained. The sections
were exposed to phosphor imaging screens (Packard Instruments
Co.) for 1 d in radiographic cassettes. The screens were analyzed
using a Cyclone phosphor imager (Packard) and a computer-
assisted OptiQuant 03.00 image processing system (Packard) (7).

**RESULTS**

Figure 1A shows the SPECT image of patient 1, made
24 h after injection of $[^{111}\text{In-DTPA}]$octreotide, with uptake
in the tumor, spleen, and normal kidney indicated. Figure
1B shows a photograph of the renal lobe from this patient,
available for autoradiography. The renal medulla and cortex
can clearly be distinguished.

Figures 2A–2C show the ex vivo autoradiograms of renal
tissue sections from the 3 patients. Radioactivity is seen to
be localized predominantly, but not exclusively, in the cor-
tex of the kidney. In the cortex, radioactivity was not
ROI with maximum DLU/mm². Radioactivity in MH, how-
CH was comparable in the 3 patients (around 75% of the
of interest (ROI) in each of these 4 areas was quanti-
with low uptake (ML) (expressed as per-
of radioactivity in CH, CL, MH, and ML (expressed as per-
portion of ROI with maximum DLU/mm²) for each kidney.

Figure 4 shows that the relative amount of radioactivity in
CH was comparable in the 3 patients (around 75% of the
ROI with maximum DLU/mm²). Radioactivity in MH, how-
ever, was more variable, ranging from around 40% of the
ROI with maximum DLU/mm² for patients 1 and 2 to 80%
in patient 3, who had the shortest interval (48 h) between
[¹¹¹In-DTPA]octreotide injection and nephrectomy. The re-
sults in the medulla of the kidney of patient 3 could not be
fully evaluated because of the low amount of medullary
tissue available.

DISCUSSION

In PRRT, the goal is to deliver an effective radiation dose
to the tumor without causing undesired effects on healthy
tissues. Improvements in the success of radionuclide ther-
apy depend on optimization of the radiation dose to the
tumor versus the dose to normal organs in individual pa-
tients. This requires application of dosimetry models suit-
able for estimating the radiation dose.

When radionuclide analogs are used for
PRRT, nephrotoxicity is an important risk. Renal toxicity
can be diminished by infusing amino acids for renal pro-
tection and by applying individual dosimetry to prevent the
absorbed dose from exceeding the maximum tolerated by
the kidneys (23–27 Gy). Nevertheless, the radiation dose
that can be administered safely to the kidneys during radio-
uclide therapy remains to be established and might depend
on the radionuclide used for PRRT. Renal toxicity after
PRRT has been described in a few patients from phase II
studies using [⁹⁰Y-DOTA,Tyr³]octreotide. Otte et al. (13)
reported on 4 patients in whom renal toxicity developed.
These 4 patients received more than 7.4 GBq/m² but no
alpha acid solution for renal protection. Two of these
patients showed stable renal insufficiency, and 2 required
hemodialysis. Paganeli et al. (14) reported on 1 patient
who, after receiving 3.3 GBq of octreotide, experienced
delayed grade II kidney toxicity. Kwakkeboom et al. (11)
reported on 1 patient whose kidney function was already
compromised at the start of therapy and who had renal
insufficiency 1 y after treatment with 29.6 GBq [¹⁷⁷Lu-
DOTA,Tyr³]octreotate.

Because current SPECT scanners have a spatial resolu-
tion of more than 1 cm (Fig. 1), accurate measurement of
regional differences in radioactivity within the cortex and
separation of radioactivity in the medulla from radioactivity
in the cortex is not possible. However, using ex vivo auto-
radiography after injection of [¹¹¹In-DTPA]octreotide, we
could show that distribution of radioactivity in the human
renal cortex and medulla was not uniform. Different parts of
the kidney will thus receive radiation doses that differ
tremendously from each other and from the calculated av-
dredose to the whole kidney. The glomeruli, which form
radiation-sensitive functional units for late radiation dam-
age, are not evenly distributed over the cortex in human
kidneys; most (about 85%) of the glomeruli are in the outer
cortical regions. Based on our findings, with the greatest
part of the radioactivity in the inner cortical zone, different
effects due to this inhomogeneity can be expected from
PRRT using radionuclides emitting particles with short
ranges, such as Auger electron emitters, α-emitters, and
low-energy β-emitters. These radionuclides will minimize
the dose to the sensitive glomeruli in the outer renal cortex.
Accordingly, renal toxicity after PRRT was found most
often in studies using the long-ranged ⁹⁰Y-labeled peptide
(13,14), whereas studies using octreotide labeled with short-
ranged ¹¹¹In found no renal toxicity, even though estimated
radiation doses to the kidneys could be as high as 40 Gy
(15). These clinical sparing effects in the kidney remain,
however, to be further investigated.

We will soon perform ex vivo autoradiography studies
using renal tissue from more patients and, if available, from
larger parts of the kidney, to build a model of the 3-dimen-

FIGURE 3. Kidney ex vivo autoradiogram of patient 2, show-
ing the 4 defined areas in the cortex and medulla.

FIGURE 4. Relative amount of radioactivity in CH, CL, MH, and
ML (expressed as percentage of ROI with maximum
DLU/mm²). pt = patient, p.i. = after injection.
sional location of radioactivity and to calculate the dosimetric consequences thereof. Furthermore, we will perform immunohistochemistry tests on adjacent sections to determine the exact histologic localization of the radioactivity in the human kidney.

CONCLUSION

After injection of \[^{111}\text{In-DTPA}]\text{octreotide}, radioactivity is retained predominantly, but not exclusively, in the renal cortex, leading to different radiation doses to different parts of the kidney.

REFERENCES


\[^{111}\text{In-DTPA}]\text{octreotide in Human Kidney • de Jong et al.} 1171