

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogs

Dik J. Kwkkeboom^a Eric P. Krenning^a Rachida Lebtahi^b Paul Komminoth^c
Beata Kos-Kudła^d Wouter W. de Herder^e Ursula Plöckinger^f
and the Mallorca Consensus Conference participants

^aDepartment of Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands;

^bNuclear Medicine Department, Bichat Hospital, Paris, France; ^cInstitute for Pathology, Stadtspital Triemli, Zürich, Switzerland; ^dSlaska Akademia Medyczna Klinika Endokrynologii, Zabrze, Poland; ^eDepartment of Internal Medicine, Section of Endocrinology, Erasmus MC, Rotterdam, The Netherlands; ^fDepartment of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin, Germany

Key Words

Radiolabeled somatostatin analogues · GEPNET ·
Neuroendocrine tumors · Carcinoids

Abstract

The purpose of this guideline is to assist physicians caring for patients with neuroendocrine tumors in considering eligibility criteria for peptide receptor radionuclide therapy (PRRT), and in defining the minimum requirements for PRRT. This guideline also makes recommendations on what minimal patient, tumor, and treatment outcome characteristics should be reported for PRRT in order to make comparisons between studies possible. It is not this guideline's aim to give specific recommendations on the use of specific radiolabeled somatostatin analogs for PRRT because different analogs are being used, and their availability depends on national law and local permissions.

Copyright © 2009 S. Karger AG, Basel

Introduction and Background

The use of radiolabeled somatostatin analogs is a relatively new treatment modality for inoperable or metastasized gastroenteropancreatic (GEP) tumors. Several different radiolabeled somatostatin analogs have been applied. Results and side effects are summarized below.

Studies with [¹¹¹In-DTPA⁰]Octreotide

Initial studies with high dosages of [¹¹¹In-DTPA⁰]octreotide in patients with metastasized neuroendocrine tumors were encouraging, although partial remissions (PRs) were exceptional. Two of 26 patients with GEP tumors who were treated with high dosages of [¹¹¹In-DTPA⁰]octreotide, and received a total cumulative dose of more than 550 mCi (20 GBq), had a decrease

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2009 S. Karger AG, Basel
0028-3835/09/0902-0220\$26.00/0

Accessible online at:
www.karger.com/nen

Dik J. Kwkkeboom
Department of Nuclear Medicine, Erasmus MC
Dr Molewaterplein 40
NL-3015 Rotterdam (The Netherlands)
Tel. +31 10 704 0132, Fax +31 10 703 5997, E-Mail d.j.kwkkeboom@erasmusmc.nl

in tumor size of in between 25 and 50%, as measured on CT scans [1]. None, however, had PR. In another study of 27 patients with GEP tumors, PR was reported in 2/26 patients with measurable disease [2]. Also, in yet another study, PR was reported in 2 of 12 GEP tumor patients [3].

Serious side effects consisted of leukemia and myelodysplastic syndrome (MDS) in 3 patients who had been treated with total cumulative doses of >2.7 Ci (100 GBq; and estimated bone marrow radiation doses of about 3 Gy) [1]. One of these patients had also been treated with chemotherapy, which may have contributed to or caused this complication. Anthony et al. [2] reported renal insufficiency in 1 patient, which was probably not treatment-related but due to preexistent retroperitoneal fibrosis. Transient liver toxicity was observed in 3 patients with widespread liver metastases. Although in these series favorable effects on symptomatology were reported, CT-assessed tumor regression was observed only in rare cases. This is not surprising, since ^{111}In -coupled peptides are not ideal for peptide receptor radionuclide therapy (PRRT) because of the small particle range and therefore short tissue penetration.

Studies with [^{90}Y -DOTA 0 ,Tyr 3]Octreotide

Another radiolabeled somatostatin analog that is used for PRRT is [^{90}Y -DOTA 0 ,Tyr 3]octreotide (^{90}Y -DOTA-TOC; OctreoTher $^{\text{®}}$). Using this compound, different phase-1 and phase-2 PRRT trials have been performed.

Otte et al. [4] and Waldherr et al. [5, 6] (University Hospital Basel, Switzerland) reported different phase-1 and phase-2 studies in patients with neuroendocrine GEP tumors. In their first reports, using a dose-escalating scheme of 4 treatment sessions up to a cumulative dose of 160 mCi (6 GBq)/ m^2 , and at which time renal protection with amino acid infusion was not performed in half of the patients, renal insufficiency developed in 4/29 patients. The overall response rate in GEP tumor patients who were treated with either 160 mCi (6 GBq)/ m^2 [5] or, in a later study, with 200 mCi (7.4 GBq)/ m^2 in 4 doses [6] was 24%. In a subsequent study, with the same dose of 200 mCi (7.4 GBq)/ m^2 administered in two sessions, complete remissions (CRs) and PRs were found in 33% of 36 patients [7]. It should be emphasized, however, that this was not a randomized trial comparing 2 dosing schemes.

Chinol et al. [8], from the European Institute of Oncology (Milan, Italy), described dosimetric and dose-finding

studies with [^{90}Y -DOTA 0 ,Tyr 3]octreotide with and without the administration of kidney-protecting agents. No major acute reactions were observed up to an administered dose of 150 mCi (5.6 GBq) per cycle. Reversible grade-3 hematological toxicity was found in 43% of patients injected with 140 mCi (5.2 GBq), which was defined as the maximum tolerated dose per cycle. None of the patients developed acute or delayed kidney nephropathy, although follow-up was short. PRs and CRs were reported by the same group in 28% of 87 patients with neuroendocrine tumors [9].

In a more detailed publication from the same group, Bodei et al. [10] report the results of a phase-1 study in 40 patients with somatostatin receptor-positive tumors, of whom 21 had GEP tumors. Cumulative total treatment doses ranged from 160 to 300 mCi (5.9–11.1 GBq) given in 2 treatment cycles. Six of 21 (29%) patients had tumor regression. The median duration of the response was 9 months.

Another study with [^{90}Y -DOTA 0 ,Tyr 3]octreotide is a multicenter phase-1 study which was performed in Rotterdam, Brussels and Tampa, in which 60 patients received escalating doses up to 400 mCi (14.8 GBq)/ m^2 in 4 cycles or up to 250 mCi (9.3 GBq)/ m^2 in a single dose, without reaching the maximum tolerated single dose [11]. The cumulative radiation dose to kidneys was limited to 27 Gy. All received amino acids concomitant with [^{90}Y -DOTA 0 ,Tyr 3]octreotide for kidney protection. Three patients had dose-limiting toxicity: 1 liver toxicity; 1 thrombocytopenia grade 4, and 1 MDS. Four of 54 (8%) patients who had received their maximum allowed dose had PR, and 7 (13%) had a minor response (MR; 25–50% tumor volume reduction). The median time to progression in the 44 patients who had either stable disease (SD), MR, or PR was 30 months.

Bushnell et al. [12] reported a favorable clinical response, determined by a scoring system that included weight, patient-assessed health score, Karnofsky score, and tumor-related symptoms, in 14/21 patients who were treated with a total cumulative dose of 360 mCi [^{90}Y -DOTA 0 ,Tyr 3]octreotide in 3 treatment cycles.

Despite differences in protocols used, CRs plus PRs in most of the different studies with [^{90}Y -DOTA 0 ,Tyr 3]octreotide are in the same range, between 10 and 30%, and therefore better than those obtained with [^{111}In -DTPA 0]octreotide.

Studies with [¹⁷⁷Lu-DOTA⁰,Tyr³]Octreotate

The somatostatin analog [DTPA⁰,Tyr³]octreotate, differs from [DTPA⁰,Tyr³]octreotide only in that the C-terminal threoninol is replaced with threonine. Reubi et al. [13] reported a ninefold increase in affinity for the somatostatin receptor subtype 2 for [DOTA⁰,Tyr³]octreotate when compared with [DOTA⁰,Tyr³]octreotide, and a 6- to 7-fold increase in affinity for their Yttrium-loaded counterparts. In a comparison in patients, it was found that the uptake of radioactivity, expressed as percentage of the injected dose of [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate, was comparable to that after [¹¹¹In-DTPA⁰]octreotide for kidneys, spleen and liver, but was 3- to 4-fold higher for 4 of 5 tumors [14].

Esser et al. [15] published the results of a comparison of dosimetry in a therapeutic setting using 3.7 GBq (100 mCi) ¹⁷⁷Lu-octreotate and 3.7 GBq ¹⁷⁷Lu-DOTATOC in the same patients. From this study it was concluded that ¹⁷⁷Lu-octreotate represents an important improvement because of the higher absorbed doses that can be achieved to most tumors with about equal doses to potentially dose-limiting organs and because of the lower tissue penetration range of ¹⁷⁷Lu if compared with ⁹⁰Y, which may be especially important for small tumors.

In a large group of patients the treatment effects of ¹⁷⁷Lu-octreotate therapy were very recently published [16]. Results in a smaller number of patients were also reported earlier [17, 18]. Patients were treated up to an intended cumulative activity of 22.2–29.6 GBq (600–800 mCi). 504 patients were treated between January 2000 and August 2006. Side effects within the first 24 h were nausea in 25% of administrations, vomiting in 10%, and pain in 10%. In 6 patients with very hormonally active neuroendocrine tumors, a clinical crisis occurred after administration due to massive release of bioactive substances. All patients recovered after adequate medical treatment [19]. Hematological side effects (WHO grade 3 or 4) occurred after 3.6% of administrations, or in 9.5% of patients. Mild and reversible alopecia was reported by 62% of patients. Serious delayed side effects occurred in 9 patients. Two had a decrease in kidney function, which was most likely unrelated to the treatment. Three patients with extensive hepatic metastases had serious liver toxicity. In 1 patient this was most likely attributable to aggressive tumor growth. In the 2 other patients this was likely caused by the therapeutic radiation dose to the liver. Both patients recovered after adequate care and therapy was resumed at a lower cycle dose without subsequent serious side effects. Lastly, 4 patients developed

MDS. In 1 patient, this could be attributed to prior chemotherapy. In the other 3 patients, MDS was more likely related to the therapy with ¹⁷⁷Lu-octreotate. In summary, serious delayed toxicity probably attributable to therapy with ¹⁷⁷Lu-octreotate was present in 5 patients (approximately 1%).

Tumor response was evaluated in 310 patients with GEP tumors. CR was found in 5 (2%) patients, PR in 86 (28%), MR in 51 (16%), SD in 107 (35%), and progressive disease in 61 (20%). Higher remission rates were positively correlated with high uptake during pre-therapy OctreoScan and a limited number of liver metastases. Median time to progression was 40 months from start of treatment in the 249 patients who either had SD or tumor regression (MR, PR and CR).

This recent study reports data about survival after therapy with ¹⁷⁷Lu-octreotate as well. Median overall survival was 46 months from start of therapy and median disease-related survival was >48 months. Comparing similar patient subgroups from different interventional and observational studies, there seemed to be a survival benefit of 3.5–6 years.

Studies with [⁹⁰Y-DOTA⁰]Lanreotide and [⁹⁰Y-DOTA⁰,Tyr³]Octreotate

Radiolabeled lanreotide, another somatostatin analog, has been advocated because of its increased affinity for somatostatin receptor subtypes 3 and 4 compared to ¹¹¹In-octreotide [20], but this claim is questionable [13]. Although radiolabeled lanreotide has been used to treat patients with GEP tumors, its affinity is poorer than that of radiolabeled [DOTA⁰,Tyr³]octreotide/octreotate for the somatostatin receptor subtype 2, which is predominantly overexpressed in GEP tumors. Eight of 39 patients (21%) with GEP tumors who were treated with [⁹⁰Y-DOTA⁰]lanreotide had regressive disease (defined as a >25% reduction in tumor size), 17 had SD (44%) and 14 had PD (36%) [20].

Recently, preliminary data have been presented of a study using ⁹⁰Y-labelled [DOTA⁰,Tyr³]octreotate (⁹⁰Y-octreotate) [21, 22]. However, the treatment protocols vary and the way of response evaluation was not clearly defined. The reported results were an objective response rate (PR) of 37% (28/75) and stabilization of the disease in 39/75 patients (52%). An important issue is that, to date, reliable dosimetry of ⁹⁰Y-octreotate is lacking.

Comparison of the Different Treatments

Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. The results that were obtained with [⁹⁰Y-DOTA⁰,Tyr³]octreotide and [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate are very encouraging, although a direct, randomized comparison between the various treatments is lacking. Also, the reported percentages of tumor remission after [⁹⁰Y-DOTA⁰,Tyr³]octreotide treatment vary. This may have several causes. (1) The administered doses and dosing schemes differ: some studies use dose-escalating schemes, whereas others use fixed doses. (2) There are several patient and tumor characteristics that determine treatment outcome, such as amount of uptake on the octreoscan, the estimated total tumor burden, and the extent of liver involvement. Therefore, differences in patient selection may play an important role in determining treatment outcome.

Other factors that can have contributed to the different results found in the different centers performing trials with the same compounds may be differences in tumor response criteria and centralized versus decentralized follow-up CT scoring. Therefore, in order to establish which treatment scheme and which radiolabeled somatostatin analogs or combination of analogs is optimal, randomized trials are needed.

PRRT Requirements

Legal Aspects

Permission to perform PRRT should be obtained according to national legislation. Ethical committee approval should be obtained and eligible patients should sign an informed consent form.

The production of the peptide should meet GMP criteria and storage should be according to national legislation.

Eligibility Criteria

- Tumor uptake on the OctreoScan should be at least as high as normal liver uptake, as judged from planar images. Comparable uptake with other somatostatin receptor imaging modalities may apply, but direct correlations are not available
- Inoperable disease
- Life expectancy at least 3–6 months

- Karnofski Performance Score >50%, or Performance Score (ECOG) <4
- Signed informed consent

Contraindications (Relative and Absolute)

- Pregnancy and lactation
 - Renal impairment (i.e. creatinine clearance <40–50 ml/min)
 - Impaired hematological function, i.e. Hgb <5 mmol/l (8 g/dl); platelets <75 × 10⁹/l; WBC <2 × 10⁹/l
 - Severe hepatic impairment, i.e. total bilirubin >3 × upper limit of normal or albumin <30 g/l and prothrombin time increased
 - Severe cardiac impairment
- Eligibility and clinical decision making should preferentially be based on multidisciplinary discussion.

Laboratory Evaluations Needed before Each Therapy Cycle

- Liver function (ALAT, ASAT, albumin, bilirubin)
- Kidney function (creatinine, urea; creatinine clearance on indication)
- Hematology (Hgb, WBC plus differential, platelet number)
- Chromogranin-A and/or other serum tumor markers if elevated at baseline

Patient Preparation and Monitoring during PRRT

When clinically feasible, long-acting somatostatin analog formulations should be stopped 6 weeks before PRRT, and patients should be switched to short-acting formulations up to 1 day before PRRT. Patients on long-acting formulations should be instructed to co-administer short-acting formulations in the first 7–10 days after their long-acting formulation has been restarted.

Infusion of amino acid solutions that contain lysine and arginine is essential to reduce kidney radiation-absorbed dose when performing PRRT. 2.5% lysine, 2.5% arginine in 1 liter saline can be infused in 4 h, starting 30 min before the administration of the radiopharmaceutical. Alternatively, other commercially available amino acid solutions can be used. One of these solutions, Aminosteril N-Hepa 8% (Fresenius AG, Bad Homburg, Germany), containing 11 g lysine, 16 g arginine, in 1,500 ml, added with 30 ml magnesium sulfate 10% and 500 ml Ringer lactate (700 mosm/l and 2,030 ml for the total solution) should be given at an infusion rate of 500 ml/h. Another one is Baxter Synthamin, containing 5.8 g lysine and 11.5 g arginine per liter. This should be infused at 500 ml/h.

For PRRT with ^{90}Y -labelled analogs, quality control with a small activity test dose and a 'Bremsstrahlungs' scintigraphy 1 h after infusion is not recommended.

When using ^{177}Lu -labelled analogs, individual dosimetry based on post-therapy scans and, if feasible, blood and urine collections, is preferred. Simplified methods, however, are needed to enable individual dosimetry in the daily clinical setting.

Written instructions should be given to patients regarding travel and contact with others after the therapy, according to national/international legislation.

Blood cell counts are preferably performed 4 and 6 weeks after each therapy cycle, and repeated every 2 weeks in case of WHO toxicity grade 3 or 4.

Treatment Scheme

Neither for ^{90}Y -labelled nor for ^{177}Lu -labelled somatostatin analogs are there randomized clinical trials available comparing optimal treatment cycle dose, optimal cycle interval, or optimal cumulative dose. Therefore, no guidelines can be given here, and treatment schemes must depend on local expertise and clinical judgment.

Discontinuation of Treatment

Progressive tumor disease during the treatment period, based either on imaging studies or on the patient's clinical condition, is usually a reason to discontinue the treatment. A rise in serum tumor markers as such does not constitute proof of tumor progression, as temporary rises due to tumor lysis may occur.

Prolonged (i.e. more than 2–3 months) WHO grade 3 or 4 hematological, renal, or hepatic toxicity may be a reason to modify the cycle dose or to discontinue treatment, according to the local protocol.

Follow-Up Laboratory Monitoring

Follow-up laboratory monitoring should comprise the evaluation of the parameters listed above under contraindications.

Follow-up laboratory monitoring should ideally be after 3 and 6 months, and thereafter every 6 months.

Follow-Up Imaging and Response Criteria

Symptomatic and biochemical response should not be reported in isolation, but always in combination with imaging response.

There are no accepted criteria for biochemical responses. It is recommended, however, to define tumor marker response as a decrease in serum levels of $\geq 50\%$

of baseline. It should be well considered that factors other than changes in tumor burden may also influence serum tumor marker levels, for instance changes in medication (e.g. somatostatin analogs).

Symptomatic responses should preferentially be reported according to the WHO toxicity criteria.

Imaging response should be according to accepted standards, i.e. WHO, RECIST (Response Evaluation Criteria In Solid Tumors), or SWOG (South West Oncology Group) criteria. The follow-up imaging modality (CT or MRI) and technique should be identical to baseline. A confirmatory study of the response status is needed before calling a response. It should be recognized that CT and MRI may underestimate responses in case of cystic or necrotic tumors.

Quality of life is an important outcome parameter in oncology. The use of the validated EORTC QLC-30 questionnaires is recommended, if possible with additional NET-specific questions that are currently in the process of validation.

Follow-Up Scheme and Duration

Follow-up response evaluation is recommended at 3 (confirmatory of 2 months) and 6 months, and 6 months thereafter. Follow-up should be continued up to relapse, and ideally lifelong. Side effects and serious adverse events should be monitored along the same scheme.

The person or persons responsible for monitoring and reporting should be determined locally.

List of Participants

List of Participants of the Consensus Conference on the ENETS Guidelines for the Standard of Care for the Diagnosis and Treatment of Neuroendocrine Tumors, Held in Palma de Mallorca (Spain), November 28 to December 1, 2007

Göran Åkerström, Department of Surgery, University Hospital, Uppsala (Sweden); Bruno Annibale, University Sapienza Roma, Rome (Italy); Rudolf Arnold, Department of Internal Medicine, Philipps University, Munich (Germany); Emilio Bajetta, Medical Oncology Unit B, Istituto Nazionale Tumori, Milan (Italy); Jaroslava Barkmanova, Department of Oncology, University Hospital, Prague (Czech Republic); Yuan-Jia Chen, Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing (China); Frederico Costa, Hospital Sirio Libanes, Centro de Oncologia, São Paulo (Brazil); Anne Couvelard, Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); Joseph Davar, Department of Cardiology, Royal Free Hospital, London (UK); Gianfranco

Delle Fave, Ospedale S. Andrea, Rome (Italy); *Barbro Eriksson*, Medical Department, Endocrine Unit, University Hospital, Uppsala (Sweden); *Massimo Falconi*, Medicine and Surgery, University of Verona, Verona (Italy); *Diego Ferone*, Departments of Internal Medicine and Endocrinological and Metabolic Sciences, University of Genoa, Genoa (Italy); *David Gross*, Department of Endocrinology and Metabolism, Hadassah University Hospital, Jerusalem (Israel); *Ashley Grossman*, St. Bartholomew's Hospital, London (UK); *Björn Gustafsson*, Medisinsk avd, Gastroseksjon, St Olavs Hospital, Trondheim (Norway); *Rudolf Hyrdel*, II. Internal Medical Department, University Hospital Martin, Martin (Slovakia); *Diana Ivan*, Endocrinology and Diabetology, Klinikum der Philipps-Universität, Marburg (Germany); *Gregory Kaltsas*, G. Genimatas Hospital, Athens (Greece); *Reza Kianmanesh*, UFR Bichat-Beaujon-Louis Mourier, Service de Chirurgie Digestive, Hôpital Louis Mourier, Colombes (France); *Günter Klöppel*, Institut für Pathologie, TU München, Munich (Germany); *Ulrich-Peter Knigge*, Department of Surgery, Rigshospitalet, Copenhagen (Denmark); *Val Lewington*, Royal Marsden, NHS Foundation Trust, Sutton (UK); *Anne Marie McNicol*, Division of Cancer Sciences and Molecular Pathology, Pathology Department, Royal Infirmary, Glasgow (UK); *Emmanuel Mitry*, Hepatogastroenterology and Digestive Oncology, Hôpital Ambroise-Paré, Boulogne (France); *Ola Nilsson*, Department of Pathology, Sahlgrenska sjukhuset, Gothenburg (Sweden); *Kjell Öberg*, Department of Internal Medicine, Endocrine Unit, University Hospital, Uppsala (Sweden); *Juan O'Connor*, Instituto Alexander Fleming, Buenos Aires (Argentina); *Dermot O'Toole*, Department of Gastroenterology and Clinical Medicine, St. James's Hospital and Trinity College Dublin, Dublin (Ireland); *Ulrich-*

Frank Pape, Department of Internal Medicine, Division of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany); *Mauro Papotti*, Department of Biological and Clinical Sciences, University of Turin/St. Luigi Hospital, Turin (Italy); *Marianne Pavel*, Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany); *Aurel Perren*, Institut für Allgemeine Pathologie und Pathologische Anatomie der Technischen Universität München, Klinikum r.d. Isar, Munich (Germany); *Marco Platania*, Istituto Nazionale dei Tumori di Milano, Milan (Italy); *Guido Rindi*, Department of Pathology and Laboratory Medicine, Università degli Studi, Parma (Italy); *Philippe Ruszniewski*, Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); *Ramon Salazar*, Institut Català d'Oncologia, Barcelona (Spain); *Aldo Scarpa*, Department of Pathology, University of Verona, Verona (Italy); *Klemens Scheidhauer*, Klinikum rechts der Isar, TU München, Munich (Germany); *Jean-Yves Scoazec*, Anatomie Pathologique, Hôpital Edouard-Herriot, Lyon (France); *Anders Sundin*, Department of Radiology, Uppsala University Hospital, Uppsala (Sweden); *Waldemar Szpak*, Westville Hospital, Mayville (South Africa); *Babs Taal*, Netherlands Cancer Centre, Amsterdam (The Netherlands); *Pavel Vitek*, Institute of Radiation Oncology, University Hospital, Prague (Czech Republic); *Marie-Pierre Vullierme*, Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); *Bertram Wiedenmann*, Department of Internal Medicine, Division of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany).

References

- Valkema R, de Jong M, Bakker WH, et al: Phase I study of peptide receptor radionuclide therapy with [¹¹¹In-DTPA⁰]octreotide: the Rotterdam experience. *Semin Nucl Med* 2002;32:110–122.
- Anthony LB, Woltering EA, Espanan GD, Cronin MD, Maloney TJ, McCarthy KE: Indium-111-pentetreotide prolongs survival in gastroenteropancreatic malignancies. *Semin Nucl Med* 2002;32:123–132.
- Buscombe JR, Caplin ME, Hilson AJ: Long-term efficacy of high-activity ¹¹¹In-pentetreotide therapy in patients with disseminated neuroendocrine tumors. *J Nucl Med* 2003; 44:1–6.
- Otte A, Herrmann R, Heppeler A, et al: Yttrium-90 DOTATOC: first clinical results. *Eur J Nucl Med* 1999;26:1439–1447.
- Waldherr C, Pless M, Maecke HR, Haldermann A, Mueller-Brand J: The clinical value of [⁹⁰Y-DOTA]-D-Phe¹-Tyr³-octreotide (⁹⁰Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. *Ann Oncol* 2001;12:941–945.
- Waldherr C, Pless M, Maecke HR, et al: Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC. *J Nucl Med* 2002;43:610–616.
- Waldherr C, Schumacher T, Maecke HR, et al: Does tumor response depend on the number of treatment sessions at constant injected dose using 90Yttrium-DOTATOC in neuroendocrine tumors? (abstract). *Eur J Nucl Med* 2002;29:S100.
- Chinol M, Bodei L, Cremonesi M, Paganelli G: Receptor-mediated radiotherapy with Y-DOTA-DPhe-Tyr-octreotide: the experience of the European Institute of Oncology group. *Semin Nucl Med* 2002;32:141–147.
- Paganelli G, Bodei L, Handkiewicz Junak D, et al: ⁹⁰Y-DOTA-D-Phe¹-Tyr³-octreotide in therapy of neuroendocrine malignancies. *Biopolymers* 2002;66:393–398.
- Bodei L, Cremonesi M, Zoboli S, et al: Receptor-mediated radionuclide therapy with ⁹⁰Y-DOTATOC in association with amino acid infusion: a phase I study. *Eur J Nucl Med Mol Imaging* 2003;30:207–216.
- Valkema R, Pauwels S, Kvols L, et al: Long-term follow-up of a phase I study of peptide receptor radionuclide therapy (PRRT) with [⁹⁰Y-DOTA⁰,Tyr³]octreotide in patients with somatostatin receptor positive tumours (abstract). *Eur J Nucl Med Mol Imaging* 2003; 30(suppl 2):S232.
- Bushnell D, O'Dorisio T, Menda Y, et al: Evaluating the clinical effectiveness of ⁹⁰Y-SMT 487 in patients with neuroendocrine tumors. *J Nucl Med* 2003;44:1556–1560.
- Reubi JC, Schar JC, Waser 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: 273–282.
- Kwekkeboom DJ, Bakker WH, Kooij PP, et al: [¹⁷⁷Lu-DOTA⁰Tyr³]octreotate: comparison with [¹¹¹In-DTPA⁰]octreotide in patients. *Eur J Nucl Med* 2001;28:1319–1325.
- Esser JP, Krenning EP, Teunissen JJ, Kooij PP, van Gameren AL, Bakker WH, Kwekkeboom DJ: Comparison of [¹⁷⁷Lu-DOTA⁰, Tyr³]octreotate and [¹⁷⁷Lu-DOTA⁰, Tyr³]octreotide: which peptide is preferable for PRRT? *Eur J Nucl Med Mol Imaging* 2006; 33:1346–1351.
- Kwekkeboom DJ, De Herder WW, Kam BL, et al: Treatment with the radiolabeled somatostatin analog [¹⁷⁷Lu-DOTA⁰, Tyr³]octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 2008;26:2124–2130.

- 17 Kwekkeboom DJ, Bakker WH, Kam BL, et al: Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate. *Eur J Nucl Med Mol Imaging* 2003;30:417–422.
- 18 Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al: Treatment with the radiolabeled somatostatin analogue [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate in patients with gastro-entero-pancreatic (GEP) tumors. *J Clin Oncol* 2005;23:2754–2762.
- 19 De Keizer B, van Aken MO, Feelders RA, de Herder WW, Kam BL, van Essen M, Krenning EP, Kwekkeboom DJ: Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate. *Eur J Nucl Med Mol Imaging* 2008;35:749–755.
- 20 Virgolini I, Britton K, Buscombe J, Moncayo R, Paganelli G, Riva P: In- and Y-DOTA-lanreotide: results and implications of the MAURITIUS trial. *Semin Nucl Med* 2002;32:148–155.
- 21 Baum RP, Söldner J, Schmücking M, Niesen A: Peptidrezeptorvermittelte Radiotherapie (PRRT) neuroendokriner Tumoren: Klinische Indikationen und Erfahrung mit ⁹⁰Yttrium-markierten Somatostatinanaloga. *Onkologie* 2004;10:1098–1110.
- 22 Baum RP, Söldner J, Schmücking M, Niesen A: Intravenous and intra-arterial peptide receptor radionuclide therapy (PRRT) using Y-⁹⁰-DOTA-Tyr³-octreotate (Y-⁹⁰-DOTA-TATE) in patients with metastatic neuroendocrine tumors (abstract). *Eur J Nucl Med* 2004;31(suppl 2):S238.