Neuro
-endocrinology

Neuroendocrinology 2013;97:86–98
DOI: 10.1159/000336086

Received: September 20, 2011
Accepted: December 11, 2011
Published online: May 4, 2012

Radionuclide Therapy via SSTR: Future Aspects from Experimental Animal Studies

Eva Forssell-Aronsson[a] Johan Spetz[a] Håkan Ahlman[b]

Departments of [a]Radiation Physics and [b]Surgery, Institute of Clinical Sciences, Sahlgrenska Cancer Centre, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Key Words

Somatostatin receptors · Octreotide · Somatostatin analogues · Neuroendocrine tumours · Carcinoid tumours · Radiation · ^{177}Lu · ^{90}Y · ^{211}At · ^{213}Bi

Abstract

There is need for better therapeutic options for neuroendocrine tumours. The aim of this review was to summarize results of experimental animal studies and raise ideas for future radionuclide therapy based on high expression of somatostatin (SS) receptors by many neuroendocrine tumours. In summary, one of the major options is individualized treatment for each patient, including choice of SS analogues, radionuclides and treatment schedules. Other options are methods to increase the treatment effect on tumour tissue (increasing tumour uptake and retention by upregulation of receptor expression and avoiding saturation of receptor binding), methods to increase the tumour tissue response (by choice of radionuclides, SS analogues or combined therapies), and methods to reduce side effects (diminished uptake and retention in critical organs and reduced normal tissue response). Furthermore, combination therapy with other radiopharmaceuticals, cytotoxic drugs or radiosensitizers can be considered to enhance the effects of radiolabelled SS analogues.

Introduction

Patients with neuroendocrine (NE) tumours often have metastatic spread at the time of diagnosis and can be palliated by interventional tumour reduction combined with somatostatin (SS) analogues. NE tumours often express somatostatin receptors (SSTR) that occur in 5 subtypes. Different NE tumour types express different SSTR subtypes, e.g. midgut carcinoids have high expression of SSTR2 and 5 [1]. Synthetic SS analogues with a longer half-life than native SS have been developed, e.g. octreotide and octreotate, with high affinity to SSTR2 and 5, medium affinity to SSTR3 and low affinity to SSTR1 and 4 [2]. A pan analogue (SOM230) was developed with high affinity to all SSTR except SSTR4 [3]. The development of imaging/therapy of NE tumours using radiolabeled SS analogues during the last two decades has been exciting. ^{111}In-[DTPA^{0},D-Phe^{1}]-octreotide (^{111}In-octreotide) is today routinely used to visualize SSTR-expressing NE tumours.

The general opinion has been that carcinoid tumours have relatively low radiosensitivity, i.e. external radiation therapy should only be used for palliation or regionally advanced/metastatic disease [4–9]. However, 20–50 Gy to the tumour by external radiation therapy has given partial/complete remission in 25–80% of the patients [10–

KARGER

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

0028–3835/13/0971–0086$38.00/0

Accessible online at:
www.karger.com/nen

Eva Forssell-Aronsson
Department of Radiation Physics, University of Gothenburg
Sahlgrenska University Hospital
SE–413 45 Gothenburg (Sweden)
Tel. +46 31 342 1000, E-Mail eva.forssell_aronsson@radfys.gu.se

Table 1. Animal models and tumour cell lines/types used with radiolabelled SS analogues

Cell line/type	Origin	Tumour type	Animal species
GOT1	human	ileal carcinoid*	nude mouse
KRJ-1	human	ileal carcinoid*	nude mouse
GOT2	human	medullary thyroid carcinoma*	nude mouse
TT	human	medullary thyroid carcinoma*	nude mouse
BON	human	pancreatic carcinoid*	nude mouse
AR42J	rat (induction with azaserine)	hyperplastic exocrine pancreatic nodule	rat, nude mouse
CA20948	rat (induction with azaserine)	pancreatic acinar tumour	rat, nude mouse
H69	human	small cell lung cancer**	nude mouse

* NE tumour; ** NE-like features.

13]. Radiolabelled SS analogues have been developed for therapy of SSTR-expressing tumours. Initially, attempts were made using ^{111}In-octreotide with limited success due to unfavourable radiation properties of ^{111}In (high photon emission) [14]. ^{177}Lu-[DOTA^0,Tyr^3]-octreotate (^{177}Lu-octreotate or ^{177}Lu-DOTATATE), ^{90}Y-[DOTA^0,D-Phe^1,Tyr^3]-octreotide (^{90}Y-DOTATOC), and ^{90}Y-[DOTA^0,Tyr^3]-octreotate (^{90}Y-DOTATATE) are now used in patients with advanced NE tumours with promising results [15–18]. Long-term follow-up of ^{177}Lu-octreotate therapy indicates longer median overall survival (48 months) and a higher response rate (80%, complete/partial responses and stable disease) [16, 19] than of chemotherapy (corresponding values: 12–37 months and <20%) [20–22]. However, the clinical results appear modest compared to the high cure rates by ^{177}Lu-octreotate in animals transplanted with human NE tumour cell lines [23–26]. This indicates that human treatment can be further optimized. Efforts are therefore spent on finding methods to enhance the therapeutic results in humans and to develop new radiolabeled SS analogues with high receptor subtype-specific affinities.

The aim of this review is to summarize data from experimental animal studies and define directions for future research to enhance the therapeutic results for NE tumours using radiolabelled SS analogues.

Animal Models

Studies in animal models are usually required before clinical trials of new pharmaceuticals. Clinically relevant models are needed to study biodistribution and dosimetric data, tumour characteristics (e.g. size, growth rate, and radiosensitivity), and normal tissue characteristics and toxicity. There are many differences between man and animals, and results from animals may be difficult to translate to the clinical situation. Few animal models exist with SSTR-expressing tumours. Two major types of models are used: (1) tumours (human or animal) growing on immunosuppressed animals (xenogeneic models), and (2) tumours growing on animals of the same species (syngeneic models) (table 1). This review does not cover human tumours transfected with SSTR, nor genetically engineered animals.

The biodistribution data of ^{177}Lu-octreotate, especially the uptake in different types of SSTR-expressing tumour tissues, varies between the animal models described (table 2).

Animal Models with Human Tumours Expressing SSTR

Few animal models with SSTR-expressing human tumours (all xenografted to mice) have been used together with radiolabelled SS analogues (table 1). The human pancreatic carcinoid cell line BON expresses SSTR [27], but may not be entirely valid for NE tumours due to its amphicrine properties [28]. The human midgut carcinoid cell line KRJ-I is of enterochromaffin cell origin [29–31]. The human midgut carcinoid cell line GOT1 has well-preserved NE differentiation, slow growth rate and high expression of mainly SSTR2 and 5 [32, 33]. The human small cell lung cancer (SCLC) cell line H69 has rapid growth and some NE features, e.g. expression of SSTR [34]. The human medullary thyroid carcinoma (MTC) cell line GOT2 has a slow growth rate and much lower SSTR expression than GOT1 [35, 36]. TT is another SSTR-expressing MTC cell line [37]. Successful therapy by ^{177}Lu-octreotate has been achieved in nude mice carrying GOT1 or H69 tumours [23, 26].

Table 2. Biodistribution, given as ^{177}Lu activity concentration [% IA/g] in various tumour-bearing animal models 1 and 7 days after injection of ^{177}Lu-octreotate

Tumour type (animal)	GOT1* (nude mouse)		GOT2* (nude mouse)		NCI-H69** (nude mouse)		AR42J (nude mouse)	CA20948 (rat)		CA20948 (rat)
Study	Kölby et al. 2005 [23, 50]		Dalmo et al. 2012 [36]		Schmitt et al. 2003 [82]		de Araújo et al. 2009 [164]	Lewis et al. 2001 [165]		De Jong et al. 2001 [24]
Injected activity (amount of peptide)	7.5 MBq (0.25 μg)		5 MBq (0.2 μg)		3.3 MBq (0.7 μg)		0.74 MBq (1 μg)	1.3 MBq (0.67 μg)		3 MBq (0.5 μg)
Time after injection	^{177}Lu activity concentration, % IA/g									
	1 day	7 days	1 day	7 days	1 day	7 days	1 day	1 day	7 days	1 day
Adrenals			0.87	0.43	0.34	0.43	2.1[a]	0.21	0.11	8.6
Blood	0.35	0.024	0.020	0.0027	0.008	0.001	0.06	0.030	0.010	0.002
Heart			0.054	0.027	0.034	0.011	0.1	0.000	0.070	
Kidneys	4.6	0.78	5.0	0.62	2.2	0.27	4.4	1.7	0.94	1.6
Liver	0.20	0.11	0.14	0.048	0.10	0.068	0.4	0.28	0.18	0.032
Muscle			0.012	0.0024	0.011	0.001	0.03	0.012	0.00	0.002
Pancreas			2.0	0.28	0.41	0.032	1.6	2.3	1.1	3.6
Spleen			0.12	0.058	0.12	0.032	0.3	0.010	0.010	0.023
Tumour	18 (16[b])	7.2 (40[b])	0.37	0.094	3.7	1.2	0.8	6.1	0.65	2.2
Dosimetry										
D/A, Gy/MBq	1.6–4.0		0.013		0.29					0.097

Data are corrected for physical decay. Mean absorbed dose to tumour per administered activity, D/A (Gy/MBq).
* NE tumour; ** NE-like features. [a] In adrenals in this study the results were expressed as % IA/organ. [b] After administration of 30 MBq (1 μg).

Animal Models with Animal Tumour Cell Lines Expressing SSTR

Since access to human transplantable SSTR-expressing cell lines has been limited, many researchers have used animal cell lines (table 1). AR42J and CA20948 are rat pancreatic cell lines induced by azaserine [38–40]; both cell lines express SSTR and have been transplanted to rats, or xenotransplanted to nude mice, and were responsive to treatment with ^{177}Lu-octreotate [24, 25, 41, 42].

Strategies for Optimizing Therapy

Several strategies can be defined to optimize radionuclide therapy by radiolabelled SS analogues (table 3). There are three major issues to consider: (1) general methods including individualized treatment performance, (2) methods to increase the treatment effect on tumour tissue, and (3) methods to reduce the toxic effects on normal tissues. Many methods have been tested in animal studies, but some studies can only be performed in patients. None of the strategies has been fully optimized for clinical use.

General Methods Including Individualization

Treatment Planning

Treatment planning should focus on delivering highest therapeutic effect to tumour, avoiding acute and severe late effects in risk organs. If possible, treatment planning should be based on data obtained with the same radiopharmaceutical as used for therapy, since the SSTR affinity is dependent on both the peptide and the radionuclide.

Fractionation. Fractionated radiation therapy may permit higher amounts of activity to be administered by allowing restitution of side effects between the fractions. The time intervals are chosen to allow such recovery. The optimal time intervals and number of fractions using radiolabelled SS analogues are still to be defined. Several

Table 3. Strategies for optimization of therapy with radiolabelled SS analogues

Individualized treatment for each patient			Methods to increase treatment effect on tumour tissue		Methods to reduce normal tissue toxicity (nephrotoxicity)
Treatment schedule	Choice of SS analogue	Choice of radionuclide	Methods to increase tumour uptake/retention of the radionuclide	Methods to increase radiobiological effect (tumour tissue)	
Activity administered	SSTR subtype expression	Half-life vs. biokinetics	Optimal amount of peptide	Combination therapy	Reduced uptake and retention of the radionuclide
Fractionation	New SS analogues	Particle range vs. tumour size and distribution	SSTR upregulation	Radiosensitizing	Reduced radiobiological effects
	New radiolabelling techniques	SSTR affinity	Increased tumour perfusion	Interaction with death signalling pathways	

studies in CA20948-bearing rats using different radiolabelled SS analogues have presented favourable therapy results using fractionation [43–46].

Administered Activity. Therapeutic amounts of ^{177}Lu-octreotate in GOT1-bearing mice resulted in increased tumour uptake and threefold increased absorbed dose per activity administered versus diagnostic amounts [23, 47]. No change of uptake into normal tissues was observed. The discrepancies may be due to differences in biodistribution of low and high amounts, or to tumour volume shrinkage combined with long retention in tumour tissue. Similar results have been reported for CA20948-bearing rats [42].

Individualized Treatment Planning Based on Individual Radiation Sensitivity

Individuals are more or less sensitive to radiation due to genetic differences, but also by influence of environmental or lifestyle factors [48]. About 5% of cancer patients suffer from severe toxicity after external radiation therapy; some genetic abnormalities/diseases are more frequent in these patients [49].

The limiting factor in radiation therapy is side effects on normal tissues. The tolerance doses are based on the most radiosensitive patients. By predicting radiation sensitivity and/or following biological effects on the most critical organs, individualized treatment can be designed with a lower frequency of side effects. Many patients can thus receive more aggressive treatment with a higher cure rate.

Choice of SS Analogue Based on SSTR Subtype Expression

NE tumour types have different SSTR subtype expression profiles; the SSTR expression profile may vary within one tumour type [1]. Midgut carcinoid tumours have high SSTR expression, and good SSTR2-binding analogues were rapidly developed. In future it would be valuable if the individual SSTR subtype expression was defined for each patient, so the most optimal radiolabelled SS analogue could be used for therapy. The affinity and internalization of a radiolabelled SS analogue depend on the entire molecule, including chelating agent and radionuclide. Animal studies demonstrated higher SSTR affinity of DOTATATE versus DOTATOC, resulting in higher tumour/normal tissue (T/NT) ratios and better therapeutic effects [24, 50, 51]. ^{177}Lu-DOTATATE had a higher tumour uptake in CA20948-bearing rats than ^{88}Y- and ^{111}In-labelled analogues [24]. ^{111}In-DOTATOC showed higher tumour/kidney absorbed dose ratios in patients than ^{111}In-DOTATATE [52], while ^{177}Lu-DOTATATE gave higher tumour/kidney ratios than ^{77}Lu-DOTATOC [53].

New SS Analogues. New SS analogues have been tested. ^{111}In-DOTA-NOC gave a higher tumour uptake and lower kidney retention than ^{111}In-DOTATOC/^{111}In-DOTATATE in CA20948- or AR42J-bearing rats [54, 55]. DOTA-conjugated multimeric [Tyr^3]-octreotide had a high tumour uptake and long tumour retention in AR42J-bearing nude mice [56]. There is a continuous search for pan-SS or multi-SS analogues. SOM230 (pasireotide) and BIM-23A779 both have high affinity for SSTR1, 2, 3 and 5 and KE108 has high affinity for all SSTR subtypes [57–60], but they have not yet been tested for radionuclide therapy.

Receptor agonists are claimed to be better for radionuclide therapy since they are internalized in contrast to the antagonists. Comparative studies are not yet conclusive. The SSTR2 agonist TATE internalized fast in AR42J ver-

sus a high-affinity SSTR2 antagonist [61]. The SS analogues SOM230 and KE108 were reported as agonists, but acted also as antagonists in AR42J cells [62]; SOM230 was not internalized in vitro or in AR42J in rats [63]. Lower internalization and higher tumour/blood and tumour/muscle values in AR42J-bearing rats were found for a ^{64}Cu-labelled antagonist (SSTR2-ANT) versus an agonist (Tyr^3-TATE). The uptake in liver and kidney was, however, much higher for the antagonist [64]. It is thus of future interest to compare the binding and internalization properties in risk organs.

New Radiolabelling Techniques. New radiolabelling techniques are developed. NOTA octreotide (IMP466) labelled with ^{18}F, or ^{68}Ga, is readily taken up by AR42J on mice resulting in high tumour/kidney ratios [65]. Glycosylated octreotide analogues have been labelled with ^{211}At, or ^{125}I, with maintained SSTR2 affinity and improved pharmacokinetics in AR42J-bearing rats [66, 67]. ^{213}Bi-labelled DOTATOC has been produced and given promising therapeutic results in one animal model [68].

Choice of Radionuclide

The optimal choice of radionuclide for therapy depends on several factors: types of radiation emitted, particle range versus tumour size, half-life versus biokinetics, and effect on SSTR affinity. Furthermore, factors such as possibility to produce the radionuclide carrier-free and with high specific activity are limiting.

Type of Radiation Emitted. The choice of radionuclide is very important: only radionuclides with high emission of electrons and/or α-particles and low emission of photons are suitable for therapy [69–72]. α-Particles give a higher biological effect than electrons per radiation dose since the linear energy transfer value is higher. The photon contribution should be considered when translating results from animal to man; promising results in animals do not directly indicate similar results in man for radionuclides with high photon emission, e.g. ^{111}In [71].

Particle Range. Therapy has been suggested/performed in animals and patients using SS analogues labelled with various radionuclides, e.g. the Auger and conversion electron emitters ^{111}In and ^{103m}Rh (low electron energy) [46, 72], the β-emitters ^{177}Lu, ^{153}Sm, and ^{161}Tb (medium electron energy) [23, 24, 26, 42, 44, 51, 73–75] and ^{90}Y, and ^{188}Re (high electron energy) [76–78] and the α-particle emitters ^{225}Ac, ^{211}At and ^{213}Bi [66–68, 79]. For radionuclides with a higher electron energy and thus longer range, the absorbed fraction/dose in small tumours will be lower than in larger tumours and tissue surrounding the tumours will be more highly exposed. This relation was clearly demonstrated in CA20948-bearing rats: ^{90}Y-DOTA-octreotide (mean electron range 12 mm) gave complete response in larger tumours, but was less effective in smaller tumours [80]. In similar studies with ^{177}Lu-octreotate (mean electron range 0.67 mm) the cure rate was much higher for smaller versus larger tumours [24].

Theoretically, short-ranged particles would give effective treatment also in larger tumours if the radionuclides were homogeneously distributed in the tumour. It has been proposed that radionuclides emitting particles with a longer range than needed for a certain tumour size can offer advantages in case of inhomogeneous SSTR expression within the tumour. In GOT1 tumours the ^{177}Lu concentration peripherally was only half of that in central parts not related to tumour size, clearly indicating a lower absorbed dose peripherally [47]. A combination of ^{90}Y-DOTATOC/DOTATATE and ^{177}Lu-DOTATATE was efficient for treating tumours of different sizes [77].

Physical Half-Life. The fast binding to tumour tissue implied that the physical half-life of the radionuclide should be short, but if T/NT increase with time (i.e., the retention time is longer in tumour than normal tissues), radionuclides with longer half-lives might be favourable. In the GOT1 model, all T/NT studied increased with time 3–14 days after injection of ^{177}Lu-octreotide [81]. Similar results were found in the GOT2 model [36].

Tumour Uptake versus Tumour Size. One important factor for evaluation of therapeutic effects of radiopharmaceuticals is if the activity concentration in tumour tissue (or T/NT values) varies with tumour size. In the H69 model, we found a higher uptake of ^{177}Lu-octreotate in smaller tumours at 24 h, but not at 3 and 7 days after injection [82].

Methods to Increase the Treatment Effect on Tumour Tissue

Methods to Increase Tumour Uptake and Retention of the Radionuclide

Optimal Amount of Peptide. The binding of SS analogues to the tumour depends on the number of peptide molecules and the number of SSTR available. For CA20948 tumours in rats, a bell-shaped binding curve appeared with a maximum at 0.5 μg [83]. In the GOT1 model the maximal uptake and T/NT values were found for 0.1–1 μg ^{111}In-octreotide with reduced values at higher peptide amounts [84].

Saturation of SSTR should be avoided, since the uptake and absorbed dose to the tumour tissue will be reduced otherwise. The effects of SSTR saturation have been clearly demonstrated. In the GOT1 model, saturation was found at peptide amounts >1 μg of ^{111}In-DTPA-octreotide [84]. In the GOT2 model, with much lower SSTR expression, saturation occurred in both tumour tissue and SSTR-expressing pancreas/adrenals for ^{177}Lu-octreotate at lower peptide levels [36]. To avoid SSTR saturation, low peptide amounts should be used which necessitates high specific activity of the radiolabelled peptide, prolonged infusion time, or fractionated administration of the radiopharmaceutical.

SSTR Upregulation. The uptake of radiolabelled SS analogues could be increased by upregulation of SSTR expression specifically in tumour tissue. Several methods have been suggested, e.g. prestimulation with radiation, unlabelled SS analogues, or other compounds [47, 85, 86]. In vitro experiments on H69 cells have demonstrated increased uptake of ^{177}Lu-octreotate by a factor of 2–7 after external irradiation, most probably due to upregulation of SSTR expression, since mRNA levels of SSTR1, 2 and 5 were increased [87]. Similar results were found in vivo in the GOT1 model [88]. Exposure to low amounts of ^{177}Lu-octreotate gave a twofold higher concentration of ^{111}In-octreotide in the tumour tissue with no increased concentration in normal tissues. Radiation-induced SSTR upregulation has been reported in other in vitro and in vivo models [41, 46, 89].

Studies on the GOT1 model clearly showed the importance of optimal timing and activity levels for the first administration. At short time intervals and/or higher activity, a reduced amount of binding of the second fraction was observed which was probably related to a lower number of SSTR available at the cell membrane. Another explanation is reduced perfusion of the tumour tissue and hence reduced penetration due to inflammation/oedema caused by irradiation from the first injection [23, 90]. At longer time intervals, recycling of SSTR, enhanced tumour perfusion or reduced intratumoural pressure may promote increased binding of radiolabelled SS analogues. Reduced intratumoural pressure might lead to improved tumour oxygenation and an enhanced radiobiological effect, further influenced by angiogenic factors [91, 92].

Pretreatment with the nucleoside analogue gemcitabine initially gave downregulation but after withdrawal upregulation of SSTR by a factor of 1.5–3 in AR42J or H69 cells treated with ^{177}Lu-octreotate [93].

Methods to Increase Radiobiological Effect on Tumour Tissue

Combination Therapy and Radiosensitizing. The effects of ionizing radiation are to some extent known. Radiation induces DNA damage, followed by cellular responses such as DNA repair, cell cycle arrest, mitotic catastrophe, necrosis and apoptosis [94, 95]. Radiation-induced effects may vary in different types of tumour cells due to the status of the signalling pathways in the cell. One method to enhance the therapeutic effect is to combine treatment with radiolabelled SS analogues with agents that potentiate the effect on tumour tissue, so-called radiosensitizers. Synergistic effects will occur if the effects by radiation and the radiosensitizer will affect signalling pathways related to cell death.

Potential Interaction between Radiation and Apoptosis-Related Pathways. Radiation-induced cell death is achieved via several signalling pathways, mostly involving apoptosis. Pre-mitotic apoptosis is associated with activation of caspase-3, while post-mitotic apoptosis relates to downregulation of antiapoptotic genes, i.e. *MAPK* and *BCL2* [95]. Radiation also induces cellular responses via various extranuclear targets and extracellular events. Radiation-induced apoptosis is mediated both via the intrinsic mitochondria-mediated and extrinsic death-receptor-mediated pathways [94, 96–99].

We have clearly demonstrated that ^{177}Lu-octreotate induces apoptosis in xenografted GOT1 tumours with a maximum at day 1 and 3 after injection [23]. In many tumours, including carcinoids, the apoptotic signalling is disrupted or reduced, which leads to relative radioresistance [100]. Carcinoids express BCL2 and MYC [101, 102]. Since BCL2 inhibits apoptosis, BCL2 inhibitors might stimulate apoptosis and increase the radiosensitivity of such tumours.

The natural ligand of the death receptors TRAILR1 and 2, TRAIL, kills tumour cells specifically without effects on normal cells. Since TRAIL has short half-life in vivo [103–106], long-acting TRAIL analogues have been produced. TRAIL-induced apoptosis has been studied in carcinoid cells in vitro. A peroxisome proliferator-activated receptor-γ (PPARγ) agonist inhibited carcinoid cell growth and promoted TRAIL-induced apoptosis [107]. Since ionizing radiation upregulates *TRAILR1* and *2* and/or their ligands causing apoptosis [106], a combination between radiation and TRAIL/PPARγ analogues might be of future interest. Several radiosensitizers have been suggested, e.g. agonistic monoclonal antibodies or recombinant ligands to death receptors, competing molecules to growth receptors, tyrosine-kinase inhibitors,

small molecule inhibitors, antisense oligonucleotides, or siRNA [108]. Some of these principles have been tested experimentally and have led to pilot clinical trials [108].

Potential Interaction between Radiation and PARP-Related Pathways. Activation of nuclear factor-κB (NF-κB)/Rel transcription factors is related to tumour formation, including malignant transformation, inhibition of apoptosis, and increased proliferation, invasiveness, angiogenesis and metastasis formation [109]. The pyridyl guanidine CHS-828 (GMX-1778) inhibits activation of NF-κB in tumour cell lines in vitro [110]. Another mode of action of CHS-828 involves depletion/reduction of nicotinamide adenine dinucleotide (NAD^+), which is related to ATP generation, ADP ribosylation and poly(ADP-ribose) polymerase 1 (PARP1) [111]. PARP1 is activated by DNA damage and binds to DNA strand breaks. NAD^+ is further metabolized into ADP-ribose polymers that are transferred to nuclear proteins including PARP1 [112, 113]. NAD^+ can be resynthesized via a salvage pathway [114]. Radiation is known to strongly activate PARP1, resulting in depletion of NAD^+/ATP energy stores and cell death [115]. One treatment option would be to use drugs to inhibit NAD^+ resynthesis, e.g. CHS-828 and FK866, to potentiate the energy deficit of tumour cells [111, 116, 117].

We have demonstrated potent anti-tumour effects of CHS-828, both in vitro and in vivo on three NE tumour cell lines (GOT1, GOT2 and BON). One weekly oral treatment with CHS-828 to nude mice resulted in necrosis and complete tumour regression in all tumour types [118]. CHS-828 also had potent effects on TT cells, xenografted neuroblastoma and SCLC NYH [110, 119, 120]. Nude mice xenografted with GOT1 tumours were cured with either 30 MBq ^{177}Lu-octreotate or with CHS-828 (250 mg/kg/week) [23, 118]. In the same model we found that lower doses of ^{177}Lu-octreotate or CHS-828 (7.5 MBq and 100 mg/kg/week, respectively) gave partial tumour regression. When the two treatment modalities were combined, at reduced doses a marked synergistic effect was seen with complete tumour regression in almost all animals [121]. We thus regard CHS-828 as a radiosensitizer. In phase I trials, patients have received FK866, or CHS-828, as monotherapy resulting in adverse effects and no tumour regression, suggesting that NAD^+ depleting drugs must be combined with therapies causing DNA damage, e.g. radiation [122].

Potential Interaction between Radiation and RAS-Related Pathways. Overexpression of *RAS* reduces the radiosensitivity in general; PI3K is one mediator of RAS-induced radiation resistance [123, 124]. *EGFR* expression and AKT phosphorylation are also associated with radiosensitivity. Inhibition of EGFR, PI3K, and AKT and RAS has demonstrated increased radiosensitivity of cancer cell lines [125, 126]. Thus, radiosensitizers could be directed against signals common for these pathways [123].

Potential Interaction between Radiation and VEGF-Related Pathways. NE tumours frequently express VEGF, which increases angiogenesis and the oxygen level [127]. It is well known that high oxygen concentration enhances radiosensitivity and that radiation increases the VEGF expression [128]. Synergistic effects of anti-VEGF therapy and radiolabelled SS analogues can most probably be achieved.

Combination Therapy with Other Radiopharmaceuticals or Cytotoxic Drugs. Many NE tumours also express other receptors or antigens. A combination of two radiolabelled pharmaceuticals that affect normal tissues differently may lead to a higher radiation dose to the tumour without increased toxicity. Likewise, a combination with cytotoxic drugs might have synergistic effects. Pretreatment with gemcitabine increased apoptosis of AR42J and H69 cells treated with ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC [93].

Reduction of Toxicity and Side Effects

The major side effects after therapy with radiolabelled SS analogues are acute effects on bone marrow (usually reversible) and late effects on kidneys [129–131]. There are two ways to reduce nephrotoxicity: (1) to reduce uptake/retention in the kidneys, and (2) to reduce toxic effects of radiation.

Methods to Reduce Uptake and Retention of the Radionuclide in the Kidneys

Radiolabelled peptides are excreted mainly via the urine and are reabsorbed in the renal proximal tubules [132–134]. To reduce nephrotoxicity, better knowledge on reabsorption, retention and toxicity mechanisms are required. Studies on rats and nude mice demonstrated dose-dependent late damage of the proximal tubules after treatment with radiolabelled SS analogues [134, 135]. Renal damage was found after 280–560 MBq ^{177}Lu-octreotate in rats, while after 90 MBq in mice [unpubl. data]. The estimated tolerance absorbed dose to the mouse kidney cortex was 24 Gy (biologically effective dose, BED: 37 Gy) [unpubl. data]. For ^{90}Y-DOTATATE in mice, severe bone marrow toxicity occurred already after 30 MBq (18 Gy to the kidney cortex); the tolerance dose to kidneys could not be determined [unpubl. data]. In pa-

tients treated with ^{90}Y-DOTATOC, a BED threshold of 28 Gy was suggested for patients with risk factors (hypertension and diabetes), otherwise a BED of 40 Gy was proposed [131].

Several transport mechanisms are involved in renal reabsorption of peptides/proteins: receptor-mediated endocytosis (via megalin/cubulin receptors and SSTR), amino acid/oligopeptide transporters, pinocytosis, and passive diffusion [136, 137]. Previous studies in vitro and in vivo indicate that endocytosis of ^{111}In-octreotide/^{111}In-octreotate is mediated via megalin/cubulin receptors on the apical cell membrane of proximal tubular cells [133, 138–141]. Another important factor is the abundance of SSTR in the kidneys: in mice, all five SSTR were expressed and high expression of all SSTR was also found in man [142–145]; only SSTR3 and 4 were found in rats [146]. The different SSTR expression profiles between species make translation of uptake/dosimetry complicated. The relation between binding and retention via megalin/cubulin receptors and SSTR is not known, but SSTR seem to be less important in man [147].

There are several strategies to reduce renal uptake: structural modification of the radiopharmaceutical (e.g. by exchange/addition/deletion of amino acids or other molecules), or use of other radionuclides/chelating agents. Using such strategies, one should be aware of potential changes of SSTR affinity, and that the resulting tumour/kidney absorbed dose ratio should not decrease.

Another way to reduce the reabsorption process is blocking by other ligands. Today, infusion with basic amino acids is clinically used during infusion of radiolabelled SS analogues to reduce renal uptake of the radionuclide. Lysine alone, or combined with arginine, has been used clinically and in rats; D-lysine may be preferred to L-lysine because of lower toxicity [135, 148–151].

In recent studies, succinylated gelatin (Gelofusine®; Braun) or lysine reduced renal uptake of ^{177}Lu- or ^{111}In-octreotate; synergistic effects were obtained with combined use [152–157]. Gelofusine did not reduce uptake of ^{111}In-octreotate in SSTR-expressing tissues and tumours [156]. Low amounts of albumin fragments specifically reduced renal uptake of ^{111}In-octreotide [158]. Dimercaptosuccinic acid (DMSA) specifically reduced kidney retention of ^{177}Lu-octreotate in rats [159]. The results suggest new possibilities for more efficient and selective renal blockade.

Methods to Reduce Radiobiological Effects in Kidneys

The radiation-induced nephrotoxicity can be reduced by radioprotecting agents; in rats treated with ^{177}Lu-octreotate, amifostine reduced the increased levels of creatinine and proteinuria, and also histologically demonstrated damage [160]. Other options are mitigating agents, e.g. ACE inhibitors and angiotensin II receptor antagonists, which prevent the effects of whole-body irradiation in rats and patients [161–163].

Fractionated therapy is used to allow recovery from acute normal tissue toxicity. It is generally assumed that late effects only depend on the total absorbed dose (no effects of dose rate, time of exposure and fractionation). It is unclear if late effects, e.g. nephrotoxicity, will be lower after fractionated radionuclide therapy. One study in rats showed that increased number of fractions and longer interval between fractions of ^{177}Lu-octreotate gave less nephrotoxicity, with maintained tumour response [135].

Conclusion

Much work is still needed to obtain optimal treatment results using radiolabelled SS analogues. This paper summarizes different strategies, some focused on enhanced treatment effects on tumour tissue and others on reduced side effects of normal tissues. Individualized treatment planning, including optimal choice of radiopharmaceutical, is a relatively straightforward way to increase the absorbed dose to the tumour. By combining radiolabelled SS analogues with compounds/drugs that can act as radiosensitizers, treatment effects can be enhanced. Beside acute bone marrow toxicity, the main limiting factor in treatment of patients today is late nephrotoxicity. Several tubular mechanisms are involved in the uptake and retention of the radiolabelled SS analogues; today only blocking agents are used to reduce such uptake. Animal studies indicate that combination of several different methods may give synergistic effects. Most strategies presented herein have been studied in animals but not yet in man. To achieve higher cure rates of patients with NE tumours using SSTR-based methods, such clinical studies are warranted.

Acknowledgments

This study was supported by grants from the from the Swedish Research Council, the Swedish Cancer Society, and BioCARE – a National Strategic Research Program at University of Gothenburg, and the King Gustav V Jubilee Clinic Cancer Research Foundation.

References

1 Kölby L, Wangberg B, Ahlman H, Tisell LE, Fjalling M, Forssell-Aronsson E, Nilsson O: Somatostatin receptor subtypes, octreotide scintigraphy, and clinical response to octreotide treatment in patients with neuroendocrine tumors. World J Surg 1998;22:679–683.

2 Weckbecker G, Lewis I, Albert R, Schmid HA, Hoyer D, Bruns C: Opportunities in somatostatin research: biological, chemical and therapeutic aspects. Nat Rev Drug Discov 2003;2:999–1017.

3 Boerlin V, van der Hoek J, Beglinger C, Poon KW, Hartmann S, Dutreix C, Kovarik JM, Bruns C, Weckbecker G, Lewis I, Schnieper P, Hofland LJ, Lamberts SW: New insights on SOM230, a universal somatostatin receptor ligand. J Endocrinol Invest 2003;26 (suppl):14–16.

4 Harris AL: Chemotherapy for the carcinoid syndrome. Cancer Chemother Pharmacol 1981;5:133–138.

5 Moertel CG: Treatment of the carcinoid tumor and the malignant carcinoid syndrome. J Clin Oncol 1983;1:727–740.

6 Chakravarthy A, Abrams RA: Radiation therapy in the management of patients with malignant carcinoid tumors. Cancer 1995; 75:1386–1390.

7 Kulke MH, Mayer RJ: Carcinoid tumors. N Engl J Med 1999;340:858–868.

8 Kimmig BN: Radiotherapy for gastroenteropancreatic neuroendocrine tumors. Ann NY Acad Sci 1994;733:488–495.

9 Horton KM, Kamel I, Hofmann L, Fishman EK: Carcinoid tumors of the small bowel: a multitechnique imaging approach. AJR Am J Roentgenol 2004;182:559–567.

10 Samlowski WE, Eyre HJ, Sause WT: Evaluation of the response of unresectable carcinoid tumors to radiotherapy. Int J Radiat Oncol Biol Phys 1986;12:301–305.

11 Abrams RA, King D, Wilson JF: Objective response of malignant carcinoid to radiation therapy. Int J Radiat Oncol Biol Phys 1987;13: 869–873.

12 Keane TJ, Rider WD, Harwood AR, Thomas GM, Cummings BJ: Whole abdominal radiation in the management of metastatic gastrointestinal carcinoid tumor. Int J Radiat Oncol Biol Phys 1981;7:1519–1521.

13 Schupak KD, Wallner KE: The role of radiation therapy in the treatment of locally unresectable or metastatic carcinoid tumors. Int J Radiat Oncol Biol Phys 1991;20:489–495.

14 De Jong M, Breeman WA, Bakker WH, Kooij PP, Bernard BF, Hofland LJ, Visser TJ, Srinivasan A, Schmidt MA, Erion JL, Bugaj JE, Macke HR, Krenning EP: Comparison of ^{111}In-labeled somatostatin analogues for tumor scintigraphy and radionuclide therapy. Cancer Res 1998;58:437–441.

15 Van Essen M, Krenning EP, Kam BL, de Jong M, Valkema R, Kwekkeboom DJ: Peptide-receptor radionuclide therapy for endocrine tumors. Nat Rev Endocrinol 2009;5:382–393.

16 Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, Feelders RA, van Aken MO, Krenning EP: Treatment with the radiolabeled somatostatin analog [^{177}Lu-DOTA^0,Tyr^3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124–2130.

17 Waldherr C, Pless M, Maecke HR, Schumacher T, Crazzolara A, Nitzsche EU, Haldemann A, Mueller-Brand J: Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq ^{90}Y-DOTATOC. J Nucl Med 2002;43:610–616.

18 Kwekkeboom DJ, Kam BL, van Essen M, Teunissen JJ, van Eijck CH, Valkema R, de Jong M, de Herder WW, Krenning EP: Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer 2010; 17:R53–R73.

19 Kwekkeboom DJ, de Herder WW, van Eijck CH, Kam BL, van Essen M, Teunissen JJ, Krenning EP: Peptide receptor radionuclide therapy in patients with gastroenteropancreatic neuroendocrine tumors. Semin Nucl Med 2010;40:78–88.

20 Ducreux MP, Boige V, Leboulleux S, Malka D, Kergoat P, Dromain C, Elias D, de Baere T, Sabourin JC, Duvillard P, Lasser P, Schlumberger M, Baudin E: A phase II study of irinotecan with 5-fluorouracil and leucovorin in patients with pretreated gastroenteropancreatic well-differentiated endocrine carcinomas. Oncology 2006;70:134–140.

21 Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG: Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol 2005;23:4897–4904.

22 Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, Yao JC: Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004;22:4762–4771.

23 Kölby L, Bernhardt P, Johanson V, Schmitt A, Ahlman H, Forssell-Aronsson E, Macke H, Nilsson O: Successful receptor-mediated radiation therapy of xenografted human midgut carcinoid tumour. Br J Cancer 2005; 93:1144–1151.

24 De Jong M, Breeman WA, Bernard BF, Bakker WH, Schaar M, van Gameren A, Bugaj JE, Erion J, Schmidt M, Srinivasan A, Krenning EP: [^{177}Lu-DOTA^0,Tyr^3] octreotate for somatostatin receptor-targeted radionuclide therapy. Int J Cancer 2001;92:628–633.

25 Breeman WA, Mearadji A, Capello A, Bernard BF, van Eijck CH, Krenning EP, de Jong M: Anti-tumor effect and increased survival after treatment with [^{177}Lu-DOTA^0,Tyr^3]octreotate in a rat liver micrometastases model. Int J Cancer 2003;104:376–379.

26 Schmitt A, Bernhardt P, Nilsson O, Ahlman H, Kölby L, Maecke HR, Forssell-Aronsson E: Radiation therapy of small cell lung cancer with ^{177}Lu-DOTA-Tyr^3-octreotate in an animal model. J Nucl Med 2004;45:1542–1548.

27 Evers BM, Townsend CM Jr, Upp JR, Allen E, Hurlbut SC, Kim SW, Rajaraman S, Singh P, Reubi JC, Thompson JC: Establishment and characterization of a human carcinoid in nude mice and effect of various agents on tumor growth. Gastroenterology 1991;101: 303–311.

28 Siddique ZL, Drozdov I, Floch J, Gustafsson BI, Stunes K, Pfragner R, Kidd M, Modlin IM: KRJ-I and BON cell lines: defining an appropriate enterochromaffin cell neuroendocrine tumor model. Neuroendocrinology 2009;89:458–470.

29 Pfragner R, Wirnsberger G, Niederle B, Behmel A, Rinner I, Mandl A, Wavrina F, Luo JS, Adamiker D, Hoegner H, Ingolic E, Schauenstein K: Establishment of a continuous cell line from a human carcinoid of the small intestine (KRJ-I): characterization and effects of 5-azacytidine on proliferation. Int J Oncol 1996;8:513–520.

30 Modlin IM, Kidd M, Pfragner R, Eick GN, Champaneria MC: The functional characterization of normal and neoplastic human enterochromaffin cells. J Clin Endocrinol Metab 2006;91:2340–2348.

31 Kidd M, Eick GN, Modlin IM, Pfragner R, Champaneria MC, Murren J: Further delineation of the continuous human neoplastic enterochromaffin cell line, KRJ-I, and the inhibitory effects of lanreotide and rapamycin. J Mol Endocrinol 2007;38:181–192.

32 Kölby L, Bernhardt P, Ahlman H, Wangberg B, Johanson V, Wigander A, Forssell-Aronsson E, Karlsson S, Ahren B, Stenman G, Nilsson O: A transplantable human carcinoid as model for somatostatin receptor-mediated and amine transporter-mediated radionuclide uptake. Am J Pathol 2001;158:745–755.

33 Nilsson O, Kölby L, Bernhardt P, Forssell-Aronsson E, Johanson V, Ahlman H: GOT1 xenografted to nude mice: a unique model for in vivo studies on SSTR-mediated radiation therapy of carcinoid tumors. Ann NY Acad Sci 2004;1014:275–279.

34 Eden PA, Taylor JE: Somatostatin receptor subtype gene expression in human and rodent tumors. Life Sci 1993;53:85–90.

35 Johanson V, Ahlman H, Bernhardt P, Jansson S, Kölby L, Persson F, Stenman G, Sward C, Wangberg B, Stridsberg M, Nilsson O: A transplantable human medullary thyroid carcinoma as a model for RET tyrosine kinase-driven tumorigenesis. Endocr Relat Cancer 2007;14:433–444.

36 Dalmo J, Rudqvist N, Spetz J, Laverman P, Nilsson O, Ahlman H, Forssell-Aronsson E: Biodistribution of ^{177}Lu-octreotate and ^{111}In-minigastrin in female nude mice transplanted with human medullary thyroid carcinoma GOT2. Oncology Reports 2012; 27:174–181.

37 Leong SS, Horoszewicz JS, Friedman M, Zeigel R, Kawinski E, Papsidero L, Chu TM, Shimaoka K, Mirand EA: A new cell-line for studies on human thyroid medullary carcinoma. Proc Am Assoc Cancer Res 1981;22: 49.

38 Logsdon CD, Moessner J, Williams JA, Goldfine ID: Glucocorticoids increase amylase mRNA levels, secretory organelles, and secretion in pancreatic acinar AR42J cells. J Cell Biol 1985;100:1200–1208.

39 Longnecker DS, Lilja HS, French J, Kuhlmann E, Noll W: Transplantation of azaserine-induced carcinomas of pancreas in rats. Cancer Lett 1979;7:197–202.

40 Roebuck BD, Yager JD Jr, Longnecker DS: Dietary modulation of azaserine-induced pancreatic carcinogenesis in the rat. Cancer Res 1981;41:888–893.

41 Melis M, Forrer F, Capello A, Bijster M, Bernard BF, Reubi JC, Krenning EP, De Jong M: Up-regulation of somatostatin receptor density on rat CA20948 tumors escaped from low dose [^{177}Lu-DOTA^0,Tyr^3]octreotate therapy. Q J Nucl Med Mol Imaging 2007; 51:324–333.

42 Muller C, Forrer F, Bernard BF, Melis M, Konijnenberg M, Krenning EP, de Jong M: Diagnostic versus therapeutic doses of [^{177}Lu-DOTA-Tyr^3]-octreotate: uptake and dosimetry in somatostatin receptor-positive tumors and normal organs. Cancer Biother Radiopharm 2007;22:151–159.

43 Slooter GD, Breeman WA, Marquet RL, Krenning EP, van Eijck CH: Anti-proliferative effect of radiolabelled octreotide in a metastases model in rat liver. Int J Cancer 1999;81:767–771.

44 Lewis JS, Lewis MR, Cutler PD, Srinivasan A, Schmidt MA, Schwarz SW, Morris MM, Miller JP, Anderson CJ: Radiotherapy and dosimetry of ^{64}Cu-TETA-Tyr^3-octreotate in a somatostatin receptor-positive, tumor-bearing rat model. Clin Cancer Res 1999;5: 3608–3616.

45 Anderson CJ, Jones LA, Bass LA, Sherman EL, McCarthy DW, Cutler PD, Lanahan MV, Cristel ME, Lewis JS, Schwarz SW: Radiotherapy, toxicity and dosimetry of copper-64-TETA-octreotide in tumor-bearing rats. J Nucl Med 1998;39:1944–1951.

46 Capello A, Krenning E, Bernard B, Reubi JC, Breeman W, de Jong M: ^{111}In-labelled somatostatin analogues in a rat tumour model: somatostatin receptor status and effects of peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging 2005;32:1288–1295.

47 Oddstig J: Therapeutic effects of ^{177}Lu-octreotate on somatostatin-receptor-expressing tumours; PhD Thesis, Department of Radiation Physics, University of Gothenburg, 2008.

48 Twardella D, Chang-Claude J: Studies on radiosensitivity from an epidemiological point of view – overview of methods and results. Radiother Oncol 2002;62:249–260.

49 Fernet M, Hall J: Genetic biomarkers of therapeutic radiation sensitivity. DNA Repair (Amst) 2004;3:1237–1243.

50 Sward C, Bernhardt P, Johanson V, Schmitt A, Ahlman H, Stridsberg M, Forssell-Aronsson E, Nilsson O, Kölby L: Comparison of [^{177}Lu-DOTA^0,Tyr^3]-octreotate and [^{177}Lu-DOTA^0,Tyr^3]-octreotide for receptor-mediated radiation therapy of the xenografted human midgut carcinoid tumor GOT1. Cancer Biother Radiopharm 2008;23:114–120.

51 Schmitt A, Bernhardt P, Nilsson O, Ahlman H, Kölby L, Forssell-Aronsson E: Differences in biodistribution between ^{99m}Tc-depreotide, ^{111}In-DTPA-octreotide, and ^{177}Lu-DOTA-Tyr^3-octreotate in a small cell lung cancer animal model. Cancer Biother Radiopharm 2005;20:231–236.

52 Forrer F, Uusijarvi H, Waldherr C, Cremonesi M, Bernhardt P, Mueller-Brand J, Maecke HR: A comparison of ^{111}In-DOTA-TOC and ^{111}In-DOTATATE: biodistribution and dosimetry in the same patients with metastatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2004;31:1257–1262.

53 Esser JP, Krenning EP, Teunissen JJ, Kooij PP, van Gameren AL, Bakker WH, Kwekkeboom DJ: Comparison of [^{177}Lu-DOTA^0,Tyr^3]octreotate and [^{177}Lu-DOTA^0,Tyr^3]octreotide: which peptide is preferable for PRRT? Eur J Nucl Med Mol Imaging 2006;33:1346–1351.

54 Cihlo J, Melicharova L, Petrik M, Laznickova A, Laznicek M: Comparison of ^{111}In-DOTA-NOC and ^{111}I-DOTA-TATE distribution in the target and dose-limiting tissues: conflicting results in vitro and in vivo. Anticancer Res 2008;28:2189–2195.

55 Wild D, Schmitt JS, Ginj M, Macke HR, Bernard BF, Krenning E, De Jong M, Wenger S, Reubi JC: DOTA-NOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. Eur J Nucl Med Mol Imaging 2003;30:1338–1347.

56 Yim CB, Dijkgraaf I, Merkx R, Versluis C, Eek A, Mulder GE, Rijkers DT, Boerman OC, Liskamp RM: Synthesis of DOTA-conjugated multimeric [Tyr^3]octreotide peptides via a combination of Cu(I)-catalyzed 'click' cycloaddition and thio acid/sulfonyl azide 'sulfo-click' amidation and their in vivo evaluation. J Med Chem 2010;53:3944–3953.

57 Bruns C, Lewis I, Briner U, Meno-Tetang G, Weckbecker G: SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. Eur J Endocrinol 2002;146:707–716.

58 Reubi JC, Eisenwiener KP, Rink H, Waser B, Macke HR: A new peptidic somatostatin agonist with high affinity to all five somatostatin receptors. Eur J Pharmacol 2002;456: 45–49.

59 Saveanu A, Gunz G, Guillen S, Dufour H, Culler MD, Jaquet P: Somatostatin and dopamine-somatostatin multiple ligands directed towards somatostatin and dopamine receptors in pituitary adenomas. Neuroendocrinology 2006;83:258–263.

60 Modlin IM, Pavel M, Kidd M, Gustafsson BI: Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther 2010;31:169–188.

61 Waser B, Tamma ML, Cescato R, Maecke HR, Reubi JC: Highly efficient in vivo agonist-induced internalization of sst2 receptors in somatostatin target tissues. J Nucl Med 2009;50:936–941.

62 Cescato R, Loesch KA, Waser B, Macke HR, Rivier JE, Reubi JC, Schonbrunn A: Agonist-biased signaling at the SST2A receptor: the multi-somatostatin analogs KE108 and SOM230 activate and antagonize distinct signaling pathways. Mol Endocrinol 2010; 24:240–249.

63 Waser B, Cescato R, Tamma ML, Maecke HR, Reubi JC: Absence of somatostatin SST(2) receptor internalization in vivo after intravenous SOM230 application in the AR42J animal tumor model. Eur J Pharmacol 2010;644:257–262.

64 Wadas TJ, Eiblmaier M, Zheleznyak A, Sherman CD, Ferdani R, Liang K, Achilefu S, Anderson CJ: Preparation and biological evaluation of ^{64}Cu-CB-TE2A-sst2-ANT, a somatostatin antagonist for PET imaging of somatostatin receptor-positive tumors. J Nucl Med 2008;49:1819–1827.

65 Laverman P, McBride WJ, Sharkey RM, Eek A, Joosten L, Oyen WJ, Goldenberg DM, Boerman OC: A novel facile method of labeling octreotide with ^{18}F-fluorine. J Nucl Med 2010;51:454–461.

66 Vaidyanathan G, Affleck DJ, Schottelius M, Wester H, Friedman HS, Zalutsky MR: Synthesis and evaluation of glycosylated octreotate analogues labeled with radioiodine and ^{211}At via a tin precursor. Bioconjug Chem 2006;17:195–203.

67 Schottelius M, Wester HJ, Reubi JC, Senekowitsch-Schmidtke R, Schwaiger M: Improvement of pharmacokinetics of radioiodinated Tyr^3-octreotide by conjugation with carbohydrates. Bioconjug Chem 2002; 13:1021–1030.

68 Norenberg JP, Krenning BJ, Konings IR, Kusewitt DF, Nayak TK, Anderson TL, de Jong M, Garmestani K, Brechbiel MW, Kvols LK: ^{213}Bi-[DOTA^0,Tyr^3]octreotide peptide receptor radionuclide therapy of pancreatic tumors in a preclinical animal model. Clin Cancer Res 2006;12:897–903.

69 Uusijarvi H, Bernhardt P, Ericsson T, Forssell-Aronsson E: Dosimetric characterization of radionuclides for systemic tumor therapy: influence of particle range, photon emission, and subcellular distribution. Med Phys 2006;33:3260–3269.

70 Uusijarvi H, Bernhardt P, Rosch F, Maecke HR, Forssell-Aronsson E: Electron- and positron-emitting radiolanthanides for therapy: aspects of dosimetry and production. J Nucl Med 2006;47:807–814.

71 Uusijarvi H, Bernhardt P, Forssell-Aronsson E: Translation of dosimetric results of preclinical radionuclide therapy to clinical situations: influence of photon irradiation. Cancer Biother Radiopharm 2007;22:268–274.

72 Bernhardt P, Forssell-Aronsson E, Jacobsson L, Skarnemark G: Low-energy electron emitters for targeted radiotherapy of small tumours. Acta Oncol 2001;40:602–608.

73 Bugaj JE, Erion JL, Johnson MA, Schmidt MA, Srinivasan A: Radiotherapeutic efficacy of ^{153}Sm-CMDTPA-Tyr^3-octreotate in tumor-bearing rats. Nucl Med Biol 2001;28: 327–334.

74 De Jong M, Breeman WA, Bernard BF, Rolleman EJ, Hofland LJ, Visser TJ, Setyono-Han B, Bakker WH, van der Pluijm ME, Krenning EP: Evaluation in vitro and in rats of ^{161}Tb-DTPA-octreotide, a somatostatin analogue with potential for intraoperative scanning and radiotherapy. Eur J Nucl Med 1995;22:608–616.

75 Lehenberger S, Barkhausen C, Cohrs S, Fischer E, Grunberg J, Hohn A, Koster U, Schibli R, Turler A, Zhernosekov K: The low-energy beta(–) and electron emitter ^{161}Tb as an alternative to ^{177}Lu for targeted radionuclide therapy. Nucl Med Biol 2011;38:917–924.

76 Stolz B, Weckbecker G, Smith-Jones PM, Albert R, Raulf F, Bruns C: The somatostatin receptor-targeted radiotherapeutic [^{90}Y-DOTA-D-Phe^1,Tyr^3]octreotide (^{90}Y-SMT 487) eradicates experimental rat pancreatic CA 20948 tumours. Eur J Nucl Med 1998;25: 668–674.

77 De Jong M, Breeman WA, Valkema R, Bernard BF, Krenning EP: Combination radionuclide therapy using ^{177}Lu- and ^{90}Y-labeled somatostatin analogs. J Nucl Med 2005; 46(suppl 1):13S–17S.

78 Zamora PO, Gulhke S, Bender H, Diekmann D, Rhodes BA, Biersack HJ, Knapp FF Jr: Experimental radiotherapy of receptor-positive human prostate adenocarcinoma with ^{188}Re-RC-160, a directly-radiolabeled somatostatin analogue. Int J Cancer 1996;65:214–220.

79 Miederer M, Henriksen G, Alke A, Mossbrugger I, Quintanilla-Martinez L, Senekowitsch-Schmidtke R, Essler M: Preclinical evaluation of the α-particle generator nuclide 225Ac for somatostatin receptor radiotherapy of neuroendocrine tumors. Clin Cancer Res 2008;14:3555–3561.

80 De Jong M, Breeman WA, Bernard BF, Bakker WH, Visser TJ, Kooij PP, van Gameren A, Krenning EP: Tumor response after [^{90}Y-DOTA^0,Tyr^3]octreotide radionuclide therapy in a transplantable rat tumor model is dependent on tumor size. J Nucl Med 2001;42: 1841–1846.

81 Bernhardt P, Kölby L, Johanson V, Benjegard SA, Nilsson O, Ahlman H, Forssell-Aronsson E: Biokinetics of ^{111}In-DTPA-D-Phe^1-octreotide in nude mice transplanted with a human carcinoid tumor. Nucl Med Biol 2001;28:67–73.

82 Schmitt A, Bernhardt P, Nilsson O, Ahlman H, Kölby L, Schmitt J, Forssel-Aronsson E: Biodistribution and dosimetry of ^{177}Lu-labeled [DOTA^0,Tyr^3]octreotate in male nude mice with human small cell lung cancer. Cancer Biother Radiopharm 2003;18:593–599.

83 De Jong M, Breeman WA, Bernard BF, van Gameren A, de Bruin E, Bakker WH, van der Pluijm ME, Visser TJ, Macke HR, Krenning EP: Tumour uptake of the radiolabelled somatostatin analogue [DOTA^0, Tyr^3]octreotide is dependent on the peptide amount. Eur J Nucl Med 1999;26:693–698.

84 Bernhardt P, Kölby L, Johanson V, Nilsson O, Ahlman H, Forssell-Aronsson E: Biodistribution of ^{111}In-DTPA-D-Phe^1-octreotide in tumor-bearing nude mice: influence of amount injected and route of administration. Nucl Med Biol 2003;30:253–260.

85 Breeman WA, de Jong M, Bernard BF, Bakker WH, Rolleman EJ, Kwekkeboom DJ, Visser TJ, Krenning EP: Effects of ligand priming and multiple-dose injection on tissue uptake of ^{111}In-pentetreotide in rats. Nucl Med Biol 1997;24:749–753.

86 Hanin FX, Pauwels S, Bol A, Breeman W, de Jong M, Jamar F: Tumor uptake of ^{68}Ga-DOTA-Tyr^3-octreotate: animal PET studies of tumor flow and acute somatostatin receptor modulation in the CA20948 rat model. Nucl Med Biol 2010;37:157–165.

87 Oddstig J, Bernhardt P, Nilsson O, Ahlman H, Forssell-Aronsson E: Radiation-induced up-regulation of somatostatin receptor expression in small cell lung cancer in vitro. Nucl Med Biol 2006;33:841–846.

88 Bernhardt P, Oddstig J, Kölby L, Nilsson O, Ahlman H, Forssell-Aronsson E: Effects of treatment with ^{177}Lu-DOTA-Tyr^3-octreotate on uptake of subsequent injection in carcinoid-bearing nude mice. Cancer Biother Radiopharm 2007;22:644–653.

89 Behe M, Koller S, Pusken M, Gross M, Alfke H, Keil B, Henzel M, Neidel HO, Schramm N, Gotthard M, Behr TM, Engenhart-Cabillic E: Irradiation-induced upregulation of somatostatin and gastrin receptors in vitro and in vivo. Eur J Nucl Med Mol Imaging 2004;31:S237–S238.

90 Msirikale JS, Klein JL, Schroeder J, Order SE: Radiation enhancement of radiolabelled antibody deposition in tumors. Int J Radiat Oncol Biol Phys 1987;13:1839–1844.

91 Heldin CH, Rubin K, Pietras K, Ostman A: High interstitial fluid pressure – an obstacle in cancer therapy. Nat Rev Cancer 2004; 4:806–813.

92 Pietras K: Increasing tumor uptake of anticancer drugs with imatinib. Semin Oncol 2004;31(suppl 6):18–23.

93 Nayak TK, Atcher RW, Prossnitz ER, Norenberg JP: Enhancement of somatostatin-receptor-targeted ^{177}Lu-[DOTA^0-Tyr^3]-octreotide therapy by gemcitabine pretreatment-mediated receptor uptake, up-regulation and cell cycle modulation. Nucl Med Biol 2008;35:673–678.

94 Verheij M, Bartelink H: Radiation-induced apoptosis. Cell Tissue Res 2000;301:133–142.

95 Shinomiya N: New concepts in radiation-induced apoptosis: 'premitotic apoptosis' and 'postmitotic apoptosis'. J Cell Mol Med 2001;5:240–253.

96 Hamada N, Matsumoto H, Hara T, Kobayashi Y: Intercellular and intracellular signaling pathways mediating ionizing radiation-induced bystander effects. J Radiat Res (Tokyo) 2007;48:87–95.

97 Zhou H, Suzuki M, Randers-Pehrson G, Vannais D, Chen G, Trosko JE, Waldren CA, Hei TK: Radiation risk to low fluences of α-particles may be greater than we thought. Proc Natl Acad Sci USA 2001;98: 14410–14415.

98 Zhou H, Ivanov VN, Gillespie J, Geard CR, Amundson SA, Brenner DJ, Yu Z, Lieberman HB, Hei TK: Mechanism of radiation-induced bystander effect: role of the cyclooxygenase-2 signaling pathway. Proc Natl Acad Sci USA 2005;102:14641–14646.

99 Azzam EI, De Toledo SM, Spitz DR, Little JB: Oxidative metabolism modulates signal transduction and micronucleus formation in bystander cells from α-particle-irradiated normal human fibroblast cultures. Cancer Res 2002;62:5436–5442.

100 Wang W, Abbruzzese JL, Evans DB, Larry L, Cleary KR, Chiao PJ: The nuclear factor-κB RelA transcription factor is constitutively activated in human pancreatic adenocarcinoma cells. Clin Cancer Res 1999;5: 119–127.

101 Wang DG, Johnston CF, Anderson N, Sloan JM, Buchanan KD: Overexpression of the tumour suppressor gene p53 is not implicated in neuroendocrine tumour carcinogenesis. J Pathol 1995;175:397–401.

102 Wang DG: Apoptosis in neuroendocrine tumours. Clin Endocrinol (Oxf) 1999;51: 1–9.

103 Ashkenazi A, Dixit VM: Death receptors: signaling and modulation. Science 1998; 281:1305–1308.

104 Johnstone RW, Frew AJ, Smyth MJ: The TRAIL apoptotic pathway in cancer onset, progression and therapy. Nat Rev Cancer 2008;8:782–798.

105 Griffith TS, Stokes B, Kucaba TA, Earel JK Jr, VanOosten RL, Brincks EL, Norian LA: TRAIL gene therapy: from preclinical development to clinical application. Curr Gene Ther 2009;9:9–19.
106 Pasquini L, Petrucci E, Riccioni R, Petronelli A, Testa U: Sensitivity and resistance of human cancer cells to TRAIL: mechanisms and therapeutical perspectives. Cancer Ther 2006;4:47–72.
107 Goke R, Goke A, Goke B, El-Deiry WS, Chen Y: Pioglitazone inhibits growth of carcinoid cells and promotes TRAIL-induced apoptosis by induction of p21waf1/cip1. Digestion 2001;64:75–80.
108 Schulze-Bergkamen H, Weinmann A, Moehler M, Siebler J, Galle PR: Novel ways to sensitise gastrointestinal cancer to apoptosis. Gut 2009;58:1010–1024.l
109 Sethi G, Sung B, Aggarwal BB: Nuclear factor-κB activation: from bench to bedside. Exp Biol Med (Maywood) 2008;233:21–31.
110 Olsen LS, Hjarnaa PJ, Latini S, Holm PK, Larsson R, Bramm E, Binderup L, Madsen MW: Anticancer agent CHS-828 suppresses nuclear factor-κB activity in cancer cells through downregulation of IKK activity. Int J Cancer 2004;111:198–205.
111 Olesen UH, Christensen MK, Bjorkling F, Jaattela M, Jensen PB, Sehested M, Nielsen SJ: Anticancer agent CHS-828 inhibits cellular synthesis of NAD. Biochem Biophys Res Commun 2008;367:799–804.
112 Hassa PO, Haenni SS, Elser M, Hottiger MO: Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? Microbiol Mol Biol Rev 2006;70:789–829.
113 Schreiber V, Dantzer F, Ame JC, de Murcia G: Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol 2006;7:517–528.
114 Khan JA, Forouhar F, Tao X, Tong L: Nicotinamide adenine dinucleotide metabolism as an attractive target for drug discovery. Expert Opin Ther Targets 2007;11:695–705.
115 Berger NA: Poly(ADP-ribose) in the cellular response to DNA damage. Radiat Res 1985;101:4–15.
116 Hasmann M, Schemainda I: FK866, a highly specific noncompetitive inhibitor of nicotinamide phosphoribosyltransferase, represents a novel mechanism for induction of tumor cell apoptosis. Cancer Res 2003;63:7436–7442.
117 Watson M, Roulston A, Belec L, Billot X, Marcellus R, Bedard D, Bernier C, Branchaud S, Chan H, Dairi K, Gilbert K, Goulet D, Gratton MO, Isakau H, Jang A, Khadir A, Koch E, Lavoie M, Lawless M, Nguyen M, Paquette D, Turcotte E, Berger A, Mitchell M, Shore GC, Beauparlant P: The small molecule GMX-1778 is a potent inhibitor of NAD^+ biosynthesis: strategy for enhanced therapy in nicotinic acid phosphoribosyltransferase-1-deficient tumors. Mol Cell Biol 2009;29:5872–5888.
118 Johanson V, Arvidsson Y, Kölby L, Bernhardt P, Sward C, Nilsson O, Ahlman H: Antitumoural effects of the pyridyl cyanoguanidine CHS-828 on three different types of neuroendocrine tumours xenografted to nude mice. Neuroendocrinology 2005;82:171–176.
119 Ludwig L, Kessler H, Wagner M, Hoang-Vu C, Dralle H, Adler G, Bohm BO, Schmid RM: Nuclear factor-κB is constitutively active in C-cell carcinoma and required for RET-induced transformation. Cancer Res 2001;61:4526–4535.
120 Svensson A, Backman U, Jonsson E, Larsson R, Christofferson R: CHS-828 inhibits neuroblastoma growth in mice alone and in combination with antiangiogenic drugs. Pediatr Res 2002;51:607–611.
121 Nilsson O, Arvidsson Y, Johanson V, Forssell-Aronsson E, Ahlman H: New medical strategies for midgut carcinoids. Anticancer Agents Med Chem 2010;10:250–269.
122 Von Heideman A, Berglund A, Larsson R, Nygren P: Safety and efficacy of NAD depleting cancer drugs: results of a phase I clinical trial of CHS-828 and overview of published data. Cancer Chemother Pharmacol 2010;65:1165–1172.
123 McKenna WG, Muschel RJ, Gupta AK, Hahn SM, Bernhard EJ: The RAS signal transduction pathway and its role in radiation sensitivity. Oncogene 2003;22:5866–5875.
124 Ling CC, Endlich B: Radioresistance induced by oncogenic transformation. Radiat Res 1989;120:267–279.
125 Miller AC, Kariko K, Myers CE, Clark EP, Samid D: Increased radioresistance of EJras-transformed human osteosarcoma cells and its modulation by lovastatin, an inhibitor of p21ras isoprenylation. Int J Cancer 1993;53:302–307.
126 Bernhard EJ, Kao G, Cox AD, Sebti SM, Hamilton AD, Muschel RJ, McKenna WG: The farnesyltransferase inhibitor FTI-277 radiosensitizes H-ras-transformed rat embryo fibroblasts. Cancer Res 1996;56:1727–1730.
127 Zhang J, Jia Z, Li Q, Wang L, Rashid A, Zhu Z, Evans DB, Vauthey JN, Xie K, Yao JC: Elevated expression of vascular endothelial growth factor correlates with increased angiogenesis and decreased progression-free survival among patients with low-grade neuroendocrine tumors. Cancer 2007;109:1478–1486.
128 Park JS, Qiao L, Su ZZ, Hinman D, Willoughby K, McKinstry R, Yacoub A, Duigou GJ, Young CS, Grant S, Hagan MP, Ellis E, Fisher PB, Dent P: Ionizing radiation modulates vascular endothelial growth factor expression through multiple mitogen activated protein kinase-dependent pathways. Oncogene 2001;20:3266–3280.
129 Otte A, Herrmann R, Heppeler A, Behe M, Jermann E, Powell P, Maecke HR, Muller J: Yttrium-90 DOTATOC: first clinical results. Eur J Nucl Med 1999;26:1439–1447.
130 Cwikla JB, Sankowski A, Seklecka N, Buscombe JR, Nasierowska-Guttmejer A, Jeziorski KG, Mikolajczak R, Pawlak D, Stepien K, Walecki J: Efficacy of radionuclide treatment DOTATATE ^{90}Y in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. Ann Oncol 2010;21:787–794.
131 Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, Baio SM, Sansovini M, Paganelli G: Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with ^{90}Y-DOTA-TOC and ^{177}Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging 2008;35:1847–1856.
132 Melis M, Krenning EP, Bernard BF, Barone R, Visser TJ, de Jong M: Localisation and mechanism of renal retention of radiolabelled somatostatin analogues. Eur J Nucl Med Mol Imaging 2005;32:1136–1143.
133 Melis M, Krenning EP, Bernard BF, de Visser M, Rolleman E, de Jong M: Renal uptake and retention of radiolabeled somatostatin, bombesin, neurotensin, minigastrin and CCK analogues: species and gender differences. Nucl Med Biol 2007;34:633–641.
134 Forrer F, Rolleman E, Bijster M, Melis M, Bernard B, Krenning EP, de Jong M: From outside to inside? Dose-dependent renal tubular damage after high-dose peptide receptor radionuclide therapy in rats measured with in vivo ^{99m}Tc-DMSA-SPECT and molecular imaging. Cancer Biother Radiopharm 2007;22:40–49.
135 Rolleman EJ, Krenning EP, Bernard BF, de Visser M, Bijster M, Visser TJ, Vermeij M, Lindemans J, de Jong M: Long-term toxicity of [^{177}Lu-DOTA^0,Tyr^3]octreotate in rats. Eur J Nucl Med Mol Imaging 2007;34:219–227.
136 Vegt E, de Jong M, Wetzels JF, Masereeuw R, Melis M, Oyen WJ, Gotthardt M, Boerman OC: Renal toxicity of radiolabeled peptides and antibody fragments: mechanisms, impact on radionuclide therapy, and strategies for prevention. J Nucl Med 2010;51:1049–1058.
137 Brenner BM, Rector FC: Brenner & Rector's The Kidney. Philadelphia, Saunders Elsevier, 2008.
138 Christensen EI, Gburek J: Protein reabsorption in renal proximal tubule-function and dysfunction in kidney pathophysiology. Pediatr Nephrol 2004;19:714–721.
139 De Jong M, Barone R, Krenning E: Megalin is essential for renal proximal tubule reabsorption of ^{111}In-DTPA-octreotide. J Nucl Med 2005;46:1696–1700.

140 Trejtnar F, Novy Z, Petrik M, Laznickova A, Melicharova L, Vankova M, Laznicek M: In vitro comparison of renal handling and uptake of two somatostatin receptor-specific peptides labeled with indium-111. Ann Nucl Med 2008;22:859–867.
141 Christensen EI, Verroust PJ: Megalin and cubilin, role in proximal tubule function and during development. Pediatr Nephrol 2002;17:993–999.
142 Bates CM, Kegg H, Grady S: Expression of somatostatin in the adult and developing mouse kidney. Kidney Int 2004;66:1785–1793.
143 Bates CM, Kegg H, Grady S: Expression of somatostatin receptors 1 and 2 in the adult mouse kidney. Regul Pept 2004;119:11–20.
144 Bates CM, Kegg H, Petrevski C, Grady S: Expression of somatostatin receptors 3, 4, and 5 in mouse kidney proximal tubules. Kidney Int 2003;63:53–63.
145 Bhandari S, Watson N, Long E, Sharpe S, Zhong W, Xu SZ, Atkin SL: Expression of somatostatin and somatostatin receptor subtypes 1–5 in human normal and diseased kidney. J Histochem Cytochem 2008;56:733–743.
146 Bruno JF, Xu Y, Song J, Berelowitz M: Tissue distribution of somatostatin receptor subtype messenger ribonucleic acid in the rat. Endocrinology 1993;133:2561–2567.
147 Rolleman EJ, Kooij PP, de Herder WW, Valkema R, Krenning EP, de Jong M: Somatostatin receptor subtype-2-mediated uptake of radiolabelled somatostatin analogues in the human kidney. Eur J Nucl Med Mol Imaging 2007;34:1854–1860.
148 Rolleman EJ, Valkema R, de Jong M, Kooij PP, Krenning EP: Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. Eur J Nucl Med Mol Imaging 2003;30:9–15.
149 De Jong M, Rolleman EJ, Bernard BF, Visser TJ, Bakker WH, Breeman WA, Krenning EP: Inhibition of renal uptake of indium-111-DTPA-octreotide in vivo. J Nucl Med 1996;37:1388–1392.
150 Hammond PJ, Wade AF, Gwilliam ME, Peters AM, Myers MJ, Gilbey SG, Bloom SR, Calam J: Amino acid infusion blocks renal tubular uptake of an indium-labelled somatostatin analogue. Br J Cancer 1993;67:1437–1439.
151 Bernard BF, Krenning EP, Breeman WA, Rolleman EJ, Bakker WH, Visser TJ, Macke H, de Jong M: D-Lysine reduction of indium-111 octreotide and yttrium-90 octreotide renal uptake. J Nucl Med 1997;38:1929–1933.
152 Eerd JV, Vegt E, Wetzels J: Gelatin-based plasma expander effectively reduces renal uptake of ^{111}In-octreotide in mice and rats. J Nucl Med 2006;47:1730–1731.
153 Vegt E, Wetzels J, Russel F: Renal uptake of radiolabeled octreotide in human subjects is efficiently inhibited by succinylated gelatin. J Nucl Med 2006;47:432–436.
154 Pool SE, Krenning EP, Koning GA, van Eijck CH, Teunissen JJ, Kam B, Valkema R, Kwekkeboom DJ, de Jong M: Preclinical and clinical studies of peptide receptor radionuclide therapy. Semin Nucl Med 2010;40:209–218.
155 Rolleman EJ, Melis M, Valkema R, Boerman OC, Krenning EP, de Jong M: Kidney protection during peptide receptor radionuclide therapy with somatostatin analogues. Eur J Nucl Med Mol Imaging 2010;37:1018–1031.
156 Melis M, Bijster M, de Visser M, Konijnenberg MW, de Swart J, Rolleman EJ, Boerman OC, Krenning EP, de Jong M: Dose-response effect of Gelofusine on renal uptake and retention of radiolabelled octreotate in rats with CA20948 tumours. Eur J Nucl Med Mol Imaging 2009;36:1968–1976.
157 Rolleman EJ, Bernard BF, Breeman WA, Forrer F, de Blois E, Hoppin J, Gotthardt M, Boerman OC, Krenning EP, de Jong M: Molecular imaging of reduced renal uptake of radiolabelled [DOTA^0,Tyr^3]octreotate by the combination of lysine and Gelofusine in rats. Nuklearmedizin 2008;47:110–115.
158 Vegt E, Eek A, Oyen WJ, de Jong M, Gotthardt M, Boerman OC: Albumin-derived peptides efficiently reduce renal uptake of radiolabelled peptides. Eur J Nucl Med Mol Imaging 2010;37:226–234.
159 Moorin RE, Meyrick DP, Rose A: Pre-clinical evaluation of 2,3-dimercaptosuccinic acid as a radiation nephrotoxicity protective agent during radiopeptide therapy of neuroendocrine malignancy. Nucl Med Commun 2007;28:261–266.
160 Rolleman EJ, Forrer F, Bernard B, Bijster M, Vermeij M, Valkema R, Krenning EP, de Jong M: Amifostine protects rat kidneys during peptide receptor radionuclide therapy with [^{177}Lu-DOTA^0,Tyr^3]octreotate. Eur J Nucl Med Mol Imaging 2007;34:763–771.
161 Moulder J, Fish B, Cohen E: Angiotensin II receptor antagonists in the treatment and prevention of radiation nephropathy. Int J Radiat Oncol Biol Phys 1998;73:415–421.
162 Moulder JE, Fish BL, Cohen EP: ACE inhibitors and AII receptor antagonists in the treatment and prevention of bone marrow transplant nephropathy. Curr Pharm Des 2003;9:737–749.
163 Cohen EP, Irving AA, Drobyski WR, Klein JP, Passweg J, Talano JA, Juckett MB, Moulder JE: Captopril to mitigate chronic renal failure after hematopoietic stem cell transplantation: a randomized controlled trial. Int J Radiat Oncol Biol Phys 2008;70:1546–1551.
164 De Araújo EB, Caldeira Filho JS, Nagamati LT, Muramoto E, Colturato MT, Couto RM, Pujatti PB, Mengatti J, Silva CP: A comparative study of ^{131}I- and ^{177}Lu-labeled somatostatin analogues for therapy of neuroendocrine tumours. Appl Radiat Isot 2009;67:227–233.
165 Lewis JS, Wang M, Laforest R, Wang F, Erion JL, Bugaj JE, Srinivasan A, Anderson CJ: Toxicity and dosimetry of ^{177}Lu-DOTA-Y3-octreotate in a rat model. Int J Cancer 2001;94:873–877.