Radiochim. Acta **95**, 303–311 (2007) / **DOI** 10.1524/ract.2007.95.6.303

Radiolanthanides in endoradiotherapy: an overview

By F. Rösch*

Institute for Nuclear Chemistry, Johannes Gutenberg University, Fritz-Strassmann-Weg 2, 55128 Mainz, Germany

(Received March 1, 2007; accepted in revised form March 26, 2007)

Radiolanthanides / Nuclear reaction / Labelling / Bifunctional chelator / Radiation dosimetry / Endoradiotherapy

Summary. Endoradiotherapy (targeted radionuclide therapy) is a systemic approach, involving a radiolabeled targeting vector with a well characterized biochemical strategy to selectively deliver a cytotoxic level of radiation to a disease site on a cellular/molecular level. The group of radiolanthanides has been considered both for imaging and therapy over many years. Some radiolanthanides have been and are increasingly applied for therapeutic purposes.

However, the clinical use of endoradiotherapeuticals containing radiolanthanides requires a complex and interdisciplinary approach. It involves, among other factors, the choice of the most suitable lanthanide radionuclide (in terms of nuclear decay parameters such as type and energy of the particles emitted, half-life, decay products *etc.*); the identification of the most promising production route; the determination of the relevant production parameters such as excitation functions, nuclear reaction yields, radionuclidic purities, specific activities *etc.*; the chemical isolation of the radiolanthanide produced from the target material (except the (n, γ) production route); the synthesis of the labelling precursor, and labelling of the precursor and the chemical purification and isolation of the labelled radiotherapeutical, ready for *i.v.* injection; and finally the investigation of pharmacological targeting parameters of the labelled radiotherapeutical *in vitro* and *in vivo* (animal experiments).

1. Introduction

The therapeutic effects of radiation have long been known. Radiation therapy is applied to the treatment of a variety of pathological conditions *via* different approaches such as focusing an external beam of photon or particle radiation on the malignancy (external beam radiation therapy) or implanting an unsealed source of radiation, usually in the form of a wire or a pellet, in close proximity to the tumour (brachytherapy). Both approaches require a knowledge of the precise location and geometrical configuration of the tumour in order to maximize destruction of cancer cells while minimizing radiation dose to neighbouring normal tissues, and they are less effective for treating multi-focal tumours and metastatic cancer sites. In contrast, endoradiotherapy (targeted radionuclide therapy) is a systemic approach, involving a radiolabeled targeting vector with a well characterized biochemical strategy to selectively deliver a cytotoxic level of radiation to a disease site on a cellular/molecular level.

The group of radiolanthanides appeared to be useful both for imaging and therapy soon after the very beginning of nuclear medicine. Some radiolanthanides have been and are still today routinely applied for therapeutic purposes. The particular potential of radiolanthanides lies in their diverse decay characteristics. The many "therapeutic" radiolanthanides provide both high linear energy transfer (LET) particles (Auger electrons, and in some cases α-particles) and lower LET β^- particles. In the latter case, the spectrum of β^- particles of varying range in tissue provided is particularly important. In addition to those very different "nuclear" parameters, the trivalent lanthanides possess very similar co-ordination chemistry and may therefore be introduced on relevant compounds in a very similar pathway.

Comprehensive reviews on those topics or individual aspects have been published recently and are recommended for detailed information; cf. for example [1–7].

The design of an effective endoradiotherapeutic agent requires a careful optimization of its two components, namely the radionuclide and the carrier system that is used to direct the radionuclide to the tumour, so that the radiation emitted during its de-excitation will have a high probability of being deposited within the malignant cell population.

Consequently, the clinical use of endoradiotherapeuticals containing radiolanthanides requires a rather complex, interdisciplinary approach. It involves, among other factors:

1. choice of the most adequate lanthanide radionuclide (in terms of nuclear decay parameters such as type and energy of the particles emitted, half-life, decay products *etc.*);
2. identification of the most promising production route;
3. determination of the relevant production parameters such as excitation functions, nuclear reaction yields, radionuclidic purities, specific activities *etc.*;
4. chemical isolation of the radiolanthanide produced from the target material; except *via* (n, γ) production route;
5. synthesis of the labelling precursor and labelling of the precursor;
6. chemical purification and isolation of the labelled radiotherapeutical, ready for *i.v.* injection;

*E-mail: frank.roesch@uni-mainz.de.

7. investigation of pharmacological targeting parameters of the labelled radiotherapeutical *in vitro* and *in vivo* (animal experiments);
8. estimation of radiation doses delivered to the biological target and to healthy organs, combining both radiation dose effects based on the nuclear decay of the radiolanthanide and pharmacokinetic parameters of the labelled compound.

This introduction aims to illustrate the complex nature of endoradiotherapy using radiolanthanides. It intends to elucidate the dedicated research needed to design a valuable therapeutical – such as it has been carried out in the framework of the COST action D18 "Lanthanide Chemistry for Diagnosis and Therapy", in particular its working group 04 on "Lanthanides in therapy: Particle emitting radiolanthanides and stable lanthanides with radiation induced by external irradiation".

2. Therapeutic radionuclides

2.1 Decay parameters

The choice of the most suitable lanthanide radionuclide is based on nuclear decay parameters such as type and energy of the particles emitted, but also half-life and decay products of the radionuclide. Table 1 summarizes radiolanthanides, which offer decay characteristics relevant for therapeutic applications.

Concerning the emission characteristics and the radiation range, the decay parameters must match the size, location and geometry of a tumour or another target tissue such as the synovium of joints. Ideally, the targeting vector containing the therapeutic radiolanthanide shall accumulate the radionuclide at or inside the tumour cell (or target tissue in general) and the emitted radiation shall destroy tumour DNA or other biological targets only, while keeping healthy, surrounding tissue free of critical radiation doses. The correlation between energy and range of different particles and their energies are illustrated in Fig. 1; from [8].

If the decay of the radiolanthanide is characterised by a high ratio of non-penetrating radiation (β^-, β^+, conversion or Auger electrons, α-particles) to the energy emitted as penetrating radiation (photons with energy of 70–400 keV or 511 keV photons resulting from annihilation of β^+), then the radionuclide becomes a candidate for radionuclide therapy. For therapy, the radionuclide should emit large fractions of particles (electrons and alpha particles) with suitable range due to the cellular and subcellular distribution. As they deposit this particle energy over short distances, higher absorbed dose is obtained locally, and will then give its surrounding normal tissue low absorbed dose [9, 10]. Low percentages of accompanying low energy photon emission of a radiolanthanide are acceptable because they might allow for imaging along with targeted therapy.

The radiolanthanide half-life, $T_{1/2}$ should correspond to the biological half-life of the radiopharmaceutical. The main part of the radioactive decay should occur after the radiopharmaceutical has been accumulated to the target site and/or a significant ratio of accumulation between target organ and non-target organs has been achieved. Furthermore, if the target/non-target ratio is high or even increases with time, long physical half-life might be favourable for therapy. However, a longer physical half-life is associated with a lower dose rate, which might lead to lower biological effects. Even very short-lived radionuclides may be useful for therapy if the radiolabelling procedure could be kept short and the radiopharmaceutical directly delivered into a target cavity.

Table 1. Lanthanide radioisotopes relevant for radiopharmaceutical chemistry and nuclear medicine. (Nuclear decay data from [60] (ae = atomic electrons, β^+ = if EC < 50%, f = fission, sp = spallation, a: for electrons, the mean energy is given).

Radio-nuclide	Decay parameters		Production route	Application
	$T_{1/2}$	Main emission (energy[a])		
^{143}Pr	13.58 d	γ, β^- (315 keV)	^{142}Ce$(n,\gamma) \rightarrow \beta^-$; f	therapy
^{147}Nd	10.98 d	γ, β^- (233 keV)	^{146}Nd(n,γ); f	therapy
^{149}Pm	2.212 d	β^- (366 keV)	^{148}Nd$(n,\gamma) \rightarrow \beta^-$	therapy
^{153}Sm	1.946 d	γ, β^- (225 keV)	^{152}Sm(n,γ)	therapy
^{149}Gd	9.2 d	γ, ae, α (3018 keV)	sp; ^{147}Sm$(\alpha,2n)$, ...	therapy
^{149}Tb	4.16 h	γ, α (3966 keV, 16.7%)	sp; ^{152}Gd$(p,4n)$, ^{141}Pr(^{12}C, $4n$),	therapy
^{152}Tb	17.5 h	ae, γ	sp; ^{152}Gd(p,n), ...	therapy
^{161}Tb	6.91 d	γ, β^- (155 keV)	^{160}Gd$(n,\gamma) \rightarrow \beta^-$	therapy
^{157}Dy	8.1 h	ae, γ	sp, ^{154}Gd(α,n), ^{159}Tb$(p,3n)$, ...	imaging
^{165}Dy	2.33 h	γ, β^- (442 keV)	^{164}Dy(n,γ)	therapy
^{166}Dy	3.40 d	γ, β^- (119 keV)	^{164}Dy$(n,\gamma)^{165}$Dy$(n,\gamma)^{166}$Dy	therapy; *in vivo* generator
^{161}Ho	2.48 h	ae (32 keV), γ	sp, ^{159}Tb$(\alpha,2n)$,	therapy
^{166}Ho	1.117 d	β^- (711 keV)	generator ^{166}Dy	therapy; *in vivo* generator
^{160}Er	1.192 d	ae (6.5 keV), γ	sp	therapy
^{165}Er	10.36 h	ae (6.6 keV)	^{165}Ho(p,n), ...	therapy
^{169}Er	9.4 d	β^- (99.6 keV)	^{168}Er(n,γ)	therapy
^{171}Er	7.52 h	β^- (359 keV)	^{170}Er(n,γ)	therapy
^{167}Tm	9.24 d	γ, ae	sp; ^{165}Ho$(\alpha,2n)$	imaging, therapy
^{166}Yb	2.362 d	γ, ae (38.9 keV)	sp; ^{169}Tm$(p,4n)$	therapy
^{175}Yb	4.19 d	γ, β^- (127 keV)	^{174}Yb(n,γ)	therapy
^{177}Lu	6.71 d	γ, β^- (133 keV)	^{176}Lu(n,γ); ^{176}Yb$(n,\gamma) \rightarrow \beta^-$	therapy

2.2 Production routes

Once a radiolanthanide is identified as a promising candidate, its most effective production route must be selected, in many cases among several optional nuclear reaction processes. The choice reflects excitation functions, nuclear reaction yields, radionuclidic purities, specific activities, need of isotopically enriched target atoms, *etc.* In general, radiolanthanides are available *via* three routes, namely irradiation of appropriate targets at nuclear reactors using thermal or epithermal neutrons, at cyclotrons using accelerated charged particles, or, thirdly, non-directly utilising radionuclide generator systems.

For neutron-induced nuclear reactions at nuclear reactors, several options are used (cf. *e.g.* [11]).

(n, γ): The irradiation of stable lanthanide targets at nuclear reactors generally results in a neutron capture nuclear reaction (n, γ). For some targets, a double neutron capture is required to produce the desired radioisotope such as for the ^{164}Dy(n, γ) ^{165}Dy $(n, \gamma)^{166}$Dy process. The radioactivity batch yield achievable is, in principle, determined according to $A = [hN]\sigma\Phi(1 - e^{-\lambda t})$, with N being the number of the lanthanide target atoms and h representing the fraction of the isotope relevant for the neutron capture; σ representing the neutron capture cross section (most relevant: σ_{th}, the probability of absorbing neutrons with energies of approximately 0.025 eV), Φ the neutron flux and $(1 - e^{-\lambda t})$ the influence of the irradiation time t; λ is the decay constant of the radionuclide. Neutron activation induced by epithermal neutrons at energies between 1 eV and 1 keV may contribute to the radionuclide production yield. In contrast to the production routes discussed below, radiochemical separation of the radiolanthanide from the irradiated target is not possible and the radiolanthanide remains carrier-added (ca).

(n, γ)–$\beta^- \rightarrow$: If the neutron capture reaction is followed by a β^- decay of the primarily produced nucleus, then a secondary radioisotope is obtained, which is not isotopic, but isotonic to the target nucleus. In this case, no-carrier-added (nca) radioisotopes are obtained.

$(n$, fission): Neutron irradiation of some nuclei such as ^{235}U induces a fission process, thereby forming – among other reaction products – a spectrum of the radiolanthanides with one maximum of isotope mass distributions at masses of about 140. These light radiolanthanides might be chemically separated from the uranium target and from the other fission products. They are nca, but not necessarily radionuclidically pure since a set of radioisotopes per lanthanide is formed in the fission process.

In the case of particle accelerator based radiolanthanide production routes, both direct and spallation reactions are possible (cf. *e.g.* [12]).

(p, xn), (d, xn), $(^3$He$, xn)$, (α, xn) *etc.*: Accelerators principally allow for the formation of nca radiolanthanides, since the bombardment with accelerated protons, deuterons and heavier ions results in nuclear processes such as (p, xn), (d, xn), $(^3$He$, xn)$, (α, xn) and many others, yielding products of different proton number. Individual radiolanthanides can be obtained according to the selected target and the chosen type and energy of the accelerated projectile.

$(p$, spallation): The high-energy proton irradiation results in the fragmentation of the target nucleus. A spectrum of nca isotopes is obtained, which need to be separated. In addition to off-line radiochemical separation processes, isotope separation on-line facilities include a mass-separation facility and provide nca isobar fractions. For the production of radiolanthanides, targets such as Ta or W are irradiated with protons of usually > 600 MeV energy.

Finally, radionuclide generator systems offer an excellent choice of radionuclide availability (cf. *e.g.* [13]). Among many parent/daughter pairs, which have been evaluated as radionuclide generator systems, several of them are generators relevant to the radiolanthanides, such ^{140}Ba/^{140}La, ^{134}Ce/^{134}La, ^{144}Ce/^{144}Pr, ^{140}Nd/^{140}Pr, ^{166}Dy/^{166}Ho, ^{166}Yb/^{166}Tm, ^{167}Tm/^{167m}Er, ^{172}Hf/^{172}Lu. The key advantages of the use of radionuclide generators include availability of the daughter radionuclide in nca form, and the convenience of obtaining the desired daughter radionuclide on demand, *i.e.* not depending on the direct access to nuclear reactors and accelerators. Recently, applications of several systems in the form of *in vivo* generators have been proposed.

2.3 Specific activities

Besides parameters such as achievable radiolanthanide batch activities, the specific activities of the product nuclei are of interest: the state of the radiolanthanide produced is either no-carrier-added (nca) or carrier-added (ca). The specific activity represents the ratio of the radionuclide radioactivity to the sum of the masses of all the isotopes of that element and is expressed as [GBq/g] or [GBq/μmol]. The route of production of a radiolanthanide obviously determines its specific activity, the (n, γ) process being the route principally not resulting in nca isotopes. Nevertheless, as powerful nuclear reactors and isotopically enriched targets are available, this production route is among the common ones, in particular (i) if high thermal neutron capture cross sections and (ii) high thermal neutron fluxes of $\Phi_{th} \geq 4 \times 10^{14}$ n/cm^2/s are available. The high cross section gives options to further increase production yields, isotopic purities and specific activities due to isotopic enrichment of the target atom. Under optimised conditions, maximum practically available specific activities relative to the theoretical specific activities reach orders of magnitudes of about 0.1%–5% for ^{166}Ho, 1%–20% for ^{153}Sm, but up to 80% for ^{177}Lu.

In therapeutic applications over the last decades, when radiolanthanides modified to particles, microspheres, or colloids and even for radiolanthanide-ligand complexes for bone metastases treatment were used, specific activities did not play a crucial role. In contrast, the recent developments of small peptides or antibodies, modified *via* covalently bound bifunctional chelators, demand radiolanthanides of very high specific activity. This is achievable best *via* accelerator-based production, neutron induced fission or (n, γ)–$\beta^- \rightarrow$ processes, or from radionuclide generator systems.

2.4 Key examples of therapeutic radiolanthanides

β^- particle emitting radionuclides

Commercially distributed therapeutic agents contain β^- particle emitting radionuclides, mostly produced in large quantities at nuclear reactors. There are β^- particle emitting radionuclides available for radionuclide therapy with a wide

variety of tissue ranges. Medium range (1000–2000 μm) and long range (> 2000 μm) β^- emitting radionuclides are ^{169}Er and ^{177}Lu (average β^- energies from 82 to 182 keV, range < 1000 μm), ^{153}Sm, ^{143}Pr, and ^{149}Pm (average β^- energies from 228 to 364 keV, range 1000–2000 μm), ^{165}Dy and ^{166}Ho (average β^- energies from 451 to 935 keV, range 2000–4000 μm).

The beta particle emission of a radionuclide results in the deposition of energy over about 5–150 or more cell diameters. These long range electrons could effectively kill malignant cells also at a relatively long distance, but will also give high radiation dose to normal tissue. Smaller tumours and small-disseminated metastases are better treated using electrons with lower energies, such as conversion and Auger electrons. A dosimetric evaluation of different radionuclides is especially important when high amounts are used for therapy. A simplified mathematical model to estimate the absorbed dose in a target organ and in the whole body in relation to the emitted particle energy, photon-to-electron energy ratio, and tumour size has been presented [9].

If the only goal from a radiation range perspective were maximizing absorbed dose fraction to tumour while minimizing irradiation of adjacent normal tissue structures, then it would appear that radionuclides emitting short-range radiation would be preferred. However, the success of radionuclide therapy is also critically dependent upon achieving homogeneous dose deposition within the tumour so that regrowth from an untreated subpopulation will be avoided Autoradiographic studies indicated the highly heterogeneous distribution of labelled molecules in tumours [15, 16]. Thus, long-range β^- particle emitting radionuclides are useful to cover a large target volume (cross-fire effect), cf. *e.g.* [7]).

α-particle emitting radionuclides

In comparison, α-particle emitting radionuclides are less applied. The range of α particles in tissue is equivalent to only a few cell diameters, offering the prospect of matching the cell-specific nature of targeted molecular carriers with radiation having a similar range of action [17]. Utilization of α-particle emitters for radionuclide therapy offers several important advantages from a radiobiological perspective. Alpha particles have higher decay energies than β emitters, generally in the range of 4.0–8.8 MeV. In contrast to low LET radiation such as β emitters, α-particles are also cytotoxic in hypoxic regions within a tumour [18]. Alpha particles are thus considered to be advantageous for therapy because of the range of only a few cell diameters, resulting in a high local deposition of energy. There are only a few α-emitting radiolanthanides that might be considered for medical application, such as ^{149}Tb [19–21].

Low energy electron emitters

The emission of a number of low energy electrons resulting from electron capture or internal conversion creates positively charged residue atoms with a potential of chemical effects. The low energy electrons are considered to be those that deposit their energy in subcellular dimensions. The extremely short range of Auger electrons (cf. Fig. 1) might require labelled compounds approaching the cell nucleus subsequent to internalisation.

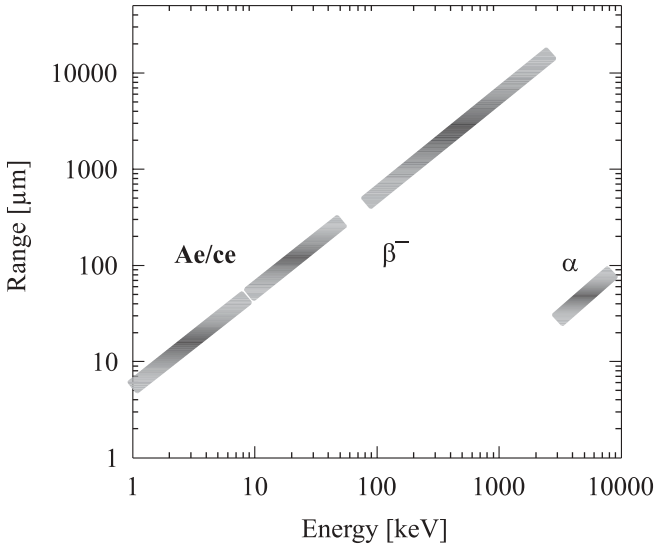


Fig. 1. Correlation between the energy of Auger electrons (ae), conversion electrons (ce), β^- electrons and α-particles and their ranges in water.

There are a number of Auger electron emitting radioisotopes among the lanthanide series. Out of those, some also emit β^+ particles that on annihilation result in two 511 keV photons which mainly contribute to the absorbed dose to normal tissues and make them not useful for therapy (^{134}Ce/^{134}La, ^{138}Nd/^{138}Pr, ^{140}Nd/^{140}Pr, ^{142}Sm/^{142}Pm). Suitable Auger emitting radionuclides for therapy are ^{153}Sm, ^{157}Eu, ^{161}Ho, ^{165}Er [22], ^{167}Tm.

Fig. 1 shows the correlation between the energy of electrons and alpha particles and their range in water (the reference material for soft tissue), from [8].

3. Radiopharmaceutical chemistry related to radiolanthanides

The design of a successful lanthanide radiopharmaceutical involves: (i) selection of a molecule (targeting vector) to deliver the radionuclide to the cell or organ either systemically after, *e.g. i.v.* injection, or directly *via* injection into the target cavity, (ii) development of a method for labelling the targeting molecule with the radiolanthanide without adversely affecting the pharmacophore moieties of the targeting vector, (iii) chemical, radiochemical, pharmacological and pre-clinical *in vivo* evaluation of the labelled compound.

Only a few of the therapeutic radionuclides mentioned above have been transferred to successful radiotherapeuticals. In terms of chemical syntheses, there are various options to transfer the radiolanthanide into a radiotherapeutical, cf. Fig. 2.

**Ln-ligand complexes*

An important group of radiolanthanide based therapeutics is the class of metal ligand complexes. Ligands shall chelate the trivalent lanthanide and provide high thermodynamic and, in particular, high kinetic complex stability *in vivo*. Typical ligands are polyamino polycarboxylate complex ligands such as EDTA and DTPA, and macrocyclic forms

thereof such as DOTA. Analogue phosphonate ligands such as EDTMP are established as well. A typical representative of this class of radiolanthanide based therapeuticals is ^{153}Sm-EDTMP, a commercial compound for palliative treatment of disseminated bone metastases.

*Ln-BFC-TV

These tumour targeting vectors (TTV) are biological molecules with high specificity to target biological components. Examples of TTV are amino acids to binding to amino acid transporters overexpressed at hypermetabolic tumour cells (reflecting increased protein synthesis rates), small peptides to recognising tumour specific transmembrane receptors (*e.g.* octreotides with high affinity to human somatostatin receptors) or monoclonal antibodies or fragments for antibody–antigen interactions. The labelling of these TTV is carried out *via* adequate complex ligands again. However, in this case the ligand shall provide both thermodynamic and kinetic stabilisation of the trivalent radiolanthanide in terms of co-ordination chemistry and the possibility to covalently couple *via* another functionality (−COOH, $-NH_2$, −SH) to the corresponding functionality of the TTV. Ligands of this class are defined as "bifunctional" chelators, BFC. The schematic approach of using BFC to transfer a radiolanthanide to a TV is illustrated in Fig. 3. For detailed information on the radiopharmaceutical chemistry of radiometals see [23]. A very successful example of this class is ^{177}Lu-labelled DOTA-octreotate derivative to treat neuroendocrine tumours.

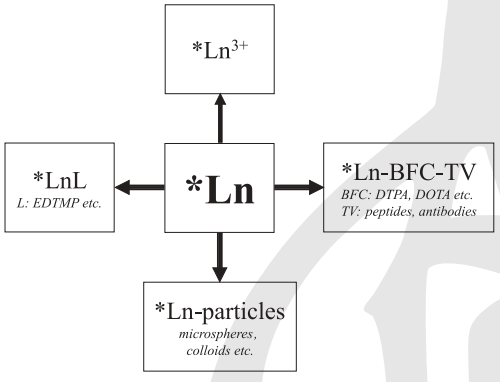


Fig. 2. Principal directions of designing radiolanthanide-based therapeuticals.

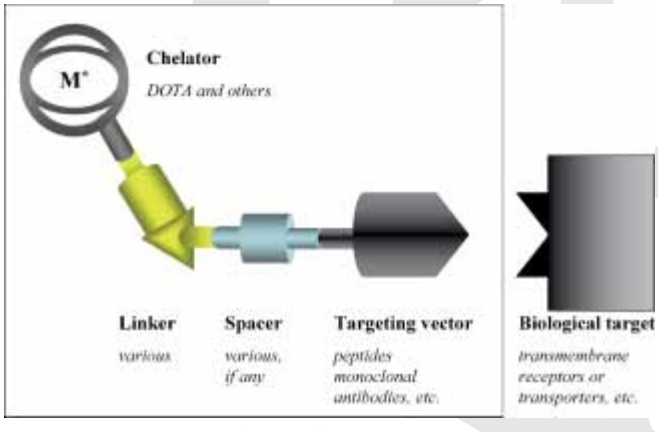


Fig. 3. Chemical design of the "bifunctional chelator" approach (BFC), cf. [23].

*Ln-particles

Intracavitary agents such as microspheres, particles, or radiocolloids are in use for radiation synovectomy. For their synthesis, dedicated physico-chemical procedures are applied, providing stable attachment of the radiolanthanide to particles of various diameters.

4. Dosimetric considerations

Dosimetric considerations are key issues in endoradiotherpy. The requirement for therapy is, in principle, that the absorbed dose to the tumour (or target) tissue should be high enough compared to that to the normal tissue. In practice, radiation doses depend on the nuclear decay characteristics of the radionuclide and to the pharmacology of the labelled radiotherapeutical.

Thus, accurate calculations of radiation dose effects of individual radiolanthanides are essential. The type of emitted radiation determines the absorbed dose to the tissues. Particles transfer their energy locally (non-penetrating radiation), while photons (penetrating radiation) do not have any determined range and will contribute to the absorbed dose. The energy of the emitted particles determines the absorbed doses to tumour and the surrounding normal tissues. Radiation of different qualities has different degrees of effectiveness in producing effects in biological systems. When radiation is absorbed in biological material, the energy is deposited along the tracks of charged particles in a pattern that is characteristic of the type of radiation involved. The linear energy transfer (LET) value determines the energy transferred per unit length as it traverses the tissue. Low LET values are found for X- and gamma radiation; higher LET values are found for neutrons, protons, α-particles and fission fragments. Also Auger electrons have relatively high LET values. These differences in density of ionisation are a major reason that neutrons, protons, and alpha particles produce more biological effects per unit of absorbed radiation dose than do more sparsely ionising radiation such as X-rays, gamma rays, or electrons.

The relative biological effectiveness (RBE), calculated as the ratio of the absorbed dose of a reference radiation, usually X-rays, required to produce the same biological effect as with a test dose of another radiation type. Thus, radiation with high LET and thus high RBE may have higher biological effect. Radiolanthanides offer suitable nuclides emitting radiation with high LET allowing for high RBE that could enhance therapy with radiopharmaceuticals.

Fig. 4 shows a comparison of the ratio between the absorbed dose rate in tumour and normal tissue (TND) for some radiolanthanides emitting (a) electrons (^{153}Sm, ^{157}Eu, ^{161}Ho, ^{167}Tm), and (b) positrons (^{134}Ce/^{134}La and ^{138}Nd/^{138}Pr) versus tumour radius. The results are from dosimetric simulations in humans assuming uniform distribution within tumour and normal tissue with 25 times higher activity concentration in the tumour compared to the normal tissue. For comparison, results for the established therapeutic radionuclides ^{131}I and ^{90}Y are included [10].

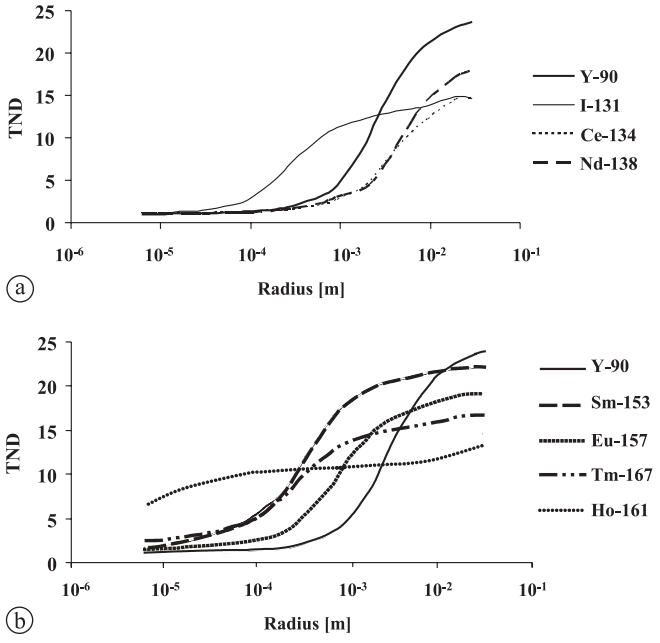


Fig. 4. The ratio between the absorbed dose rate in tumour and normal tissue (TND) for some radiolanthanides emitting electrons (^{153}Sm, ^{157}Eu, ^{161}Ho, ^{167}Tm), and positrons (^{134}Ce/^{134}La and ^{138}Nd/^{138}Pr) *versus* tumour radius. The results are from dosimetric simulations in humans assuming uniform distribution within tumour and normal tissue with 25 times higher activity concentration in the tumour compared to the normal tissue. For comparison, results for ^{131}I and ^{90}Y are included.

Furthermore, an estimation of the radiation dose delivered by the labelled compound to the target organ and to healthy tissues is important. In this case, pharmacological parameters of the chemical compound and the uptake kinetics are important factors. Usually, these data rely on organ uptake distribution measurements of the radiotherapeutical in mice or rat. However, since in most cases photon emission by the therapeutic radiolanthanide is either missing or is non-quantitative, direct measurements of uptake kinetics in humans are difficult to obtain. In this case, surrogate trivalent metals such as the rare-earth radioisotope ^{86}Y are of interest [24].

5. Examples of radiolanthanide therapeuticals

The main indications for use of radiotherapeuticals are in oncology, rheumatology and cardiology.

Tumour therapy: Radiolanthanides have been applied in therapy of bone metastases and for bone marrow ablation prior to stem cell transplantation for haematological malignancies using various phosphonates, and for various tumour forms using monoclonal antibodies and peptide hormone analogues labelled with ^{153}Sm, ^{149}Pm, ^{149}Tb, ^{161}Tb, ^{166}Ho and ^{177}Lu.

Radiation synovectomy: Radiation synovectomy has been used for 50 years, usually with ^{90}Y or ^{198}Au, but also with ^{153}Sm, ^{165}Dy, ^{166}Ho and ^{169}Er. This therapeutic procedure for rheumatoid arthritis, inflammatory joint diseases, persistent synovial perfusion, and other joint diseases is widely used in many countries. The treatment consists of the injection of a beta-emitting radionuclide into the joint capsule in order to eliminate diseased synovium through irradiation, and to improve joint function.

Vascular therapy: The use of β^- emitting radionuclides in the control of restenosis in post angioplasty patients is currently under investigation at many leading cardiovascular research centres, using either balloon catheters filled with liquid radioisotopes or radionuclide coated metallic stents. Solutions of ^{166}Ho and ^{153}Sm(III) salts are potential liquid radiation sources for such brachytherapy.

Depending on the options of preparation of radiolanthanide-based therapeuticals (cf. Fig. 2), specific classes of therapeuticals are obtained. These are summarized below. For a detailed discussion of individual radiolanthanides studied for therapeutic applications, cf. [8].

Microspheres, particles, radiocolloids

Intracavitary agents such as radiocolloids have been used and are in use for radiation synovectomy as an alternative to surgical synovectomy in patients with chronic rheumatoid arthritis. Among the radiolanthanides, ^{169}Er, ^{165}Dy and ^{153}Sm have been applied in addition to ^{90}Y and other non-trivalent radioelements [25]. Because of the leakage of radiocolloids from the joint to the lymph node, ferric hydroxide macro aggregates of 5–10 μm diameter were introduced as a particulate [26], labelled with short-lived ^{165}Dy and longer-lived ^{169}Er [27], ^{166}Ho [28], and ^{153}Sm [29]. In parallel, ^{153}Sm labelled hydroxyapatite microspheres [30] demonstrated promising uniform biodistribution and a very low cumulative leakage in animals.

Me^{3+} *ligand complexes*

Multidentate chelators are needed to form complexes because *in vivo* dissociation of the radiolanthanide from the chelate invariably results in bone and liver uptake. While for many applications this uptake is undesirable since it leads to non-specific irradiation of these (presumably) non-target tissues, for the palliative therapy of disseminated bone metastases, the radiolanthanide accumulation on the hydroxyapatite structure is desired. Therefore, ligands with intermediate complex formation constants are selected or ligands, which tender an additional binding capacity to hydroxyapatite. In analogy to known 99mTc complexes with substituted phosphonates, substituted amine-methylene phosphonic acids such as EDTMP (ethylenediamine-tetramethylene-phosphonic acid), DOTMP (1,4,7,10-cyclododecyl-tetraaminetetramethylene phosphonic acid), and DTPMP (diethylenetriamine-pentamethylene-phosphonic acid) have been investigated for the radiolanthanides. [^{153}Sm-EDTMP] has become commercially available, while for the application of ^{166}Ho, due to its lower specific activity, the kinetically inert ligand DOTMP was discussed [31].

Peptides and proteins labelled via bifunctional chelating agents

Trivalent (radio)lanthanides cannot be coupled directly to amino acid sequences of peptides and proteins. Stabilizing a metallic radioisotope *in vivo* thus requires a dedicated derivatisation of peptides and proteins by covalently binding a bifunctional chelator (BFC) to selected

amino acids. Acyclic and cyclic poly(aminocarboxylate) ligands such as ethylenediamine-tetraacetic acid (EDTA), diethylenetriamin-pentaacetic acid (DTPA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) and 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), originally developed to chelate and link In, Y, and Cu to peptides and proteins, were adopted for the trivalent radiolanthanides. Although acyclic multidentate chelating ligands such as DTPA provide a high degree of *in vivo* kinetic stability of the complexes, a decrease of thermodynamic and kinetic complex stability is observed if one of the appended arms necessary for metallic co-ordination is occupied by the covalent link to the peptide or protein [*e.g.* 32–36].

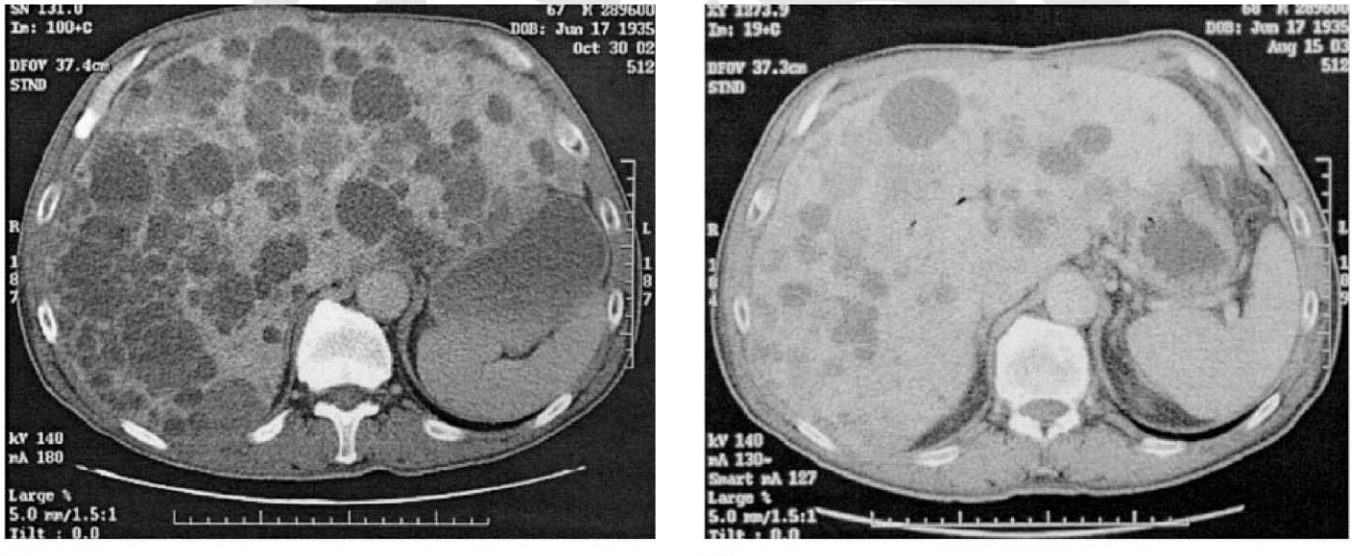
One approach to overcome this problem is to synthesize functional derivatives of DTPA with linker moieties attached to the ethylene backbone, guaranteeing its octadenticity towards the metal centre while still providing a covalent link to the amino acid of choice [32, 33, 37–40]. Another approach is to introduce a macrocyclic polyazamacrocyclic polycarboxylate ligand, known to form more kinetically inert complexes [19, 41–44].

Somatostatin receptor expressing tumours have successfully been treated with the small peptide [^{177}Lu]DOTA-(D)Phe^{1}-Tyr^{3}-octreotate with promising results [45, 46]. This analogue shows the highest tumour uptake of all clinically tested somatostatin analogues so far. This compound has been shown to have a very favourable impact on tumour regression and animal survival in a rat model. Highest cure rate was obtained in small tumours compared to larger tumours [47].

Another peptide of interest is bombesin, which is an analogue of human gastrin-releasing peptide (GRP) that binds to GRP receptors with high affinity and specificity. The GRP receptor is over-expressed on a variety of human cancer cells including prostate, breast, lung, and pancreatic cancers. The ^{177}Lu-labelled bombesin peptide analogue DO3A-amide-βAla-BBN has so far been studied in normal mice [48].

One of the most impressive examples is ^{177}Ln-DOTA-DPhe^{1}-Tyr^{3}-octreotate. This high affinity of the octapeptide octreotide to somatostatin receptors made it a relevant therapeutic targeting vector for somatostatin receptor expressing (neuroendocrine) tumours. It is in routine use to treat patients. Fig. 5 illustrates the positive results of this type of endoradiotherapy, from [49].

Monoclonal antibodies are another sort of tumour targeting vectors, increasingly used in endoradiotherapy. For example, ^{177}Lu has been used for therapy using radiolabeled monoclonal antibodies (MAb) CC49 and RS7. MAb CC49 binds to the tumour-associated antigen TAG-72 found in a wide range of human carcinomas. In an experimental therapy model for human carcinoma ^{177}Lu-labelled CC49 was shown to delay the growth or eliminate established human colon carcinomas in athymic mice [50, 51]. Intraperitoneally injected ^{177}Lu-labelled CC49 has also been used clinically in patients with ovarian cancer [52]. Phase I and phase I/II clinical trials have been performed in patients with ovarian carcinoma, demonstrating that intraperitoneal radioimmunotherapy with this compound is well tolerated and appears to have antitumour activity against chemotherapy-resistant ovarian cancer in the peritoneal cavity [53], and that marrow suppression was the dose-limiting toxic effect [54]. Furthermore, a phase I trial was designed to examine the feasibility of combining interferon (to increase the expression of the TAG-72 antigen) and Taxol (radiosensitising and antitumour effect) with intraperitoneal radioimmunotherapy (^{177}Lu-labelled CC49) of recurrent or persistent ovarian cancer confined to the abdominal cavity after first line therapy. The combination was well tolerated, with bone marrow suppression as the dose-limiting toxicity [55]. Tumour targeting and therapeutic efficacy of ^{177}Lu-labelled RS7 (against epithelial glycoprotein-1) was evaluated in a human non-small cell lung carcinoma xenograft model. Elimination of estab-



(a) (b)

Fig. 5. Endoradiotherapy with the radiolabeled somatostatin analog [^{177}Lu-DOTA-octreotate] in patients with endocrine gastroenteropancreatic tumors, from [49]: Computed tomography scans in a patient with a metastasized nonfunctioning endocrine pancreatic tumour before treatment (**a**) and 3 months after the last treatment (**b**): decrease in number of cystic liver lesions and the decrease in total liver size.

lished tumours was shown and [^{177}Lu]DOTA-RS7 might be effective for radioimmunotherapy [56].

^{153}Sm-labelled monoclonal antibodies have been performed against tumour-associated antigens. The biodistribution of ^{153}Sm-labelled OC125 monoclonal antibody, in whole or F(ab′)2 fragment form, has been studied in nude mice transplanted with human ovarian adenocarcinoma line expressing the CA125 antigen [57]. Promising therapeutic results on nude mice were obtained using ^{153}Sm-labelled anti-CEA antibodies, showing significant anti-tumour effects including tumour necrosis. ^{153}Sm-anti-CEA may thus be a potential agent in clinical radioimmunotherapy of CEA expressing tumours [58]. A few smaller peptides have also been labelled with ^{153}Sm. Favourable biodistribution and promising therapeutic efficacy of the somatostatin analogue [^{153}Sm]CMDTPA-Tyr^3-octreotate were demonstrated in rats transplanted with rat pancreatic tumour [59]. ^{153}Sm-labelled bombesin peptide analogue DO3A-amide-βAla-BBN has been studied in normal mice [48].

6. Conclusion

Several radiolanthanides are more suitable for tumour therapy than the radionuclides used routinely today. Radiolanthanides particularly suitable for therapy are ^{169}Er, ^{161}Tb, ^{177}Lu, ^{175}Yb and ^{161}Ho, the latter being most suitable for very small tumours (< 0.1 mm). This set of radiolanthanides provides a variety of nuclear parameters such as half-lives, types and energy of emitted particles, yet with chemical similarities. The approach of using one and the same targeting vector labelled with selected individual radioisotopes of a number of 4 *f*-elements may provide an optimum choice of therapeutic strategies. Making radiolanthanide-based therapeuticals available routinely, however, asks for a dedicated network of radiolanthanide production and radiopharmaceutical chemistry.

Acknowledgment. The author would like to thank the European Commission for supporting the COST Action D18 “Lanthanide Chemistry for Diagnosis and Therapy” and all the members of working group 04 for their co-operation.

References

1. Larson, S. M., Carrasquillo, J. A., Reynolds, J. C.: Radioimmunodetection and radioimmunotherapy. Cancer Invest. **2**, 363 (1984).
2. Spencer, R. P., Seevers Jr., R. H., Friedman, A. M.: *Radionuclides in Therapy*. CRC Press, Boca Raton (1987).
3. Hoefnagel, C. A.: Radionuclide therapy revisited. Eur. J. Nucl. Med. **18**, 408 (1991).
4. Volkert, W. A., Goeckeler, W. F., Erhardt, G. J., Ketring, A. R.: Therapeutic radionuclides: production and decay property considerations. J. Nucl. Med. **32**, 174 (1991).
5. Volkert, W. A., Hoffman, T. J.: Therapeutic radiopharmaceuticals. Chem. Rev. **99**, 2269 (1999).
6. Cutler, C. S., Smith, C. J., Ehrhardt, G. J., Tyler, T. T., Jurisson, S. S., Deutsch, E.: Current and potential therapeutic uses of lanthanide radioisotopes. Cancer Biother. Radiopharm. **15**, 531 (2000).
7. Zalutsky, M. R.: Radionuclide therapy. In: *Handbook of Nuclear Chemistry*. Vol. 4 (Vértes, A,. Nagy, S., Klencsár, Z., eds.) Kluwer Academic Publishers, The Netherlands (2003), p. 315.
8. Rösch, F., Forssell-Aronsson, E.: Radiolanthanides in nuclear medicine. In: *Metal Ions and their Complexes in Medication*. (Sigel, A., Sigel, H., Dekker, M., eds.) Inc. New York & Basel Eds. (2004), vol. 42, p. 77.
9. Bernhardt, P., Benjegard, S. A., Kolby, L., Johanson, V., Nilsson, O., Ahlman, H., Forssell-Aronsson, E.: Dosimetric comparison of radionuclides for therapy of somatostatin receptor-expressing tumors. Int. J. Radiat. Oncol. Biol. Phys. **51**, 514 (2001).
10. Uusijärvi, H., Bernhardt, P., Mäcke, H., Rösch, F., Forssell-Aronsson, E.: Electron- and positron-emitting radiolanthanides for therapy: aspects of dosimetry and production. J. Nucl. Med. **47**, 807 (2006).
11. Mirzadeh, S., Mausner, H.-J., Garland, M. A.: Reactor-produced medical radionuclides. In: *Handbook of Nuclear Chemistry*. Vol. 4 (Vértes, A,. Nagy, S., Klencsár, Z., eds.) Kluwer Academic Publishers, The Netherlands (2003), p. 1.
12. Qaim, S. M.: Cyclotron production of medical radionuclides. In: *Handbook of Nuclear Chemistry*. Vol. 4 (Vértes, A,. Nagy, S., Klencsár, Z., eds.) Kluwer Academic Publishers, The Netherlands (2003), p. 47.
13. Rösch, F., Knapp, F. F.: Radionuclide generators. In: *Handbook of Nuclear Chemistry*. Vol. 4 (Vértes, A,. Nagy, S., Klencsár, Z., eds.) Kluwer Academic Publishers, The Netherlands (2003), p. 81.
14. Jang, Y. H., Blanco, M., Dasgupta, S., Keire, D. A., Shively, J. E., Goddard, W. A. I.: Mechanism and energetics for complexation of Y-90 with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), a model for cancer radioimmunotherapy. J. Am. Chem. Soc. **121**, 6142 (1999).
15. Sands, H., Jones, P. L., Shah, S. A., Palme, D., Vessele, R. L., Gallagher, B. M.: Correlation of vascular permeability and blood flow with monoclonal antibody uptake by human Clouser and renal cell xenografts. Cancer Res. **48**, 188 (1988)
16. Gridley, D. S., Ewart, K. L., Coa, J. D., Stickney, D. R.: Hyperthermia enhances localization of 111In-labeled hapten to bifunctional antibody in human colon tumor xenografts. Cancer Res. **51**, 1515 (1991).
17. Zalutsky, M. R., Vaidyanathan, G.: Astatine-211-labeled radiotherapeutics: an emerging approach to targeted alpha-particle radiotherapy. Curr. Pharm. Design **6**, 1433 (2000).
18. Langmuir, V.K, Sutherland, R. M.: Radiobiology of radioimmunotherapy: current status. Antibody Immunoconj. Radiopharm. **1**, 195 (1988).
19. Allen, B. J., Blagojevic, N.: Alpha- and beta-emitting radiolanthanides in targeted cancer therapy: the potential role of terbium-149. Nucl. Med. Commun. **17**, 40 (1996).
20. Allen, B. J., Goozee, G., Iman, S., Leigh, J., Beyer, G.: Proceedings of the 6th International Conference on Radiopharmaceutical Dosimetry, Gatlinburg, TN (1996), p. 392.
21. Allen, B. J., Goozee, G., Sarkar, S., Beyer, G., Morel, C., Byrne, A. P.: Production of terbium-152 by heavy ion reactions and proton induced spallation. Appl. Radiat. Isotopes **54**, 53 (2001).
22. Beyer, G.-J., Zeisler, S. K., Becker, D. W.: The Auger-electron emitter ^{165}Er: Excitation function of the ^{165}Ho(p, n)^{165}Er process. Radiochim. Acta **92**, 219 (2004).
23. Mäcke, H., Good, S.: Radiometals (non-Tc, non-Re) and bifunctional labelling chemistry. In: *Handbook of Nuclear Chemistry*. Vol. 4 (Vértes, A,. Nagy, S., Klencsár, Z., eds.) Kluwer Academic Publishers, The Netherlands (2003), p. 279.
24. Rösch, F., Herzog, H., Stolz, B., Brockmann, J., Köhle, M., Mühlensiepen, H., Marbach, P., Müller-Gärtner, H. W.: Uptake kinetics of the somatostatin receptor ligand [^{86}Y]DOTA-DPhe^1-Tyr^3-octreotide ([^{86}Y]SMT487) using positron emission tomography in non-human primates and calculation of radiation doses of the ^{90}Y-labelled analogue. Eur. J. Nucl. Med. **26**, 358 (1999).
25. Deutsch, E. J., Brodack, J. W., Deutsch, K. F.: Radiation synovectomy revisited. Eur. J. Nucl. Med. **20**, 1113 (1993).
26. Zalutsky, M. R., Venkatesan, P., English, R., Shortkroff, S., Sledge, C., Adelstein, S.: Radiation synovectomy with ^{165}Dy-FHMA: lymph node uptake and radiation dosimetry calculations. Nucl. Med. Biol. **12**, 457 (1986).
27. Ruotsi, A., Hypen, M., Rekonen, A., Oka, M.: Erbium-169 *versus* triamcinolone hexacetonide in the treatment of rheumatoid finger joints. Ann. Rhem. Disease **38**, 45 (1979).

28. Song, J., Suh, C. H., Park, Y. B., Lee, S. H., Yoo, N. C., Lee, J. D., Kim, K. H., Lee S. K.: A phase I/IIa study on intra-articular injection of holmium-166-chitosan complex for the treatment of knee synovitis of rheumatoid arthritis. Eur. J. Nucl. Med. **28**, 489 (2001).
29. Shin, B. C., Park, K. B., Jang, B. S., Lim, S. M., Shim, C. K.: Preparation of ^{153}Sm-chitosan complex for radiation synovectomy. Nucl. Med. Biol. **28**, 719 (2001).
30. Chinol, M., Vallabhajosula, S., Goldsmith, S. J., Klein, M. J., Deutsch, K. F., Chinen, L. K., Brodack, J. W., Deutsch, E. A., Watson, B. A., Tofe, A. J.: Chemistry and biological behavior of samarium-153 and rhenium-186-labeled hydroxyapatite particles: potential radiopharmaceuticals for radiation synovectomy. J. Nucl. Med. **34**, 1536 (1993).
31. Bayouth, J. E., Macey, D. J., Kasi, L. P., Garlich, J. R., McMillan, K., Dimopoulos, M. A., Champlin, R. E.: Pharmacokinetics, dosimetry and toxicity of holmium-166-DOTMP for bone marrow ablation in multiple myeloma. J. Nucl. Med. **36**, 730 (1995).
32. Brechbiel, M. W., Gansow, O. A.: Backbone-substituted DTPA ligands for ^{90}Y radioimmunotherapy. Bioconj. Chem. **2**, 187 (1991).
33. Brechbiel, M. W., Gansow, O. A., Atcher, R. W., Schlom, J., Esteban, J., Simpson, D. E., Colcher, D.: Synthesis of 1(*p*-isothiocyanatobenzyl) derivatives of DTPA and EDTA. Antibody labeling and tumor-imaging studies. Inorg. Chem. **25**, 2772 (1986).
34. Brockmann, J., Rösch, F.: Determination of stability constants in Y-DTPA-peptide-systems: Evaluation of a radiochemical method using n.c.a. yttrium-88. Radiochim. Acta **87**, 79 (1999).
35. Broan, C. J., Cox, J. P. L., Craig, A. S., Kataky, R., Parker, D., Harrison, A., Randall, A. M., Ferguson, G.: Structure and solution stability of indium and gallium complexes of 1,4,7-triazacyclononanetriacetate and of yttrium complexes of 1,4,7,10-tetraazacyclododecanetetraacetate and related ligands: kinetically stable complexes for use in imaging and radioimmunotherapy. X-ray molecular structure of the indium and gallium complexes of 1,4,7-triazacyclononane-1,4,7-triacetic acid. J. Chem. Soc. Perkin Trans. **2**, 87 (1991).
36. Loncin, M. F., Desreux, J. F., Merciny, E.: Coordination of lanthanides by two polyamino polycarboxylic macrocycles: formation of highly stable lanthanide complexes. Inorg. Chem. **25**, 2646 (1986).
37. Ugur, O., Kostakoglu, L., Hui, E. T., Fisher, D. R., Garmestani, K., Gansow, O. A., Cheung, N. V., Larson, S. M.: Comparison of the targeting characteristics of various radioimmunoconjugates for radioimmunotherapy of neuroblastoma: dosimetry calculations incorporating cross-organ beta doses. Nucl. Med. Biol. **23**, 1 (1996).
38. Keana, J. F. W., Mann, J. S.: Chelating ligands functionalized for facile attachment to biomolecules. A convenient route to 4-isothiocyanatobenzyl derivatives of diethylenetriaminepentaacetic acid (DTPA) and ethylenediaminetetraacetic acid. J. Org. Chem. **55**, 2868 (1990).
39. Roselli, M., Schlom, J., Gansow, O. A., Brechbiel, M. W., Mirzadeh, S., Pippin, C. G., Milenic, D. E., Colcher, D.: Comparative biodistribution studies of DTPA-derivative bifunctional chelates for radiometal labeled monoclonal antibodies. Int. J. Radiat. Appl. Instrum. B **18**, 389 (1991).
40. Cummins, C. H., Rutter Jr., E. W., Fordyce, W. A.: A convenient synthesis of bifunctional chelating agents based on diethylenetriaminepentaacetic acid and their coordination chemistry with yttrium(III). Bioconj. Chem. **2**, 180 (1991).
41. Moi, M. K., DeNardo, S. J., Meares, C. F.: Stable bifunctional chelates of metals used in radiotherapy. Cancer Res. **50**, 789 (1990).
42. Li, M., Meares, C. F.: Synthesis, metal chelate stability studies, and enzyme digestion of a peptide-linked DOTA derivative and its corresponding radiolabeled immunoconjugates. Bioconj. Chem. **4**, 275 (1993).
43. Li, M., Meares, C. F., Zhong, G., Miers, L., Xiong, C. Y., De Nardo, S. J.: Labeling monoclonal antibodies with 90yttrium- and 111indium-DOTA chelates: a simple and efficient method. Bioconj. Chem. **5**, 101 (1994).
44. Bhalgat, M. K., Roberts, J. C., Mercer-Smith, J. A., Knotts, B. D., Vessella, R. L., Lavallee, D. K.: Preparation and biodistribution of copper-67-labeled porphyrins and porphyrin-A6H immunoconjugates. Nucl. Med. Biol. **24**, 179 (1997).
45. De Jong, M., Valkema, R., Jamar, F., Kvols, L. K., Kwekkeboom, D. J., Breeman, W. A., Bakker, W. H., Smith, C., Pauwels, S., Krenning, E. P.: Somatostatin receptor-targeted radionuclide therapy of tumors: preclinical and clinical findings. Semin. Nucl. Med. **32**, 133 (2002).
46. Kwekkeboom, D. J., Bakker, W. H., Kooij, P. P., Konijnenberg, M. W., Srinivasan, A., Erion, J. L., Schmidt, M. A., Bugaj, J. L., De Jong, M., Krenning, E. P.: [^{177}Lu-DOTAOTyr^3]octreotate: comparison with [^{111}In-DTPA]octreotide in patients. Eur. J. Nucl. Med. **28**, 1319 (2001).
47. De Jong, M., Breeman, W. A., Bernard, B. F., Bakker, W. H., Schaar, M., van Gameren, A., Bugaj, J. E., Erion, J., Schmidt, M., Srinivasan, A., Krenning, E. P.: [^{177}Lu-DOTA(0),Tyr^3] octreotate for somatostatin receptor-targeted radionuclide therapy. Int. J. Cancer **92**, 628 (2001).
48. Hu, F., Cutler, C. S., Hoffman, T., Sieckman, G., Volkert, W. A., Jurisson, S. S.: Pm-149 DOTA bombesin analogs for potential radiotherapy. *In vivo* comparison with Sm-153 and Lu-177 labeled DO3A-amide-betaAla-BBN(7-14)NH(2). Nucl. Med. Biol. **29**, 423 (2002).
49. Kwekkeboom, D. J., Teunissen, J. J., Bakker, W. H., Kooij, P. P., de Herder, W. W., Feelders, R. A., van Eijck, C. H., Esser, J.-P., Kam, B. L., Krenning, E. P.: Radiolabeled somatostatin analog [^{177}Lu-DOTA0,Tyr^3]octreotate in patients with endocrine gastroenteropancreatic tumors. J. Clin. Oncol. **20**, 2754 (2005).
50. Schlom, J., Siler, K., Milenic, D. E., Eggensperger, D., Colcher, D., Miller, L. S., Houchens, D., Cheng, R., Kaplan, D., Goeckeler, W.: Advantage of dose fractionation in monoclonal antibody-targeted radioimmunotherapy. Cancer Res. **51**, 2889 (1991).
51. Schott, M. E., Schlom, J., Siler, K., Milenic, D. E., Eggensperger, D., Colcher, D., Cheng, R., Kruper Jr., W. J., Fordyce, W., Goeckeler, W.: Biodistribution and preclinical radioimmunotherapy studies using radiolanthanide-labeled immunoconjugates. Cancer **73**, 993 (1994).
52. Macey, D. J., Meredith, R. F.: A strategy to reduce red marrow dose for intraperitoneal radioimmunotherapy. Clin. Cancer Res. **5**, 3044s (1999).
53. Meredith, R. F., Partridge, E. E., Alvarez, R. D., Khazaeli, M. B., Plott, G., Russell, C. D., Wheeler, R. H., Liu, T., Grizzle, W. E., Schlom, J., LoBuglio, A. F.: Intraperitoneal radioimmunotherapy of ovarian cancer with lutetium-177-CC49. J. Nucl. Med. **37**, 1491 (1996).
54. Alvarez, R. D., Partridge, E. E., Khazaeli, M. B., Plott, G., Austin, M., Kilgore, L., Russell, C. D., Liu, T., Grizzle, W. E., Schlom, J., LoBuglio, A. F., Meredith, R. F.: Intraperitoneal radioimmunotherapy of ovarian cancer with ^{177}Lu-CC49: a phase I/II study. Gynecol. Oncol. **65**, 94 (1997).
55. Meredith, R. F., Alvarez, R. D., Partridge, E. E., Khazaeli, M. B., Lin, C. Y., Macey, D. J., Austin Jr., J. M., Kilgore, L. C., Grizzle, W. E., Schlom, J., LoBuglio, A. F.: Intraperitoneal radioimmunochemotherapy of ovarian cancer: a phase I study. Cancer Biother. Radiopharm. **16**, 305 (2001).
56. Stein, R., Govindan, S. V., Chen, S., Reed, L., Richel, H., Griffiths, G. L., Hansen, H. J., Goldenberg, D. M.: Radioimmunotherapy of a human lung cancer xenograft with monoclonal antibody RS7: evaluation of 177Lu and comparison of its efficacy with that of 90Y and residualizing 131I. J. Nucl. Med. **42**, 967 (2001).
57. Kraeber-Bodere, F., Mishra, A., Thedrez, P., Faivre-Chauvet, A., Bardies, M., Imai, S., Le Boterff, J., Chatal, J. F.: Pharmacokinetics and biodistribution of samarium-153-labelled OC125 antibody coupled to CITCDTPA in a xenograft model of ovarian cancer. Eur. J. Nucl. Med. **23**, 560 (1996).
58. Li, G. P., Zhang, H., Zhu, C. M.: Radioimmunotherapy with 153Sm-CEA monoclonal antibody in nude mice bearing human colon carcinoma: an experimental study. Di Yi Jun Yi Da Xue Xue Bao **23**, 1 (2003).
59. Bugaj, J. E., Erion, J. L., Schmidt, M. A., Srinivasan, A.: Radiotherapeutic efficacy of (153)Sm-CMDTPA-Tyr(3)-octreotate in tumor-bearing rats. Nucl. Med. Biol. **28**, 327 (2001).
60. Browne, E., Firestone, R. B.: *Table of Radioactive Isotopes*. (Shirley, V. S., ed.) Wiley, New York (1986).