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Overview of transition metal and lanthanide complexes as diagnostic tools

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Abstract

This review presents an overview of various elements used in the preparation of imaging contrast agents. After a brief introduction to the history of the development of labelling agents, a review of magnetic resonance imaging (MRI) and radio labelled imaging (RI) agents is presented. On the one hand, transition metals were investigated, allowing more special attention to manganese, iron and technetium. Classification of the metal chelates is done taking into account the chemical structure of the compounds. Information on stability, lipophilicity and toxicity of the chelates is given. On the other hand, lanthanide complexes, especially Gadolinium chelates, were investigated, taking into account the chemical structure, the stability, the lipophilicity and the toxicity of the compounds. The various techniques for labelling were analysed and information presented about peptides, antibody and cell labelling. Finally, the authors carry out a brief review of the imaging contrast agents used in the study of several organ systems, i.e. vascular structures, liver, spine and brain, heart, kidneys, skeleton, lungs and abdominal diseases.

Keywords: Imaging contrast agents; Transition metal complexes; Lanthanides

1. Generalities

Radio imaging (RI) and magnetic resonance imaging (MRI) are important tools in the non-invasive diagnostics of diseases and tumours. Improving the contrast and the selectivity for target organs led to more sensitive and more accurate detection. This is why contrast agents have been developed for many years. Radio isotopes of iodine played a pioneering role since their early use in thyroid metabolism studies and in the in vitro techniques of radioimmunoassays [1,2]. However, iodine is not efficient for improving the contrast in MRI and none of the

iodine isotopes have both ideal nuclear properties and availability for large scale use for in vivo diagnostics, there has been intense interest in developing more adapted contrast agents [3]. Alternative contrast agents have been found in different families as IIIa (^{111}In, ^{201}Tl) but the most widely used were selected from transition metals and rare earths (^{51}Cr, ^{52m}Mn, Mn, Fe, ^{99m}Tc, ^{188}Re, Gd, Yb and Dy) [4–12]. Some of them are normally present in the body as trace elements (Mn, Fe, Cr) and are considered less toxic for this reason. Nevertheless, as pointed out by Misselwitz et al. [13], even trace elements may induce adverse even toxic effects when the regulations of enteral absorption is bypassed by parenteral administration. The toxicity of metals having no physiological role is well known (Tl, ^{111}In, ^{99m}Tc, Re and Gd).

To reduce metal ion toxicity, the concepts of covalent binding, chelation, coupling to proteins and amino-acids or glucide polymers, inclusion into dextrins, liposomes or cells and weakly dissociated salts have been investigated. Covalent binding has been mainly used for radiolabelling of proteins and pharmaceuticals using iodine but enzymatic deiodination problems [14,15] and the poor applicability of iodine isotopes for radio imaging have considerably reduced the interest in that method.

Formation of weakly dissociated salts, chelation and other methods, which are, from an analytical point of view, particular cases of the former, are of general applicability and are widely used for the preparation of contrast agents based on metallic ions. The chelating method is of particular interest in that both the acute and the long term toxicity of both the metal and the chelating agents are dramatically reduced owing to the complexation.

This review will focus on the most frequently used contrast agents in both RI and MRI, i.e. transition metals and rare earths and discuss how adequate binding can ensure the safety, the targeting and the efficiency of contrast agents.

2. Complexes: generality, stability, lipophilicity and toxicity

2.1. Transition metals

Four transition metals are often mentioned in the labelled complexes used as imaging contrast agents. They are divided in two groups according to the Mendeleev classification and imaging use.

The low molecular weight metals, manganese and iron are used in contrast agents which induce the relaxation of water protons, i.e. decrease T_1 and/or T_2 values in MRI [16–18]. This results in a greater signal intensity differential between abnormal and normal tissues. They are used mainly in MRI, although ^{52m}Mn has been proposed for RI [5].

The higher molecular weight metals, radio isotopes of technetium and rhenium are used as contrast agents for RI.

2.1.1. Manganese

Manganese ions contain unpaired electrons giving them paramagnetic properties which facilitate T_1 relaxation by interacting with water protons [19]. Mn^{2+} with five unpaired electrons in the 3d orbital is the most efficient but Mn^{3+}, especially as a porphyrin complex (e.g. Mn TPP_S4) has also been used.

Mn^{2+} is administered in complexed forms to diminish the toxicity of the free metal ions and mainly to improve the urinary elimination without significant loss of the paramagnetic properties [20]: as manganese is an essential trace element present in all mammalian cells, it is generally assumed in the radiologic community that less attention must be given to the release of this element in the body [21–23]. This is true after manganese ingestion. Regulation of enteral absorption limits the toxicity [23,24]. However, if manganese is injected intravenously, the regulation is bypassed and potentially deleterious effects on metabolic pathways involving manganese or exchangeable cations as cofactors may occur.

The normal whole-body content in humans is 12–20 mg and the daily turnover is 5–8 mg. These values are low when compared with the MRI doses employed which range from 15 to 45 mg of metal [25] [26–35].

Manganese is an activating agent and a cofactor of various enzymes such as pyruvate carboxylase [22], superoxide dismutase [22], glutamine synthetase [36] and alkaline phosphatase [37]. It is involved in oxidation–reduction processes [38,39], in phosphorylation [23,37,40,41], in fermentation [38] and in the synthesis of cholesterol, fatty acids, mucopolysaccharides and chondroïtin sulfate [23,37,38,40–42].

Manganese is also localised in mitochondria with a metabolic function as a coenzyme in protein synthesis [28,34,36]. It increases cytochrome P-450 dependent drug hydroxylation activity [36]. Porphyrins that contain manganese instead of Iron were found in mammalian and human red cells [39]. Manganese is a divalent cation that may compete with several ions such as iron and calcium [36] or replace them in enzymatic systems. This is the case for zinc, cobalt, nickel [43] and magnesium [38].

The enteral absorption of manganese is concentrated primarily in the liver [22,30,38]. The high uptake in the pancreas suggests an important role for manganese in pancreatic functioning.

In the intravenous administration of manganese, the normal regulatory mechanisms are bypassed and the uptake of free ions is found in several tissues such as the liver, pancreas, kidneys, gastric mucosa, cardiomyocytes, salivary glands, thyroid and pituitary gland [44–47].

In the circulation, manganese ions are bound to proteins. The Mn^{3+} can be bound to transferin and cross the blood–brain barrier by transport mechanisms [36,48,49]. As to Mn^{2+}, it is bound to an α-macroglobulin.

It had been postulated that Mn^{2+} scavenges oxygen radicals and was oxidised to Mn^{3+} which is complexed by various ligands and became a toxic species with cytotoxic effects [36,50].

For manganese ions, the gastrointestinal tract is the major route of elimination whereas urinary excretion represents only about 0.1% [22,36,46,51,52].

Because high blood levels of free manganese may be toxic [53–62], it is very important that the metal be complexed as a stable chelate [26,28,63,64] to be injected as a contrast agent in MRI. The best ligand for the Mn^{2+} is the dipyridoxyl diphosphate (DPDP) (Fig. 1).

Its three dimensional structure has been determined [63]. The Mn–DPDP is a stable, highly water-soluble hexadentate chelate but it is less stable than corresponding complexes of Zn^{2+} ($k = 10^{-18,95}$), Cu^{2+} ($k = 10^{-22,08}$) or Fe^{3+} ($k = 10^{-33,52}$) so that transchelation is possible in the body [63]. This ligand was chosen with the intention of being recognised by a membrane transport specific of the liver [65,66]. Nevertheless, Mn–DPDP is not entirely specific for the liver and is taken up by the pancreas, the kidneys and the adrenal glands.

The acute toxicity of Mn–DPDP is reduced by a factor of ca. 10 [26,28,64] compared with $MnCl_2$.

A similar reduction factor was found in cardiovascular side effects between Mn–DPDP and $MnCl_2$ [59,67].

Nevertheless, the diagnostic dose of 10 μmol kg^{-1} of Mn–DPDP may lead to a free manganese blood level higher than that known to potentially produce the first toxic effects (± 2.5 μmol kg^{-1}), considering in vivo a release of 50% of the free manganese from the complex [51,56].

Contrary to the free manganese ion (Mn^{2+}), the Mn–DPDP complex allows urinary excretion of the complexed metal at about 40–45% [68]. Hepatobiliary excretion remains at 45–50% [28,47] and the body retention was found to be ca. 5–6% [28].

After intravenous injection of a 10 μmol kg^{-1} solution of Mn–DPDP, several benign side effects have been reported. Facial flushing was the most frequently encountered [69], the next most common reactions were warm sensations and nausea, metallic taste and headaches [6,69,70].

In conclusion, Mn–DPDP, despite the decomplexation which occurs to a non negligible degree can provide enhanced MRI which offers improved lesion detection and characterisation.

Nevertheless, slow-drip infusion is much better tolerated than more rapid injection [29,71].

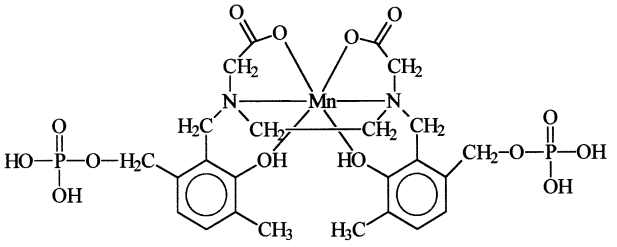


Fig. 1. Dipyridoxyl diphosphate complex of Mn^{2+} (Mn DPDP).

2.1.2. Iron

The transition metal iron contains unpaired electrons. Contrary to the low molecular weight paramagnetic metal chelates (e.g. Mn^{2+}) iron as an oxide is a member of a group of superparamagnetic materials which mainly affect T_2 values. The largest number of unpaired electrons that is attainable for transition metal ions is five (e.g. Mn^{2+} and Fe^{3+}) but iron must not be directly compared with the manganese ion because rather than a water-soluble chelate, slightly soluble particles of iron oxides are used. This contrast agent can be prepared in small and large particles. The larger ones are ferromagnetic and contain multiple alignable magnetic domains whereas the small particles of a few nanometers in diameter have a single alignable magnetic domain and are highly paramagnetic (superparamagnetic).

In vitro measurements indicated that the relaxivity (i.e. the capacity to change proton spin relaxation rate per unit concentration) was 75 times stronger than gadolinium for transverse magnetisation. Iron is a transition metal whose whole-body content is approximately three magnitudes higher than that of manganese and its use as a contrast agent leads neither to a higher level of free iron ions nor to toxicity. The iron released from this contrast agent may become incorporated into the body's iron store hematopoesis [72]. Moreover, ferrumoxide is a biomineral substance that has been found in various organisms such as magnetotactic bacteria, insects, fishes and possibly birds and dolphins in which it is believed to play a role in magnetic navigation. In humans, magnetite was recently found to occur in some parts of the normal brain as an endogenous tissue constituent [73].

With a view to develop a contrast agent for MRI, nanoparticles of magnetite [74] were prepared and bound to dextran [75]. The dextran–magnetite particles (DMP) obtained presented an iron core of 4–10 nm [76]. Intravenous injection of a preparation into rats shows that the DMP has a short half-time of blood clearance (11 min) and was accumulated particularly in the liver [77,78].

Other contrast agents such as ferrumoxtran [79–82], chondroïtin sulfate iron colloïd [83–87], endorem [88,89], ferumoxsil [90], AMI 25 [91–93], AMI 227 [94], magnetic starch microspheres (MSM) [95] and oral magnetic particles (OMP) [96–99] are also used as MRI agents.

Another approach to prepare tailored contrast agents is the labelling of peripherical blood lymphocytes by the liposome-mediated incorporation of dextran–magnetite particles (DMP) [100].

Superparamagnetically labelled neutrophils were used as inflammation-specific contrast agents [101]. Monoclonal antibodies conjugated to magnetic particles were also developed to obtain tailored contrast agents [102].

2.1.3. Other metals

Other elements from the first transition metal group can be used as contrast agents.

2.1.3.1. Copper. Copper has been studied, particularly for Copper(II) pyruvaldehyde bis-(*N*-4-methylthiocarbazone) [103,104] and several isotopes of Copper such as ^{62}Cu, ^{65}Cu, ^{67}Cu were also bound to serum albumine [104].

2.1.3.2. Chromium. Chromium [105] has been used either as ^{51}Cr for cell radiolabelling or as non radioactive chromium for killer lymphocyte labelling. Non radioactive chromium does not act as an imaging agent and has to be determined using GFAAS after blood sampling.

2.1.3.3. Nickel. Ni–DTPA doped agarose gel is a phantom material for Gd–DTPA enhancement measurements [106,107]. Nevertheless, this element is of little use compared with manganese and iron.

2.1.4. Technetium

In the second period of the transition metals group, Technetium is the most often used contrast agent. In the early 1950s, the discovery of the $^{99}Mo/^{99m}Tc$ generator was a revolution in radiopharmaceutical diagnostics. Indeed, the radiolabelled compounds used before this discovery need the proximity of a Cyclotron to produce radioisotopes.

The development of the ^{99m}Tc generator by W. Tucker and M. Greene allowed the rapid expansion of medical diagnostics.

From the production of pertechnetate in 1960 [108], to the development of ^{99m}Tc sulfur colloïd [109,110], ^{99m}Tc albumin [111,112], ^{99m}Tc diethylenetriamine pentaacetic acid (DTPA) [113–115], ^{99m}Tc diphosphonate [116–118], ^{99m}Tc dimercaptosuccinate [119], ^{99m}Tc isonitriles leading to Sestamibi [120], ^{99m}Tc tetrapeptides leading to mertiatide [121], and finally to ^{99m}Tc labelled cells [122–132].

Two important advances led to the rapid proliferation of ^{99m}Tc in nuclear medicine: the development of a generator $^{99}Mo/^{99m}Tc$ that could be eluted with isotonic saline [133] and the development of a single vital kit containing both the reducing and the chelating agents [114].

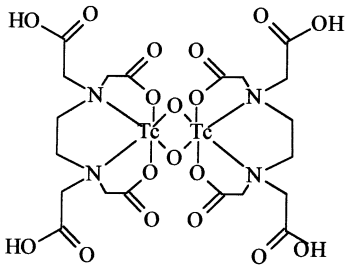
Diagnostic radiopharmaceuticals are generally labelled with single photon-emitting radionuclides. ^{99m}Tc is a radionuclide readily available with optimum decay characteristics and with excellent physical properties (E_γ of 140 keV and $t_{1/2}$ of 6 h), so it became the most heavily used.

Technetium chelates are used in various fields and the chemical structures are quite different from one to another. Information about the three dimensional structure of most Tc complexes has been collected by Dewanjee [134]

Tc complexes might be divided into four classes:

The first class (Fig. 2) includes complexing agents that contain carboxylic acid functions and amine or hydroxyl groups. The ligands most often used are ethylenediamine tetra-acetate (EDTA) (Fig. 2)[134], diethylenetriamine pentaacetate (DTPA) [114,135], citrate [136], gluconate and glucoheptonate [137], inulin [138], caseidine [139], mannitol [140], penecillamin-acetazolamide [141,142], pyridoxylene glutamate (PG), Tetracycline [143] and hepato-diiminodiacetate [144–152] and *N*(2,6-dimethylphenylcarbamoylmethyl)-iminodiacetate derivatives.

The stability constants (K_a) and the lipophilicity ($\log P$) of these chelates are quite different, so they are used to study different organ systems, taking into account the need or not to cross the blood–brain barrier.



Tc EDTA

Fig. 2. Example of a technetium complex of the first class: Tc–EDTA.

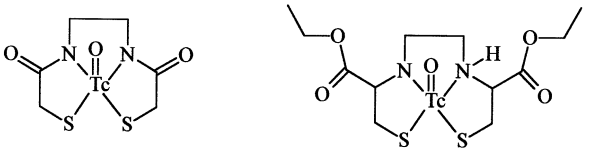
The second class (Fig. 3) includes thiol derivatives that can complex ^{99m}Tc often with a higher stability constant than those chelates of the first class.

Among the numerous agents are, dimercaptosuccinic acid (DMSA) [119], cystein [153], acetylcystein [154], glutathion [155], [*NN*′-bis(mercapto acetamido) ethylenediamine] (DADS) (Fig. 3) [156,157], ketoxa bis(thiosemicarbazone) (KTS) [158], mercaptoacetyltriglycine (MAG3) [149], dihydrotiotic acid [159], mercaptoisobutyric acid [160], 6-mercaptopurine [161] and [*NN*′-1,2-ethylendiyl-bis-L-cystein diethylester (Bicisate®, Neurolite® or ECD) (Fig. 3) [162]. The three dimensional structure and optical properties of Tc–N_xS_y complexes have been studied and correlated to their imaging efficacy [157].

In this class several compounds are interesting for different reasons. DADS and its derivatives are well secreted by the renal tubules and used in the exploration of the kidney system.

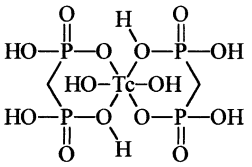
^{99m}Tc–KTS is a neutral lipophilic chelate useful for labelling structure that must cross the phospholipidic membranes.

^{99m}Tc–ECD is a lipophilic chelate that can cross the blood–brain barrier and allows the investigation of the cerebral perfusion. This compound has an ester group which hydrolyses quite slowly in the blood which allows it to preserve its lipophilicity and to cross the blood–brain barrier giving a high cerebral uptake. On the other hand, a fast hydrolysis of the ester function in the brain results in retention of the more hydrophilc metabolite in that organ.



Tc DADS **Neurolite TcECD**

Fig. 3. Examples of a hydrophilic (Tc–DADS) and a lipophilic (Tc–ECD) complexes of the second class.



TcMDP

Fig. 4. Example of a technetium complex of the third class (Tc–MDP).

The third class (Fig. 4) of technetium chelates is characterised by the presence of phosphorus in the derivatives.

This class includes polyphosphate [140,163], pyrophosphate [164], hydroxyethylenediphosphonate (HEDP) [116], methylene diphosphonate (MDP) (Fig. 4) [117], hydroxymethylene diphosphonate (HMDP) [118,165–168] and 1,2-bis [bis-(2-ethoxyethyl) phosphino]ethane (tetrofosmine) [169].

This class is particularly dedicated to investigating bone imaging.

The fourth class (Fig. 5) of technetium chelating agents includes isonitrile and oxime derivatives:(2-methoxy-2-methylpropyl) isonitrile (Sestamibi®) (Fig. 5) [170], [bis[1,2-cyclohexane-dionedioximato(1)-*O*]-[1,2-cyclohexanedione-dioximato(2)-*O*] methyl–borato(2)-*NN′N″N‴N⁗N⁗⁗*]chlorotechnetium (Teboroxime®) [171], numerous derivatives of boronic acid adducts of technetium dioxime complexes (BATOs) (Fig. 5) [172,173], ^{99m}Tc propyleneamineoxime (PNAO) [174], Hexamethyl propyleneamine oxime (HM-PAO CERETEC®) particularly the more efficient D,L HM–PAO isomer (Fig. 5) [175] and ^{99m}Tc 3,3-(1,3 propanediyl-diimino) bis(3 methyl-2-butanoneoxime) (PnAO) [176].

Cyclams, despite their structural analogy with class I complexes, have been cited also among the compounds of this class [175]. The lipophilic agents of class IV are especially used as myocardial and brain perfusion agents.

Tc is the principal radio labelling agent and represents about 85% of the nuclear diagnostic market.

2.1.5. Rhenium

Rhenium is also used in medical imaging but not with much interest [177–179].

2.2. Lanthanides

In the Rare Earth family, gadolinium(III) is the most important imaging agent considering the number of reports using this metal ion.

The lanthanides are also paramagnetic and these MRI contrast agents induce the relaxation of water protons decreasing T_1 and/or T_2 values [16–18,180].

The relaxivity of a paramagnetic metal chelate consists of two components: the inner-sphere and the outer-sphere relaxivities.

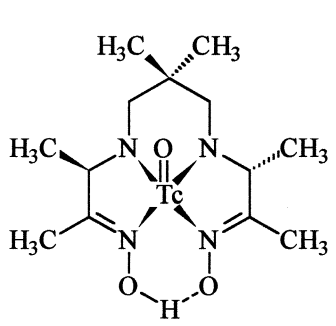
At a fixed radiofrequency (f) the inner-sphere T_1 and T_2 relaxivities ($^{f}r_{1,2}$)is a function of the inner-sphere water coordination number (w), the effective magnetic moment (μ_{eff}), the internuclear distance between the paramagnetic center and water proton (r) and the correlation time (T_c).

$$fr_{1,2} = \frac{w \cdot \mu_{eff}^2 \cdot T_c}{r^6} \tag{1}$$

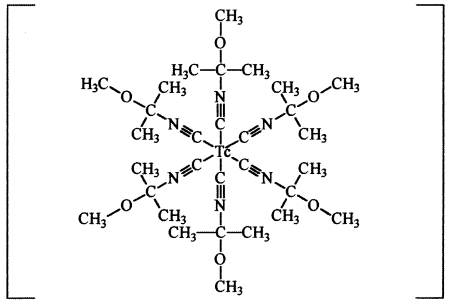
Here the correlation time represents the rotational correlation time (T_r), electron spin relaxation time (T_s) and the inner-sphere water exchange correlation time (T_m) (Fig. 6) as follows.

$$1/T_c = 1/T_r + 1/T_s + 1/T_m \tag{2}$$

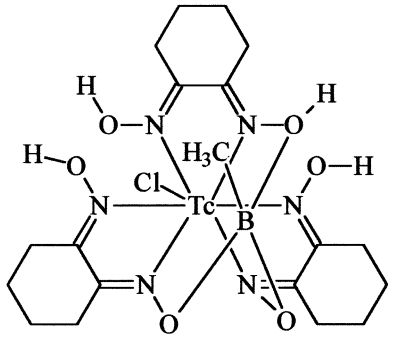
For low molecular weight gadolinium(III) chelates, T_r is the shorter correlation time and overall relaxation rate.



Tc d,l HM PAO CERETEC ™



Tc MIBI



Bato's Cardiotec™

Fig. 5. Examples of technetium complexes of the fourth class: oxime (D,L HM–PAO), bato's (Cardiotec®) and isonitrile (Sestamibi®).

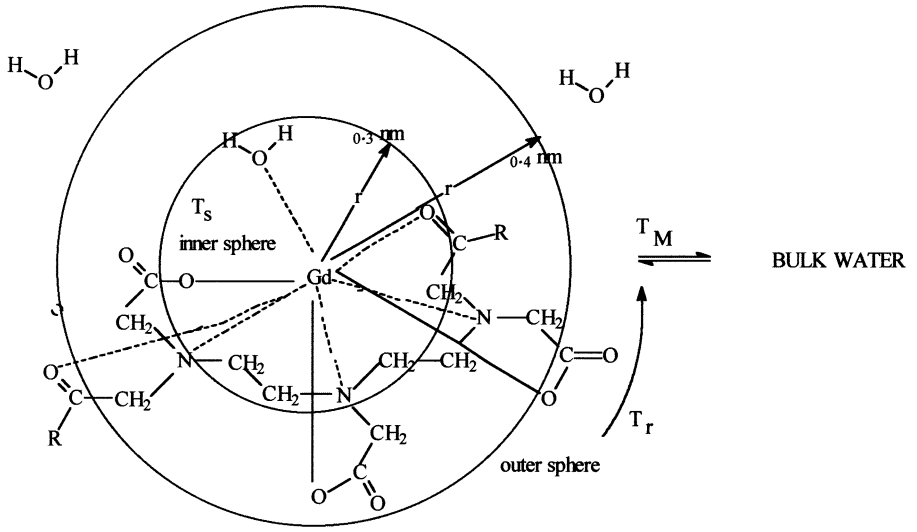


Fig. 6. Interactions between gadolinium complexes and water resulting in relaxation of water protons.

In many Gd chelates, only one water molecule is coordinated to the paramagnetic agent. Gadolinium(III) chelates are found to have greater relaxivities than transition metal chelates, presumably due to gadolinium(III) ion 4f orbitals

Although lanthanides have no known role in living systems, the free ion toxicity is not negligible. Complexes of these ions are tolerated much more by organisms (> 100 fold), leading to the exclusive use Rare Earth metal ion chelate complexes.

2.2.1. Gadolinium

Gadolinium is a lanthanide with an atomic weight of 157.25 g/at. which is a medium weight for a metal of this family. It is used as a gadolinium(III) ion. The physicochemical properties of Gd^{3+} chelates were well reviewed by Chang [181] especially for gadodiamide. Gadolinium(III) binds weakly with serum proteins and can be displaced by ligands such as citrate [182,183]. Injected as ionic solutions, lanthanide salts generally hydrolyse to form hydroxides that are taken up by the reticuloendothelial system, with accumulation in the body, especially in the liver, spleen and bone [183–185]. The lanthanide ion excretion paths are both urine and faeces [183,184] in contrast to the manganese ion for example where the gastro-intestinal elimination route is almost exclusive [22,36,46,51,52]. As a metal chelate, the renal excretion is greatly increased and consequently the toxicity decreases [186,187].

The Gadolinium(III) is complexed by various chelates to form three different groups:

- ionic and hydrophilic complexes,
- non ionic and hydrophilic complexes,
- ionic and lipophilic complexes.

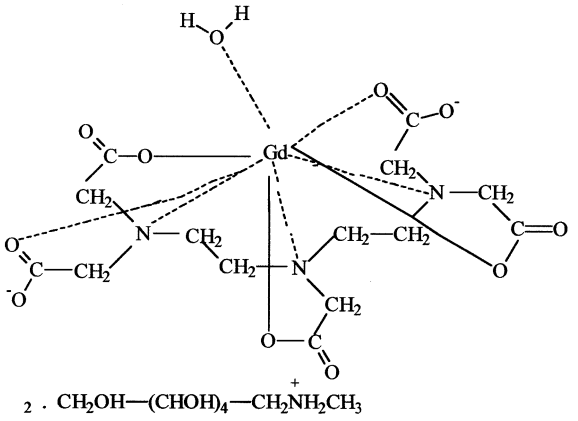


Fig. 7. Gadopentetate Magnevist™ (Gd–DTPA).

The first group includes gadolinium(III) diethylenetriamine penta-acetate (Gd–DTPA, Gadopentetate; Fig. 7), Gd(III) 1,4,7,10 tetrazacyclododecane *NN′N″N‴*-tetra-acetate (Gd–DOTA, Gadoterate; Fig. 8) [188] and Gd(III) polyaspartate [189]. These gadolinium(III) complexes are generally octacoordinated chelates. The stability of the gadolinium chelates is very important, with pK_a values often greater than 20 [190,191]. So after injection of a 0.1 mmol kg^{-1} solution (clinical dose) the free gadolinium ion concentration in the blood is below the detection limits of most analytical methods. Moreover, Gadolinium chelates are cleared from the body by the kidneys before an equilibrium concentration can be attained by reaction with the cations (Zn^{2+}, Cu^{2+},...) and the anions (PO_4^{3-}, OH^-, CO_3^{2-}) present in the blood.

The synthetic homopolypeptide polyaspartate (30 000 kD) binds up to 40 gadolinium(III) ions per mole of polymer and the relaxivity of this compound is higher than that of commonly used gadolinium chelates.

Gadolinium contrast agents are generally administrated by infusion. Initially, the gadolinium chelate is only located in the blood which represents about 8% of the

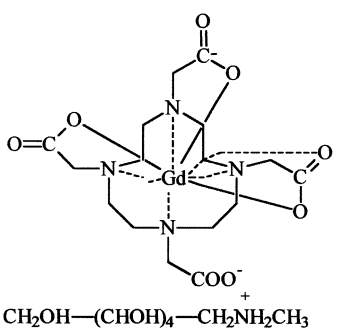


Fig. 8. Gadoterate Dotarem™ (Gd–DOTA).

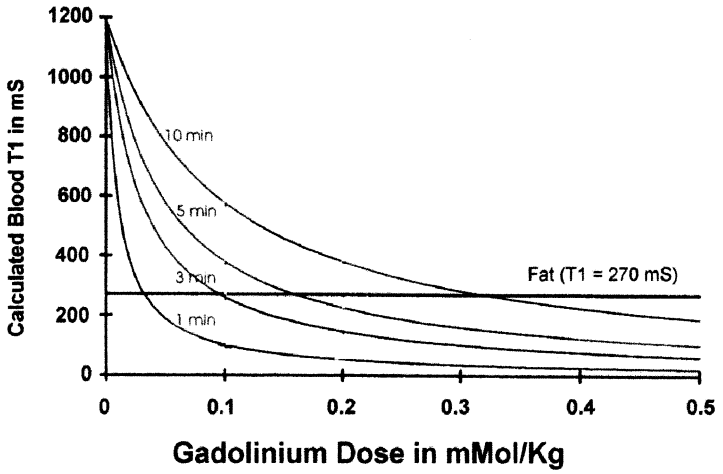


Fig. 9. Calculated values for blood T_1 as a function of infused gadolium dose and infusion time compared to fat T_1 (background).

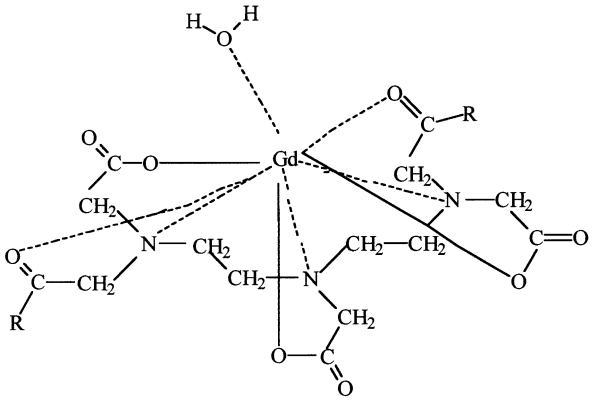
body mass. After a few minutes, gadolinium is redistributed into the extra cellular fluid space which constitutes about 30% of the body mass. To shorten the T_1 relaxation time of the water proton of the blood or target organ, the concentration of the gadolinium solution injected and the infusion rate are two important parameters.

The acquisition time is also an important factor which must take into account the distribution of the contrast agent in the body, to visualise the compartment (blood) or the target organ to be analysed.

For example, to make blood appear bright compared with background tissues, it is necessary to give a sufficient dose of gadolinium to make the blood T_1 short compared with the T_1 of background tissues. For a gadolinium chelate with a relaxivity of 4 mM^{-1} s^{-1} [181] and assuming that blood represents about 8% of the body mass and that no recirculation occurs, the blood T_1 calculated values for various infusion times, are shown in Fig. 9. A gadolinium dose of at least 0.2 mmol kg^{-1} is needed after allowing for redistribution into the extracellular fluid compartment, to make the blood T_1 short compared with the T_1 of the background represented by fat ($T_1 = 270$ mS).

The second class is represented by non ionic (neutral) hydrophilic chelates of gadolinium(III) such as: Gd^{3+} diethylenetriamine penta-acetate bismethylamide (Gd–DTPA–BMA, Gadodiamide) (Fig. 10) and a macrocyclic chelate analog of Gd–DOTA where an acetic acid function is replaced by a 2-propanol radical (Gd–HP–DO3A, gadoteridol) (Fig. 11) [181]. The same considerations on stability and clearance of gadolinium chelates of the second class can be done [191].

The third class of gadolinium complexes includes the Gd benzyl-oxy-methyl derivative of diethyltriamine penta-acetate dimethylglucamine salt (Gd–BOPTA.dimeg) and Gd ethoxybenzyl diethylentriamine pentaacetate (Gd–EOB–DTPA) (Fig. 12) [192–196].



R = $NHCH_3$: **Gadodiamide Omniscan™**

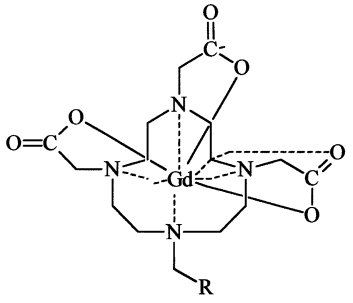
Fig. 10. Example of a gadolinium complex of the second class.

The Gd–BOPTA chelate is cleared mainly by the kidneys and at 2–4% via the hepatobiliary system [197–203]. The Gd–EOB–DTPA chelate appears less hydrophilic than the Gd–BOPTA chelate (Fig. 13) and is cleared by the hepatobiliary system at about 50% of the injected dose, the remaining amount being excreted via the kidneys [199,202,204]. Although Gd–EOB–DTPA is characterised by much more hydrophilic properties than the gadolinium complexes of the class two, it shows an hepatocellular specific uptake [193,194]. These two agents are well tolerated and no toxic actions were observed [197,198,203–207].

2.2.2. Other lanthanides

Several other lanthanides were used as magnetic resonance imaging agents but are uncommon.

Lanthanum, cerium, praseodimium, dysprosium, ytterbium and lutetium were investigated as liver specific contrast agents [192], but showed no advantages over



R = $CH(OH)CH_3$: **Gadoteridol Prohance™ (GdHP DO_3A)**

Fig. 11. Example of a neutral hydrophilic chelate of the second class.

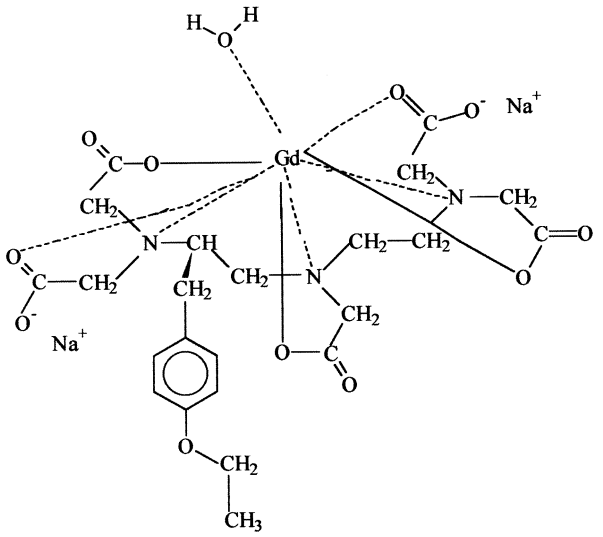


Fig. 12. (4*S*)-4-(4-ethoxybenzil)-3,9-(carboxylatomethyl)-3,6,9-triazaundecandioic acid disodium salt, Gd complex (EOB–DTPA).

more commonly used compounds. These were studied as the EOB–DTPA chelate as an iodine-free liver specific contrast agent.

Europium is frequently used as a tracer in time resolved fluoroimmunoassays [208]. For MRI, the Eu–DTPA chelate has been used to label target cells [209].

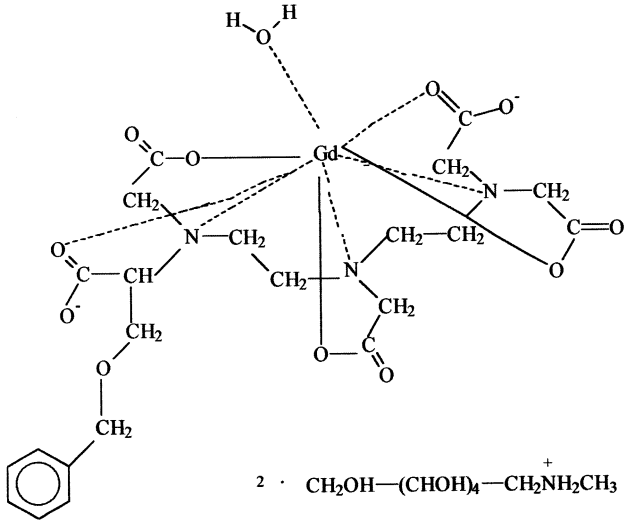


Fig. 13. 4-carboxy-5,8,11-tris-(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-cac acid, salified with meglumine, Gd complex (Gd–BOPTA/dimeg).

Dysprosium is also proposed as a lanthanide complex, with DTPA–BMA as a ligand in myocardial investigations [12] and as a potential marker of cell membrane integrity [210], with HP–DO3A as a ligand in brain investigations [211].

Holmium ^{166}Ho microspheres were proposed for hepatic investigations by computer tomography (SPECT)[212].

Ytterbium is also used as diagnostic agent with ^{169}Yb cis dichlorodimethionine platinum in scintigraphy [213,214].

3. Labelling methods

Technetium is the radionuclide used most in the labelling of biological molecules. The binding of technetium to organic compounds can be recognised in two ways corresponding to low affinity binding and high affinity binding, respectively.

3.1. Low affinity binding

High capacity but low affinity sites exists in a protein, such OH, NH_2 and COOH radicals that can be bound with ^{99m}Tc by incubation. These sites represent about 80% of the capability of protein binding [215]. Nevertheless, ^{99m}Tc bound to the low affinity sites can be removed by the diethylenetriamine pentaacetate free ligand (DTPA). So research has been focused on devising methods to bind ^{99m}Tc to the more stable high affinity sites to avoid the release of free Tc ions in the body.

3.2. High affinity binding

The low capacity but high affinity sites represent about 20% of the total binding sites of proteins. The high affinity binding sites are thought to be associated with sulphydryl groups [215,216]. Additional sulphydryl groups can be produced by reduction of the disulphide bonds existing in the protein structure. Stannous chloride provides a slow and mild reduction that does not destroy all interchain disulphide linkages [217–219]. Nevertheless, Fab and $F(ab')_2$ fragments are more sensitive to stannous reduction. Monoclonal antibodies labelled with ^{99m}Tc using a pretinning method are stable in vitro against a challenge with EDTA and human serum albumin. They exhibit a similar immunoreactivity as radioiodinated compounds. The binding of high affinity sites is realised through a transfer ligand that has a weak affinity for the ^{99m}Tc ion.

3.3. Labelling of molecules

3.3.1. Peptides

Two methods have been used to label peptides with ^{99m}Tc:

- the direct method,
- the bifunctionnal chelating agent method.

3.3.1.1. Direct method. The direct method binds technetium to sulphydryl groups that have been produced by reduction of a cysteine bridge in the peptide.

The direct method is simple, rapid, efficient and may be realised with easily available reagents [220–223].

3.3.1.2. Bifunctional chelating agent method. The general procedure consists in protecting the free amino groups of lysine by a BOC protective group, then the bifunctionnal chelating agent is attached to the terminal amino group of the peptide by an amide bond. The BOC protection is removed and the conjugate purified by HPLC before labelling with technetium via a transchelation process [222,224–228].

The most commonly used peptides as radiopharmaceuticals are octreotide [220,221], RC 160 [220–222,229,230], peptides for imaging infection [226,227,231] and vascular thrombi [232–235].

3.3.2. Fab fragments

The direct method for labelling Fab′ fragments may use the pretinning method [217] or the Schwartz method [236] using 2-mercaptoethanol or 2-aminoethanethiol as a reducing agent. The free sulphydryl groups generated are labelled with ^{99m}Tc. The labelling efficiency is greater than 95% and the in vivo stability is good [237].

As an alternative to generating endogenous free sulphydryl groups, free thiol groups may be introduced into immunoglobulin through reaction with 2-iminothiolactone [238].

3.3.3. Antibodies

Peptides and antibodies can be labelled in two ways:

- the direct labelling method,
- the indirect labelling method.

3.3.3.1. The direct labelling method. In this technique, two types of binding sites can be bound to Technetium. It is important that the low affinity binding sites do no react with Technetium, because after an in vivo injection, free Technetium may be detected in the blood. The high affinity binding sites, are thought to be associated with free sulphydryl groups [217,216]. More sites can be produced as before by reduction of disulphide bonds on the immunoglobulin molecule (Fig. 14) [217]. The labelled ^{99m}Tc antibodies obtained by the pretinning method are stable in vitro and in vivo. If less than 4% of the disulphide bonds are reduced, the structural integrity is relatively preserved [218,239].

The Schwartz method uses 2-mercaptoethanol or 2-aminoethanethiol as reducing agents [241]. The incubation time is shorter than that of the pretinning method ($\pm$30 min) but it is necessary to eliminate the excess of reducing agent by size exclusion chromatography. The free sulphydryl sites are then labelled with ^{99m}Tc by transcomplexation of the ^{99m}Tc from a weaker ligand such as pyrophosphate, phosphonate, gluconate, glucoheptonate or glucarate [241]. It seems that reduced antibodies may be stored frozen on lyophilised for subsequent labelling with ^{99m}Tc [240,241].

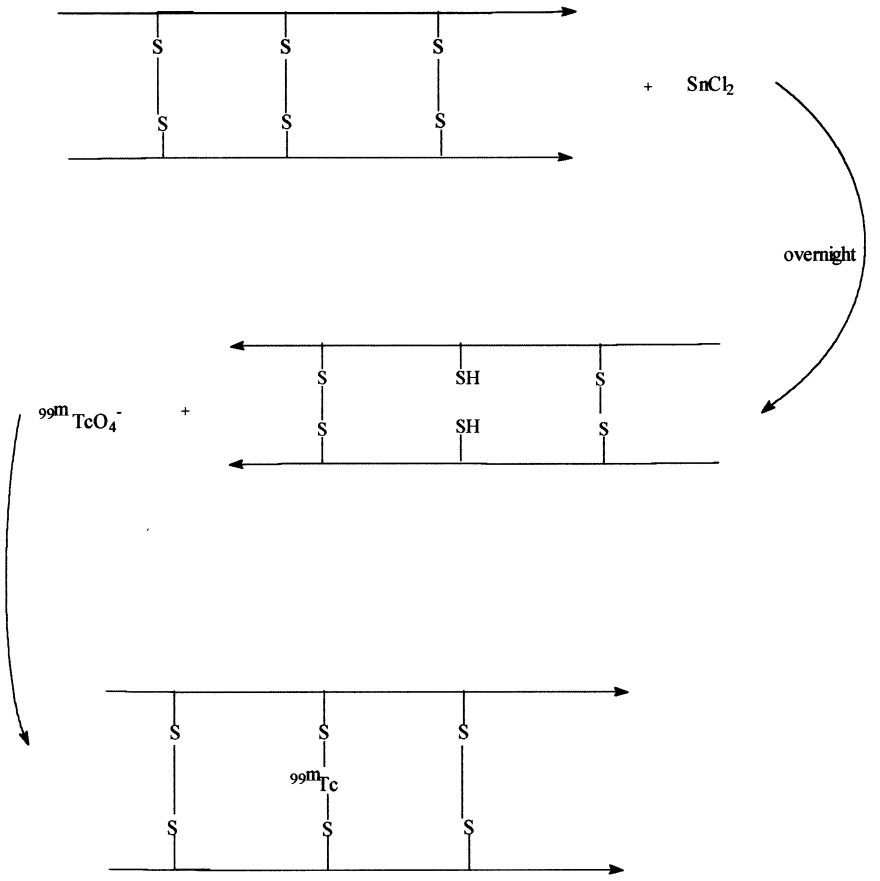


Fig. 14. Pretinning method.

3.3.3.2. Indirect labelling methods. Attempts were made to label monoclonal antibodies by ^{99m}Tc through a DTPA immunogobulin complex as used for ^{111}In, but non specific labelling with low affinity sites of the protein occurred [215,242,243]. Better labelling was obtained by replacing DTPA by metallothionein ligand and transchelation of ^{99m}Tc from a weaker ligand [140].

To avoid binding of Technetium to the low affinity sites of the protein, a preformed chelate approach has been used (Fig. 15) [244,245]. A thiolactone diaminodithiol chelating agent was used to give a ^{99m}Tc stable complex [246] the pertechnetate being reduced with stannous chloride or sodium dithionite [243,244,247,248].

The complex is then converted to an active ester for conjugation to the lysine groups on the immunoglobulin. This technique gives an efficiency of 35–50%. Nevertheless, the technetium complex is well defined and stable [242] and this method allows one to label $F(ab')_2$ fragments without undesired cleavage.

By substitution of the immunoglobulin with three chelating groups, Baidoo et al. [246] were able to achieve a relatively high labelling efficiency of the antibody directly with ^{99m}Tc without the need for a preformed chelate approach.

Najafin et al. synthesised Tetrakis (diaminotetrathiol [249] whereas Yokoyama et al. prepared keto-bis-thiosemicarbozone bifunctionnal chelates [250] and Schwartz et al. synthesised N. hydroxysuccinimide ester of 6 hydrazinonicotinic acid [251,252]. The latter appears to give high specific activity peptides and proteins.

The $^{99m}TcO_2N_4$–biotin chelate was used to label biotinylated antibodies [253].

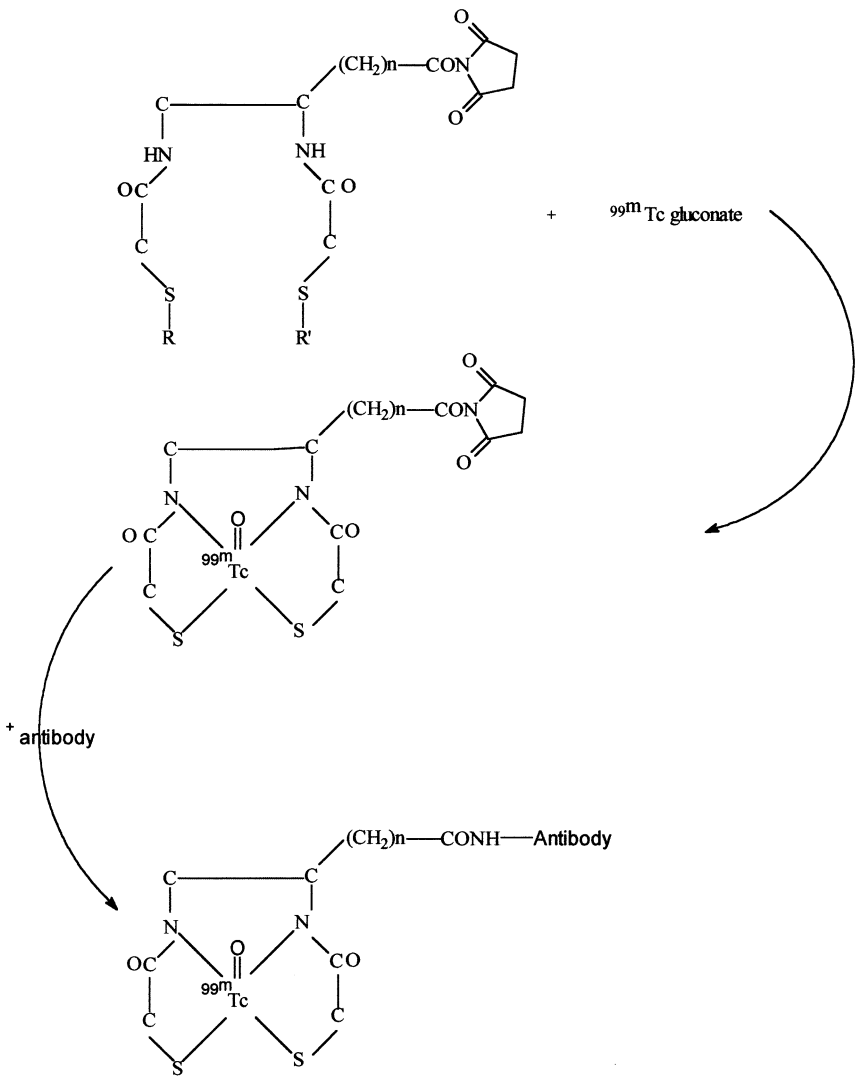


Fig. 15. Example of a preformed chelate approach.

Magnetite particles were also used to label antibodies as contrast agents for MRI. In one procedure, magnetite was bound to dextran (DMP) in the first step to give hydrophilic particles of well controlled size [75]. Then the DMP was bound to biotin. In a second procedure, monoclonal antibodies were biotinylated and streptavidin was added. The high affinity of streptavidin to biotin allows an irreversible linkage of the former. Then the biotinylated DMP was added and the labelled MRI agent was obtained in the sequence: monoclonal antibody → biotin → streptavidin → biotin DMP [254–256].

3.3.4. Cells

Various labelling agents were used to label cells and especially ^{111}In and ^{99m}Tc. In this review, only ^{99m}Tc is discussed.

3.3.4.1. White blood cells (WBC). ^{111}In labelled WBC have been available since the early 1970s, although ^{99m}Tc labelled WBC were only developed in the 1980s [122–128,257,258]. One of the more commonly used labelling agents is ^{99m}Tc hexamethylpropyleneamine oxime (HMPAO). However, treatment with labelled WBC require a blood separation and reinfusion procedure which limits its advantage.

Magnetite particles were also used to label WBCs. There were bound to dextran in a first step, with control of the size shown to be 4–12 nm [75]. Subsequently, the labelling of WBCs was realised by liposome mediated incorporation [100].

3.3.4.2. Red blood cells (RBC). ^{99m}Tc RBC have been available since the late 1970s [130,131,259–261]. In the beginning, an in vivo technique was used in which a kit-derived tin ion containing a phosphate bone imaging agent was administrated intravenously. After a brief period of equilibration, the pertechnetate was also administrated intravenously. Then, the tin ion-sensitised RBCs bind free ^{99m}Tc but the labelling efficiency is relatively low ($\pm$ 85%) and free technetium could be taken up by various organs [132].

Then, in vitro procedures were developed, the first one by Brookhaven National Laboratories with about 92% labelling efficiency but with a blood separation and reinfusion procedure and a second one by Mallinckrodt Medical with a 96% labelling efficiency.

4. Contrast agents for diagnostic applications

4.1. Vascular structures

Gadolinium chelates are used to investigate vessels [262–266]. The T_1 shortening effect of gadolinium increased the blood signal-to-noise ratio of MR angiography pulse sequences. Gadolinium pentetate dimeglumine (Gd–DTPA–DME) is one of the most commonly used gadolinium chelates in this investigation [262,267–270].

^{99m}Technetium included in liposomes or polyethylene coated liposomes [271] have also been used recently as ^{99m}Tc red blood cells. ^{99m}Tc platelets have been proposed also for thrombus imaging [272].

4.2. Liver

Gadolinium chelates were used in the investigation of the liver. Non specific agents such as Gd diethylentriamine pentaacetate (GD–DTPA) gadoteridol and gadodiamide, are used frequently [181,273] and the conspicuity of liver metastases is improved substantially with dynamic MRI [274].

More specific agents: Gd–BOPTA.DMG, Gd–EOB.DTPA and Gd–2,5-BPA–DO3A are used as lipophilic agents allowing then to be selectively taken up by the hepatocytes and its mechanism of transport [198,199,202–206,275–283].

Technetium chelates especially hepato-iminodiacetic acid derivatives were used also as RI contrast agents in this field [116,147–152,284–286].

4.3. Spine and brain

Gadolinium DTPA and gadolinium chelates salified by meglumine and gadodiamide without significant adverse effects were used to investigate the spine and brain [287–300].

Recent data suggest that using dysprosium chelates (Dy–HP–DO3A) could result in higher contrast [301]. Attempts based on Gd MRI have been made also to discriminate Alzheimer disease [302] Technetium chelates such as Tc–PNAO, Tc–HMPAO and Tc–ECD were used also especially to investigate cerebral blood perfusion [135,162,173–175,303]. Tc–ECD and analogues can be used in diseases that do not disrupt the blood–brain barrier.

4.4. Heart

Technetium chelates as RI contrast agents were used often. The lipophilicity of the molecules must be higher than that of Tc–DTPA. The class four chelates with sestamibi, tetrofosmin and teboroxime are typically the most well adapted to these investigations [169,170,172,304].

Positively charged lipophilic technetium chelates, such as sestamibi [119] and tetrofosmine [169] with a half-life of more than 12 h are used in heart exploration. Neutral ^{99m}Tc chelates such as teboroxime, one of the boron adducts of technetium dioximes (BATOs), are rapidly taken up by the myocardium and released rapidly [168,305–308]. With teboroxime imaging must be completed within 10 min after injection.

A review of Tc cardiac agents has been published by Leppo, DePuey and Johnson [304]. No specific contrast enhancers are proposed for MRI of the heart but paramagnetic metalloporphyrins developed early for tumour imaging have been tested as markers of myocardial infarcts [309].

4.5. Colorectal

Technetium is used as a labelling agent [310] to image colorectal carcinoma. In this field, ^{99m}Tc radiolabelled antibodies or Fab′ fragments are commonly used [311–314]. Gd–texaphyrin has been investigated for human colon cancer xenograft detection in mice [315].

4.6. Kidneys

Technetium contrast agents were used, especially the class one comprising chelating agents such as DTPA, DOTA and polyaspatate, to investigate kidneys [121,134–136,141,142,316,317].

MRI is not currently used for kidney imaging but dynamic measurements could be useful for studying renal function non invasively [318].

4.7. Skeleton

Technetium phosphorus (third class as described above) complexes were used as contrast agents in this field [163–166].

4.8. Lungs

Technetium chelates and technetium labelled antibodies were used as contrast agents in investigations of the lungs [319,320].

Only dynamic procedures allow one to discriminate malignant from benign nodules using MRI after bolus injection of Gd contrast agents [321].

4.9. Abdominal disease

^{99m}Tc was used also to label contrast agents and red blood cells that are used in the investigation of abdominal diseases [322].

Hexamethylpropylene amine oxime (HMPAO) is one of the chelates used in this field [122–128,323,324].

References

[1] W.M. Tunbridge, P. Harsoulis, A.W. Goolden, Br. Med. J. 3 (1974) 89.
[2] R.S. Yalow, S.A. Benson, J. Clin. Invest. 39 (1960) 1157.
[3] R.M. Reilly, Nucl. Med. Commun. 14 (1993) 347.
[4] S.S Zoghbi, M.L. Thakur, A. Gottschalk, et al., J. Nucl. Med. 22 (1981) 32.
[5] A. Buck, N. Nguyen, C. Burger, S. Ziegler, L. Frey, G. Weigand, et al., Eur. J. Nucl. Med. 23 (1996) 1619.
[6] B. Hamm, T.J. Vogl, G. Branding, B. Schuell, M. Taupitz, K.J. Wolf, et al., Radiology 182 (1992) 167.
[7] S. Lundqvist, S.O. Hietala, K. Karp, Acta Radiol. 36 (1995) 58.

[8] W.C. Eckelman, Eur. J. Nucl. Med. 22 (1995) 249.
[9] G.L. Griffiths, D.M. Goldenberg, H. Diril, H.J. Hansen, Cancer 73 (1994) 761.
[10] A.C. Chang, Invest. Radiol. 28 (1993) S21.
[11] W. Krause, G. Schuhmann-Giampieri, M. Bauer, W.R. Press, P. Muschick, Invest. Radiol. 31 (1996) 502.
[12] S. Nilsson, G. Wikstrom, A. Ericsson, M. Wikstrom, A. Oksendal, A. Waldenstrom, et al., Acta Radiol. 37 (1996) 27.
[13] B. Misselwitz, A. Mühler, H.-J. Weinmann, Invest. Radiol. 30 (1995) 611.
[14] D.J. Hnatovich, Nucl. Med. Biol. 17 (1990) 49.
[15] D.J. Hnatovich, Semin. Nucl. Med. 20 (1990) 80.
[16] R.B. Lauffer, Chem. Rev. 87 (1987) 901.
[17] A.D. Watson, S.M. Rocklage, M.J. Calvin, Contrast media, in: D.D. Stark, W.G. Bradley (Eds.), Magnetic Resonance Imaging, 2nd edn., CV Mosby, St. Louis, MO, 1991.
[18] M.F. Tweedle, Relaxation agents in NMR imaging, in: J.-C.G. Bunzli, G.R. Choppin (Eds.), Lanthanide Probes in Life, Chemical and Earth Sciences, Elsevier, New York, NY, 1990, pp. 127–179.
[19] I. Bertini, C. Luchinat, Unpaired electron-nuclear coupling detected in NMR: nuclear relaxation, in: NMR of Paramagnetic Molecules in Biological Systems, Benjamin/Cummings, Menlo Park, CA, 1986.
[20] P.C. Lauterbur, M.H. Mendonca-Dias, A.M. Rudin, Front. Med. Biol. Eng. 1 (1978) 752.
[21] H.A. Schoerder, J.J. Balassa, I.H. Tipton, J. Chronic. Dis. 19 (1966) 545.
[22] M. Saric, Manganese, in: L. Friberg, G.F. Nordberg, V.B. Vouk (Eds.), Handbook on the Toxicology of Metals: Specific Metals, vol. II, Elsevier, Amsterdam, 1986, pp. 354–377.
[23] C.S. Reddy, A.W. Hayes, Food-born toxicants: manganese, in: A.W. Hayes (Ed.), Principles and Methods of Toxicology, Raven Press, New York, 1989, pp. 67–110.
[24] E.J. Underwood, Tace elements, in: E.J. Underwood (Ed.), Toxicants Occuring Naturally in Foods, National Academy of Sciences, Washington, DC, 1973, pp. 43–87.
[25] H.G. Seiler, A. Sigel, H. Siegel (Eds.), Handbook on Metals in Clinical and Analytical Chemistry, Marcel Dekker, New York, 1994, p. 467.
[26] K.O. Lim, D.D. Stark, P.T. Leese, A. Pfefferbaum, S.M. Rocklage, S.C. Quai, Radiology 178 (1991) 79.
[27] B. Hamm, T.J. Vogl, G. Branding, B. Schuell, M. Taupitz, K.J. Wolf, et al., Radiology 182 (1992) 167.
[28] G. Elizondo, C.J. Fretz, D.D. Stark, S.M. Rocklage, S.C. Quay, D. Worch, et al., Radiology 178 (1991) 73.
[29] H.B. Gehl, R. Urhahn, K. Bohndorf, P. Klever, S. Hauptmann, K.P. Lodemann, et al., Radiology 186 (1993) 795.
[30] D. Grand, E. Holtz, K. Zech, Proceedings of the 10th Annual Scientific Meeting of ESMRMB, Rome, Italy, 1993, p. 251.
[31] Y. Baba, M.M. Lerch, A. Tanimoto, B.P. Krept, A.K. Saluja, L. Zhao, et al., Invest. Radiol. 29 (1994) S300.
[32] K. Wieghardt, Angew. Chem. 101 (1989) 1179.
[33] R.M. Leach, M.S. Liburn, World Rev. Nutr. Diet. 32 (1978) 123.
[34] G.C. Cotzias, Physiol. Rev. 38 (1958) 503.
[35] D. Borg, G.C. Cotzias, J. Clin. Invest. 37 (1958) 1269.
[36] M. Aschner, J.L. Aschner, Neurosci. Biobehav. Rev. 15 (1991) 333.
[37] J. Falbe, M. Regitz (Eds.), Römpp Chemie Lexikon, Georg Thieme Verlag, Stuttgart, 1991, pp. 2624–2625.
[38] F. Hauschild, Pharmakologie und Grundlagen der Toxikologie, Thieme, Leipzig, 1961, p. 409.
[39] A. Barbeau, Neurotoxicology 5 (1984) 13.
[40] R.A. Goyer, Toxic effect of metals, in: C.D. Klaassen, M.O. Amdor, J. Doull (Eds.), Casarette and Doull's Toxicology: The basic Science of Poisons, MacMillan, New York, 1986, p. 582-635.
[41] D.J. Horvath, Trace elements and Health, in: P.M. Newberne (Ed.), Trace Substances and Health: A Handbook, Marcel Dekker, New York, 1976, pp. 319–356.

[42] M.F. Utter, Med. Clin. N. Am. 60 (1976) 713.
[43] V.H. Ferm, Adv. Teratol. 5 (1972) 51.
[44] A. Lyden, B.S. Larsson, N.G. Lindquist, World Health Organ. 52 (1983) 205.
[45] S.A. Mirowitz, T.J. Westrich, J. Hirsch, Radiology 181 (1991).
[46] H. Carswell, Q. Mag. Magn. Reson. Spring (1992) 7.
[47] S.M. Rocklage, S.C. Quay, D. Worah, Diagn. Imaging Int. (1988) 78.
[48] T.J. Mosher, P.G. Lacey, T.F. Barron, K.P. McNamara, A.G. Devenyi, Increased signal intensity in the basal ganglia on T_1-weighted MRI correlates with elevated erythrocyte manganese in patients with chronic liver desease. Proceeding of the 2nd Meeting SMR, San Francisco CA, 1994.
[49] R.A. Gibbons, S.N. Dixon, K. Hallis, A.M. Russell, B.F. Sanson, H.W. Simonds, Biochim. Biophys. Acta 444 (1976) 1.
[50] F.S. Archibald, C. Tyree, Arch. Biochem. Biophys. 256 (1987) 638.
[51] P.I. Folb, Manganese toxicity, in: M.N.G. Dukes, J.K. Aronson (Eds.), Side Effects of Drugs Annual, vol. 16, Elsevier, Amsterdam, 1993, p. 406.
[52] R. Penalver, Ind. Med. Surg. 24 (1955) 1.
[53] D.J. Sanchez, J.L. Domingo, J.M. Llobet, C.L. Keen, Toxicol. Lett. 69 (1993) 45.
[54] Manganese, in: Environmental Health Criteria 17, World Health Organization, Geneva, 1981.
[55] W.S. Webster, A.A. Valois, Neurotoxicology 8 (1987) 437.
[56] K. Wieghardt, Mangan: Ein essentielles Spurenelement. Beiträge der Koordinationschemie. Schering Lecture der Schering Forschungsgesellschaft, Berlin 1993.
[57] G.L. Wolf, L. Baum, Am. J. Radiol. 141 (1983) 193.
[58] D.L. Baly, B. Lönnerdal, C.L. Keen, Toxicol. Lett. 25 (1985) 95.
[59] H. Brurok, J. Schjott, K. Berg, J.O.G. Karlsson, P. Jynge, Invest. Radiol. 30 (1995) 159.
[60] P. Jynge, H. Brurok, J. Schjott, K. Berg, J.O. Karlsson, Physiologic effects of MnDPDP and $MnCl_2$ in isolated rat heart. Proceedings of the 12th Meeting of the SMRM, New York, NY, 1993.
[61] N. Agata, H. Tanaka, K. Shigenobu, Eur. J. Pharmacol. 222 (1992) 223.
[62] W.S. Webster, Teratology 33 (1986) 6b.
[63] S.M. Rocklage, W.P. Cacheris, S.C. Quay, et al., Inorg. Chem. 28 (1989) 477.
[64] S.M. Rocklage, M. Vanwagoner, Hepatobiliary contrast agents: an overview of the development of manganese dipyridoxyl diphosphate (MnDPDP). In: Ferruccients: An overview of the development of manganese dipyridoxyl diphosphate (MnDPDP). In: J.T. Ferrucci, D.D. Stark (Eds.), Liver imaging, Andover Medical, Boston, 1990, pp. 374–383.
[65] L. Lumeng, A. Lui, T.K. Li, J. Clin. Invest. 66 (1980) 688.
[66] S.M. Rocklage, S.C. Quay, D. Worah, Magn. Reson. Imaging 6 (1988) 19.
[67] P. Jynge, A. Asplund, J. Schjott, R. Towart, J.O.G. Karlsson, H. Refsom, Cardiovascular effects of MnDPDP compared to $MnCl_2$. Proceedings of the 2nd Meeting of SMR, San Francisco, CA, 1994.
[68] D.L. White, J.M. Tongol, C.L. Roco, K.A. Muetterties, B.L. Engelstad, Clearence, excretion, and organ distribution of Mn from the MRI contrast agent manganese–dipyridoxal–diphosphate (MnDPDP). Proceedings of the 7th Meeting of the SMRM, San Francisco, CA, 1988.
[69] K.O. Lim, D.D. Stark, P. Leese, A. Pfefferbaum, S.M. Rocklage, S.C. Quay, Radiology 178 (1991) 79.
[70] M.E. Bernardino, S.W. Young, J.K.T. Lee, B. Hamm, M. Laniado, K.P. Lodemann, et al., Radiology 183 (1992) 53.
[71] E. Rummeny, C. Ehrenheim, H.B. Gehl, et al., Invest. Radiol. 26 (1991) 142.
[72] H.G. Seiler, A. Sigel, H Siegel (Eds.), Handbook on Metals in Clinical and Analytical Chemistry, Marcel Dekker, New York, 1994, p. 411.
[73] J.L. Kirschvink, A. Kobayashi-Kirschvink, B.J. Woodford, Proc. Natl. Acad. Sci. USA 89 (1992) 7683.
[74] O. Clement, R. Guimaraes, E. de Kerviler, G. Frija, Invest. Radiol. 29 (1994) 226.
[75] R.S. Molday, D. MacKenzie, J. Immunol. Methods 52 (1982) 353.
[76] J.W. Bulte, M.W. De Jonge, R.L. Kamman, F. Zuiderveen, T.H. The, L. de Leij, et al., Acta Neurochir. -Suppl. 57 (1993) 30.
[77] J.W.M. Bulte, M.W.A. De Jonge, R.L. Kamman, K.G. Go, F. Zuiderveen, B. Blaauw, et al., Magn. Reson. Med. 23 (1992) 215.

[78] D.D. Stark, Eur. J. Radiol. 14 (1992) 124.
[79] M.G. Harisinghani, S. Saini, R. Weissleder, E.F. Halpern, W. Schima, D.L. Rubin, et al., Radiology 202 (1997).
[80] S.J. McLachlan, M. Morris, M.A. Lucas, L.M. Baum, Acad. Radiol. 3 (1996) 295.
[81] P. Reimer, B. Tombach, H. Daldrup, T. Hesse, G. Sander, T. Balzer, et al., Radiology 36 (1996) 124.
[82] L.M. Hamberg, P. Boccalini, G. Stranjalis, G.J. Hunter, Z. Huang, E. Halpern, et al., Magn. Reson. Med. 35 (1996) 168.
[83] Y. Suto, M. Ametani, T. Kato, M. Hashimoto, M. Kamba, S. Sugihara, et al., J. Comput. Assist. Tomogr. 20 (1996) 283.
[84] M. Kamba, Y. Suto, T. Kato, Acta Radiol. 35 (1994) 570.
[85] T. Kato, Y. Suto, T. Matsuo, J. Comput. Assist. Tomogr. 17 (1993) 603.
[86] D. Avnir, S. Braun, O. Lev, M. Ottolenghi, Chem. Mater. 6 (1994) 1605.
[87] Y. Suto, T. Kato, T. Matsuo, M. Kamba, Y. Shimatani, Y. Ohuchi, et al., Acta Radiol. 34 (1993) 226.
[88] E.J. Rummeny, P. Reimer, H. Daldrup, P.E. Peters, Radiology 35 (1995) 252.
[89] R.C. Haldemann Heusler, E. Wight, B. Marincek, J. Magn. Reson. Imaging 5 (1995) 385.
[90] A. Denys, L. Arrive, V. Servois, B. Dubray, D. Najmark, A. Sibert, et al., Radiology 193 (1994) 665.
[91] J.L. Duerk, G.C. Hurst, J. Magn. Reson. Imaging 4 (1994) 413.
[92] B. Ham, M. Reichel, T. Vogl, M. Taupitz, K.J. Wolf, Rofo Fortschr. (1994) 52.
[93] P. Vassallo, C. Matei, W.D. Heston, S.J. McLachlan, J.A. Koutcher, R.A. Castellino, Radiology 193 (1994) 501.
[94] B.P. Kreft, A. Tanimoto, S. Leffler, J.P. Finn, A.N. Oksendal, D.D. Stark, J. Magn. Reson. Imaging 4 (1994) 373.
[95] F.P. Boudghene, T. Bach-Gansmo, J.D. Grange, S. Lame, C. Nantois, C. Wallays, et al., J. Magn. Reson. Imaging 3 (1993) 107.
[96] T. Bach-Gansmo, Acta Radiol.-Suppl. 387 (1993) 1.
[97] D. MacVicar, T.F. Jacobsen, R. Guy, J.E. Husband, Clin. Radiol. 47 (1993) 183.
[98] A.N. Oksendal, T. Bach-Gansmo, T.F. Jacobsen, H. Eide, E. Andrew, Acta Radiol. 34 (1993) 187.
[99] J.W.M. Bulte, L.D. Ma, R.L. Magin, R.L. Kamman, C.E. Hulstaert, K.G. Go, Magn. Reson. Med. 29 (1993) 32.
[100] F.M. Krieg, R.Y. Andres, K.H. Winterhalter, Magn. Reson. Imaging 13 (1995) 393.
[101] M. Suzuki, H. Honda, T. Kobayashi, T. Wakabayashi, J. Yoshida, M. Takahashi, et al., Byori 13 (1996) 127.
[102] H. Young, P. Carnochan, J. Zweit, J. Babich, S. Cherry, R. Ott, Eur. J. Nucl. Med. 21 (1994) 336.
[103] C.J. Mathias, S.R. Bergmann, M.A. Green, J. Nucl. Med. 36 (1995) 1451.
[104] H. Young, P. Carnochan, J. Zweit, J. Babich, S. Cherry, R. Ott, J. Nucl. Biol. Med. 38 (1994) 89.
[105] P. Borella, A. Bargellini, S. Salvioli, C.I. Medici, A. Cossarizza, J. Immunol. Methods 186 (1995) 101.
[106] P.S. Tofts, B. Shuter, J.M. Pope, Magn. Reson. Imaging 11 (1993) 125.
[107] C. Shellabarger, P. Richards, Bulletin of the Medical Department, Brookhaven National Laboratory, July 1960.
[108] H.L. Atkins, P. Richards, L. Sciffer, Nucl. Appl. 2 (1966) 27.
[109] H.S. Stern, J.G. McAfee, G. Subramanian, J. Nucl. Med. 7 (1966) 665.
[110] J.G. McAfee, H.S. Stern, C.F. Fueger, M.S. Baggish, G.B. Holzman, I. Zolle, J. Nucl. Med. 5 (1964) 936.
[111] M.M. Gwyther, E.O. Field, Int. J. Appl. Radiat. Isot. 17 (1966) 485.
[112] P. Richards, H.L. Atkins, Jpn. J. Nucl. Med. 7 (1968) 165.
[113] W.C. Eckelman, P. Richards, J. Nucl. Med. 11 (1970) 761.
[114] W.C. Eckelman, P. Richards, J. Nucl. Med. 10 (1971) 245.
[115] Y. Yano, J. McRae, D.C. Van Dyke, H. Anger, J. Nucl. Med. 14 (1973) 73.
[116] G. Subramanian, J.G. McAfee, R.J. Blair, F.A. Kallfelz, F.D. Thomas, J. Nucl. Med. 16 (1975) 744.

[117] J.A. Bevan, A.J. Tofe, J.J. Benedict, M.D. Francis, B.L. Barett, J. Nucl. Med. 21 (1980) 961.
[118] T.H. Lin, A. Khentigan, H.S. Winchell, J. Nucl. Med. 15 (1974) 34.
[119] B.A. Rhodes, H.S. Stern, J.A. Buchanan, I. Zolle, H.N. Wagner Jr., Radiology 99 (1971) 613.
[120] A. Taylor, D. Eshima, A.R. Fritzberg, P.E. Christian, S. Kasina, J. Nucl. Med. 27 (1986) 795.
[121] G.V. Taplin, N.D. Poe, Radiology 85 (1965) 365.
[122] P. Harper, K.A. Lathrop, A. Gottschalk, USAEC Technical Information Service, 1966, pp. 335–358.
[123] P. Richards, W.D. Tucker, S.C. Srivastava, Int. J. Appl. Radiat. Isot. 33 (1982) 793.
[124] R.F. Fleay, Australas. Radiol. 12 (1968) 265.
[125] W. Hauser, H.L. Atkins, K.G. Nelson, P. Richard, Radiology 94 (1970) 679.
[126] S.L. Kountz, S.H. Yeh, J. Wood, R. Cohn, J.P. Kriss, Nature 215 (1967) 1397.
[127] O. Charamaza, M. Budikova, J. Nucl. Med. 8 (1969) 301.
[128] L.R. Chervu, M.D. Blaufox, Semin. Nucl. Med. 12 (1982) 224.
[129] H.S. Winchell, M.S. Lin, B. Shipley, T. Sargent, A. Katchalsky-Katzir, J. Nucl. Med. 12 (1971) 678.
[130] G. Subramanian, J.G. McAfee, Radiology 99 (1971) 192.
[131] S.E. Halpern, M. Tubis, S.J. Ensow, et al., J. Nucl. Med. 13 (1972) 45.
[132] S.E. Halpern, M. Tubis, M. Golden, J. Kinsa, J. Endow, C. Walsh, J. Nucl. Med. 13 (1972) 723.
[133] C.P. Fliegel, M.K. Dewanjee, L.B. Holman, Radiology 110 (1974) 407.
[134] M.K. Dewanjee, Semin. Nucl. Med. 20 (1990) 1, 5.
[135] P.S. Callery, B. Faith, M.D. Loberg, A.T. Fields, E.B. Harvey, M.D. Cooper, J. Med. Chem. 19 (1976) 962.
[136] H.D. Burns, D.T. Sowa, L.G. Marzilli, J. Pharm. Sci. 67 (1978) 1434.
[137] B.W. Bistow, G. Subramanian, R.L. Heertum, R.W. Henderson, G.M. Gagne, R.C. Hall, J. Nucl. Med. 18 (1977) 455.
[138] H.D. Burns, P. Worley, H.N. Wagner Jr., et al., in: N. Heindel (Ed.), Design of Technetium Radiopharmaceuticals. Chemistry of Radiopharmaceuticals, Masson, New York, 1978, pp. 269–289.
[139] A.J. Van Wyk, P.J. Fourie, W.H. Van Zyl, M.G. Lotter, P.C. Minnaar, Eur. J. Nucl. Med. 4 (1979) 445.
[140] M. Molter, G. Kloss, J. Label. Compd. Radiopharm. 18 (1981) 19.
[141] A.D. Nunn, J. Label. Compd. Radiopharm. 18 (1981) 155.
[142] A.D. Nunn, M.D. Loberg, Hepathobiliary agents, in: R.P. Spenser (Ed.), Radiopharmaceuticals: Stucture–Activity Relationships, Grune and Stratton, New York, 1981, p. 539.
[143] I. Ikeda, O. Inoue, J. Uchida, et al., Proceedings of the First World Congress for Nuclear Medicine, Tokyo, 1974.
[144] G. Subramanian, M.V. Singh, J. Chander, B. Singh, Eur. J. Nucl. Med. 1 (1976) 243.
[145] B. Johannson, P. Syhre, H. Spies, Jahresber. Zent. Kernforsch. Rossendorf Zfk. 312 (1976) 53.
[146] A. Davison, M. Sohn, C. Orvig, et al., J. Nucl. Med. 20 (1979) 641.
[147] A.G. Jones, A. Davison, M.R. La Tegola, J.W. Brodack, C. Orvic, M. Sohn, et al., J. Nucl. Med. 23 (1982) 801.
[148] A. Yokohama, Y. Terauchi, K. Horiuchi, J. Nucl. Med. 17 (1976) 816.
[149] A.R. Fritzberg, S. Kasina, D. Dshima, D.L. Johnson, J. Nucl. Med. 27 (1986) 111.
[150] P. Dugal, E.A. Eikman, T.K. Natarajan, H.W. Wagner Jr., J. Nucl. Med. 13 (1972) 428.
[151] T.H. Lin, A. Khentigan, H.S. Winchell, J. Nucl. Med. 15 (1974) 613.
[152] F.C. Hunt, D.J. Maddalena, M.G.Yeates, Proceeding of First World Congress for Nuclear Medicine, Tokyo, 1974.
[153] S. Vallabhajosula, R.E. Zimmerman, M. Picard, O. Stritzkc, I. Meha, R.S. Hellman, et al., J. Nucl. Med. 30 (1989) 599.
[154] G. Subramanian, J.G. McAfee, E.G. Beu, R.J Blair, R.E. O'Mara, P.H. Rallston, Radiology 102 (1972) 701.
[155] Y. Cohen, R. Perez, R. Henry, A. Bardy, C. Pannecicre, C. R. Acad. Sci. Hebd. Seances Acad. Sci. D 275 (1972) 1719.
[156] J.A. Bevan, A.J. Tofe, J.J. Benedict, J. Nucl. Med. 275 (1980) 967.
[157] D. Eshima, A.R. Fritzberg, A. Taylor, Semin. Nucl. Med. 20 (1990) 28.
[158] A. Yokohama, Y. Terauchi, K. Horiuchi, J. Nucl. Med. 17 (1976) 816.
[159] P. Dugal, E.A. Eikman, T.K. Natarajan, H.W. Wagner Jr., J. Nucl. Med. 13 (1972) 428.
[160] T.H. Lin, A. Khentigan, H.S. Winchell, J. Nucl. Med. 15 (1974) 613.

[161] F.C. Hunt, D.J. Maddalena, M.G.Yeates, Proceeding of First World Congress for Nuclear Medicine, Tokyo, 1974.
[162] S. Vallabhajosula, R.E. Zimmerman, M. Picard, et al., J. Nucl. Med. 30 (1989) 599.
[163] G. Subramanian, J.G. McAfee, et al., Radiology 102 (1972) 701.
[164] Y. Cohen, et al., C. R. Acad. Sci. Hebd. Seances Acad. Sci. D 275 (1972) 1719.
[165] J.A. Bevan, A.J. Tofe, J.J. Benedict, J. Nucl. Med. 275 (1980) 967.
[166] G. Subramanian, J.G. McAfee, R.J. Blair, et al., J. Nucl. Med. 16 (1975) 1137.
[167] A.G. Jones, M.D. Francis, M.A. Davis, Semin. Nucl. Med. 6 (1976) 3.
[168] M.A. Davis, A.L. Jones, Semin. Nucl. Med. 6 (1976) 19.
[169] J.D. Kelly, A.M. Foster, B. Higley, et al., J. Nucl. Med. 34 (1993) 222.
[170] B.L. Holman, A.G. Jones, J. Lister-James, et al., J. Nucl. Med. 25 (1984) 1350.
[171] E.N. Treher, J. Gougoutas, M. Malley, A.D. Nunn, S.E. Unger, J. Label. Compd. Radiopharm. 23 (1986) 118.
[172] A.D. Nunn, T. Feld, E.N. Treher, US patent 4705849 (1987).
[173] K. Linder, T. Feld, P.N. Juri, A.D. Nunn, E.N. Treher, J. Nucl. Med. 28 (1987) 592.
[174] R.D. Neirinnckx, L.R. Canning, I.M. Piper, D.P. Nowotnik, R.D. Pickett, R.A. Holmes, et al., J. Nucl. Med. 28 (1987) 191.
[175] H.F. Kung, Semin. Nucl. Med. 20 (1990) 150.
[176] D.E. Troutner, W.A. Volkaert, T.J. Hoffman, R.A. Holmes, Int. J. Appl. Radiat. Isot. 35 (1984) 467.
[177] G. Rouchias, Chem. Rev. 74 (1974) 531.
[178] W.T. Goedemùans, K.J. Panek, G.J. Ensing, M.T. Delong, in: M. Nicolini, G. Bandoli, U. Mazzi (Eds.), Technetium and Rhenium in Chemistry and Nuclear Medicine, Cortina International Raven, Verona, 1990, p. 595.
[179] J.P. Dizio, C.J. Anderson, A. Davison, G.J. Ehrhardt, K.E. Carlson, M.J. Welch, et al., J. Nucl. Med. 33 (1992) 558.
[180] R.L. Kamman, K.G. Go, L.M. Vencken, H.J.C. Berendsen, Spine 12 (1987) 257.
[181] A.C. Chang, Invest. Radiol. 28 (1993) S21.
[182] S.M. Rocklage, D. Worah, S-H. Kim, Magn. Reson. Med. 22 (1991) 216.
[183] C.H. Evans, The Occurrence and Metabolism of Lanthanides, Plenum, New York, 1990, p. 285.
[184] P.W. Durbin, M.H. Willams, M. Gee, R. Newman, J.G. Hamilton, Proc. Soc. Exp. Biol. 91 (1956) 78.
[185] G. Magnusson, Acta Pharmacol. Toxicol. 20 (1963) 1.
[186] H.J. Weinmann, R.C. Brasch, W.R. Press, G.E. Wesby, Am. J. Radiol. 142 (1984) 619.
[187] W.P. Norris, H. Lisco, A.M. Brues, in: G.C. Kyker, E.B. Anderson (Eds.), Rare Earths in Biochemical and Medical Research, Atomic Energy Commission, Washington, DC, 1956, p. 102.
[188] P.E. Sijens, M.J. van den Bent, P.J. Nowak, P. van Dijk, M. Oudkerk, Magn. Reson. Med. 37 (1997) 222.
[189] J. Seghers, P. De Nayer, C. Beckers, Clin. Chem. 34 (1988) 2160.
[190] C.A. Chang, Eur. J. Solid. State Inorg. Chem. 28 (1991) 237.
[191] W.P. Cacheris, S.C. Quay, S.M. Rocklage, Magn. Reson. Imaging 8 (1990) 467.
[192] W. Krause, G. Schuhmann-Giampieri, M. Bauer, W.R. Press, P. Muschick, Invest. Radiol. 31 (1996) 502.
[193] S.A. Schmitz, A. Muhler, S. Wagner, K.J. Wolf, Invest. Radiol. 31 (1996) 154.
[194] P. Reimer, E.J. Rummeny, K. Shamsi, T. Balzer, H.E. Daldrup, B. Tombach, et al., Radiology 199 (1996) 177.
[195] O. Clement, A. Muhler, V.S. Vexler, R. Kuwatsuru, Y. Berthezene, W. Rosenau, et al., J. Magn. Reson. Imaging 3 (1993) 71.
[196] G. Marchal, X. Zhang, Y. Ni, P. Van Hecke, J. Yu, A.L. Baert, Magn. Reson. Imaging 2 (1993) 665.
[197] F. Cavagna, P. Tirone, E. Felder, et al., in: P.A. Rinck, R.N. Muller (Eds.), New Developments in Contrast Agent Research, Blonay, Switzerland, 1991, p. 83.
[198] C. De Hean, L. Gozzini, J. Magn. Reson. Imaging 3 (1993) 179.
[199] A.N. Oksendal, P.A. Hals, J. Magn. Reson. Imaging 3 (1993) 157.
[200] G. Pirovano, V. Lorusso, P. Tirone, et al., J. Magn. Reson. Imaging 3 (1993).

[201] G. Schuhmann-Giamperi, in: Rinck-Muller (Ed.), New Development in Contrast Agent Research, Proceedings of the Third Special Topic Seminar of the European Magnetic Resonance Forum, Hamburg, 23–25 September, 1992, p. 1–14.
[202] G. Schuhmann-Giamperi, J. Schmitt-Willich, W.R. Press, et al., Radiology 183 (1992) 59.
[203] T.J. Vogl, W. Pegios, C. McMahon, J. Balzer, J. Waltzinger, G. Pervano, et al., Am. J. Roentgenol. 157 (1992) 887.
[204] B.K. Hamm, T. Stars, A. Muehler, et al., Radiology 193 (1994) 275.
[205] P. Reimer, E.J. Rummeny, H. Daldrup, et al., in: The 9th European Congress of Radiology, Vienna, 1995, p. 293.
[206] Shamsi, T. Blazer, H.P. Niendorf, in: The 9th European Congress of Radiology, Vienna, 1995, p. 293.
[207] C. Mayorga, T. Obispo, L. Jimeno, M. Blanca, J. Moscoso del Prado, J. Carreira, et al., Toxicology 97 (1995) 225.
[208] S. Akimoto, T. Ohki, T. Ichikawa, K. Akakura, J. Shimazaki, Hinyokika Kiyo-Acta Urol. Jpn. 40 (1994) 987.
[209] R. Pacifici, S. Di Carlo, A. Bacosi, I. Altieri, S. Pichini, P. Zuccaro, J. Immunol. Methods 161 (1993) 135.
[210] A. Ericsson, T. Bach-Gansmo, F. Niklasson, A. Hemmingsson, Acta Radiol. 36 (1995) 41.
[211] V.M. Runge, J.W. Wells, Invest. Radiol. 31 (1996) 395.
[212] J.H. Turner, P.G. Claringbold, P.F. Klemp, P.J. Cameron, A.A. Martindale, R.J. Glancy, et al., Nucl. Med. Commun. 15 (1994) 545.
[213] K. Kukulski, J. Liniecki, D. Brykalski, O. Zadrozna, J. Kapuscinski, Nucl. Med. Commun. 16 (1995) 747.
[214] W.G. Franke, T. Schmiedel, A. Grundmann, U. Popel, K. Schomacker, J. Gossel, Nuklearmedizin 32 (1993) 188.
[215] C.H. Paik, L.N.B. Phan, J.J. Hong, et al., Int. J. Nucl. Med. Biol. 12 (1985) 3.
[216] J. Steigman, H.P. Willams, N.A. Solomon, J. Nucl. Med. 28 (1987) 721.
[217] B.A. Rhodes, Nucl. Med. Biol. 18 (1991) 667.
[218] B.A. Rhodes, P.A. Zamora, K.D. Newell, E.F. Valdez, J. Nucl. Med. 27 (1986) 685.
[219] E.B. Hawkins, K.D. Pant, B.A. Rhodes, Antibody Immunoconjug. Radiopharm. 3 (1990) 17.
[220] M.L. Thakur, G. Halmos, J. Jan, J. Nucl. Med. 35 (1994) 359.
[221] M.L. Thakur, E. John, J. Il, H.R. Reddy, G. Halmos, A.V. Schally, J. Nucl. Med. 36 (1995) 92.
[222] M.L. Thakur, H. Kolan, R. Wiaderkiewicz, J. Il, R. Duggaraju, Nucl. Med. Biol. 24 (1997) 105.
[223] H. Kolan, J. Li, M.L. Thakur, Peptide Res. 9 (1996) 144.
[224] E.P. Krenning, D.J. Kwekkeboom, W.H. Bakker, W.A.P. Breeman, P.P.M. Kooij, H.Y. Oei, et al., Eur. J. Nucl. Med. 20 (1993) 716.
[225] W.B. Edwards, C.G. Fields, C.J. Andersen, T.S. Pagjeau, M.J. Welch, G.B. Fields, J. Med. Chem. 37 (1994) 3749.
[226] J.W. Babich, W. Graham, S.A. Barrow, S.C. Dragotakes, R.G. Trompkins, R.H. Rubin, et al., J. Nucl. Med. 34 (1993) 2176–2181.
[227] A.J. Fischman, D. Rauh, H. Solomon, J.W. Babich, R.G. Tompkins, D. Kroon, et al., J. Nucl. Med. 34 (1993) 2130–2134.
[228] A.J. Fischman, J.W. Babich, H.W. Strauss, J. Nucl. Med. 34 (1993) 2253.
[229] G. Weckbecker, F. Raulf, B. Stolz, C. Bruns, Pharmac. Ther. 60 (1993) 245.
[230] W.A.P. Breeman, L.J. Hoflan, van der Pluijm, P.M. van Koetzveld, M. de Jong, B. Setyono-Han, et al., Eur. J. Nucl. Med. 21 (1994) 328.
[231] J. Van der Laken, O.C. Boerman, W.J.G. Oyan, M.T.P. van de Ven, J. Makarewicz, R.A.M.J. Claessens, et al., Eur. J. Nucl. Med. 21 (1994) 790.
[232] M. Hosono, N. Sone, K. Endo, Nucl. Med. Biol. 22 (1993) 71.
[233] L.C. Knight, R. Radcliffe, A.H. Maurer, J.D. Rodwell, V.L. Alvarez, J. Nucl. Med. 35 (1994) 80.
[234] S. Lastoria, P. Muto, P. Varella, S.J. Goldsmith, J.D. Bernardy, M. Salvatore, Radiology 300 (1994) 193.
[235] S. Vallabhajosula, K.S.M. Ali, S.J. Goldsmith, H. Lipszyc, D.A. Bastidas, J. Lister-James, S. Buttram, et al., J. Nucl. Med. 34 (1993) 66.

[236] C. Berche, J.P. Mach, J.D. Lombroso, C. Langlais, F. Aubry, F. Buchegger, Br. Med. J. Clin. Res. 285 (1982) 1447.
[237] A.D. Podoloff, Y.Z. Patt, S.A. Curley, E.E. Kim, V.A. Bhadkamkar, R.E. Smith, Semi. Nucl. Med. 23 (1993) 89.
[238] E. Joiris, B. Bastin, J.R. Thornback, Nucl. Med. Biol. 18 (1991) 353.
[239] M.L. Thakur, J. DeFulvio, M.D. Richard, C.H. Park, Nucl. Med. Biol. 18 (1991) 227.
[240] A. Schwartz, A. Steinstrabber, J. Nucl. Med. 28 (1987) 721.
[241] Z.M. Zhang, R.J. Ballinger, K. Sheldon, I. Boxen, Nucl. Med. Biol. 19 (1992) 607.
[242] D. Lanteigne, D.J. Hnatowich, Int. J. Appl. Radiat. Isot 35 (1984) 617.
[243] R.L. Childs, D.J. Hnatowich, J. Nucl. Med. 26 (1985) 293.
[244] A.R. Fritzberg, P.G. Abrams, P.L. Beaumier, Proc. Natl. Acad. Sci. USA 85 (1988) 4025.
[245] A.R. Fritzberg, R.W. Berninger, S.W. Hadley, D.W. Wester, Pharm. Res. 5 (1988) 325.
[246] K.E. Baidoo, U. Scheffel, S.Z. Lever, Cancer Res. (Suppl.) 150 (1990) 799.
[247] S. Kasina, T.N. Rao, A. Srinivasan, J.A. Sanderson, J.N. Fitzner, J.M. Reno, J. Nucl. Med. 32 (1991) 1445.
[248] H.B. Breitz, D.R. Fisher, P.L. Weiden, J.S. Durham, B.A. Ratliff, M.J. Bjorn, et al., J. Nucl. Med. 34 (1993) 908.
[249] A. Najafi, M.M. Alauddin, M.E. Siegel, et al., Int. J. Radiat. Appl. Instrum. B 18 (1991) 179.
[250] Y. Arano, A. Yokoyama, T. Furukawa, K. Horiuchi, T. Yahata, H. Saji, et al., J. Nucl. Med. 28 (1987) 1027.
[251] D.A. Schwartz, M.J. Abrams, M. Hauser, F.C. Gaul, S.K. Larsen, D. Rauh, Bioconjugate Chem. 2 (1992) 333.
[252] M.J. Abrams, M. Juweid, C.I. tenKaate, D.A. Schwatz, M.M. Hauser, F.E. Gaul, et al., J. Nucl. Med. 31 (1990) 2022.
[253] B. Nock, F. Evrard, G. Paganelli, H.R. Mäcke, J. Nucl. Biol. Med. 38 (1994) 460.
[254] P.C. Weber, D.H. Ohlendorf, J.J. Wendoloski, F.R. Salemme, Science 243 (1989) 85.
[255] J.W.M. Bulte, Y. Hoekstra, R.L. Kamman, R.L. Magin, A.G. Webb, R.W. Briggs, et al., Magn. Reson. Med. 25 (1992) 148.
[256] R. Weissleder, A. Bogdanov, M. Papisov, Magn. Reson. Q. 8 (1992) 55.
[257] W.C. Eckelman, P. Richards, W. Hauser, H. Atkins, J. Nucl. Med. 12 (1971) 22.
[258] P.H. Henneman, C.S. Marcus, S.H. Inkelis, J.A. Butler, F.J. Baumgartner, Pediatrics 85 (1990) 838.
[259] D.G. Pavel, A.M. Zimmer, V.N. Patterson, J. Nucl. Med. 18 (1977) 305.
[260] T.D. Smith, P. Richards, J. Nucl. Med. 17 (1976) 126.
[261] S.C. Srivatava, R.L. Chervu, Semin. Nucl. Med. 14 (1984) 68.
[262] J. Haustein, H.P. Niendorf, G. Krestin, T. Louton, Schuhmann-Grampieri, W. Clauss, et al., Invest. Radiol. 27 (1992) 153.
[263] M.R. Prince, Radiology 191 (1994) 155.
[264] M.R. Prince, C. Arnoldus, J.K. Frosili, J. Magn. Reson. Imaging 6 (1996) 162.
[265] M.R. Prince, E.K. Yucel, J.A. Kaufmann, D.C. Harrisson, S.C. Geller, J. Magn. Reson. Imaging 3 (1993) 877.
[266] N.M. Rofsky, J.C. Weireb, M.A. Bosniak, R.B. Libes, B.A. Bimbaum, Radiology 180 (1991) 85.
[267] D.W. Chakeres, P. Schmalbrock, M. Bogan, et al., Am. J. Roetgenol. 156 (1991) 161.
[268] J.L. Creasy, R.R. Price, T. Presbrey, D. Goins, C.L. Partain, R.M. Kessler, Radiology 175 (1990) 280.
[269] T.M. Grist, H.D. Sostman, J.R. McFall, T.K. Foo, C.E. Spitzer, L. Witty, et al., Radiology 189 (1993) 523.
[270] H.J. Cloft, K.J. Murphy, M.R. Prince, J.A. Brunberg, Magn. Reson. Imaging 14 (1996) 593.
[271] E. Varoglu, K.Y. Polat, G. Tastekin, F. Akcay, C. Polat, Clin. Nucl. Med. 21 (1996) 645.
[272] J. Lister-James, S. Vallabhajosula, B.R. Moyer, D.A. Pearson, B.J. McBride, M.A. De Rosch, et al., J. Nucl. Med. 38 (1997) 105.
[273] D.G. Mitchell, MRI Clin. N. Am. (1996) 37.
[274] V.M. Runge, J.W. Wells, N.M. Williams, Invest. Radiol. 31 (1996) 472.
[275] P.V. Harper, R. Beck, D. Charleston, K.A. Lathrop, Nucleonics 22 (1964) 50.
[276] O. Clément, A. Muhler, V. Vexler, Y. Berthezene, R.C. Brasch, Invest. Radiol. 27 (1992) 612.
[277] A. Davies, C. de Haen, Drugs Future 16 (1991) 1001.

[278] M. Rowland, T.N. Tozer, Clinical Pharmacokinetics Concepts and Applications, Lea and Febriger, Philadelphia, 1989, p. 197.
[279] P. Pavone, S. Giuliani, G. Cardone, R. Occhiato, P. Di Rienzi, Q.A. Petroni, Radiology 179 (1991) 693.
[280] A-E Mahfouz, B. Hamm, K-J Wolf, Radiology 190 (1994) 49.
[281] D.G. Mitchell, S. Sanjay-Saini, J. Weinreb, E.E. De Lange, V.M. Runge, J.E. Kuhlman, Radiology 193 (1994) 49.
[282] V.M. Runge, J.W. Wells, N.M. Williams, Invest. Radiol. 31 (1996) 11.
[283] S.A. Schmitz, S. Wagner, G. Schuhmann-Giampieri, W. Krause, K.J. Wolf, Radiology 202 (1997) 407.
[284] B.W. Winston, G. Subramanian, G.M. Gagne, R.W. Henderson, J.G. McAfee, R.C. Hall, et al., Radiology 128 (1978) 793.
[285] R.J. Baker, J.C. Bellen, P.M. Ronai, J. Nucl. Med. 16 (1975) 720.
[286] E. Zerbib, J.Ph. Deutsch, M. Atlani, Y. Hecht, C. Buffet, J. Radiol. 77 (1996) 683.
[287] E.J. Russell, G.K. Geremia, C.E. Johnson, M.S. Huckman, R.G. Ramsey, J. Washbum-Bleck, et al., Radiology 165 (1987) 609.
[288] G.K. Stimac, B.A. Porter, D.O. Olson, R. Gerlach, M. Genton, Am. J. Radiol. 151 (1988) 1185.
[289] P.M. Ruggieri, G.A. Laub, T.J. Masaryk, M.T. Modic, Radiology 171 (1989) 785.
[290] A.D. Elster, D.M. Moody, Radiology 177 (1990) 627.
[291] A. Villringer, B.R. Rosen, J.W. Belliveau, J.L. Ackerman, R.B. Lauffer, R.B. Bricton, Magn. Res. Med. 6 (1988) 164.
[292] S.W. Atlas (Ed.), Magnetic Resonance Imaging of the Brain and Spine, Raven Press, New York, 1991, p. 223.
[293] M.G. Hueftle, M.T. Modic, J.S. Ross, T.J. Masaryk, J.R. Carter, R.G. Wilber, et al., Radiology 167 (1988) 817.
[294] S.D. Boden, D.O. Davis, T.S. Dina, C.P. Parker, S. O'Malley, J.L. Sunner, et al., Radiology 182 (1992) 59.
[295] G. Sze, Radiol. Clin. N. Am. 26 (1988) 1009.
[296] G. Sze, A. Abramson, G. Krol, D. Lin, J. Amster, R.D. Zimmerman, et al., Am. J. Radiol. 150 (1988) 911.
[297] W.P. Dillon, D. Norman, T.H. Newton, K. Bolla, A. Mark, Radiology 170 (1989) 229.
[298] W. Lin, E.M. Haacke, A.S. Smith, et al., J. Magnet. Reson. Imaging 2 (1990) 357.
[299] G. Marchal, J. Michiels, H. Bosmans, P. Van Hecke, J. Comput. Assist. Tomogr. 16 (1992) 25.
[300] S. Ekholm, E. Jonsson, L. Sandvik, M. Fagerlund, S. Holtas, B. Isberg, et al., Acta Radiol. 37 (1996) 223.
[301] V.M. Runge, J.W. Wells, Invest. Radiol. 31 (1996) 395.
[302] G.J. Harris, R.F. Lewis, A. Satlin, C.D. English, T.M. Scott, D.A. Yurgelun-Todd, et al., Am. J. Psychiatry 153 (1996) 721.
[303] R.C. Walovitch, T.C. Hilly, S.T. Garrity, E.H. Cheesman, B.A. Burguess, D.H. O'Leary, et al., J. Nucl. Med. 30 (1989) 1892.
[304] J.A. Leppo, E.G. DePuey, L.L. Johnson, J. Nucl. Med. 21 (1991) 2012.
[305] L.L. Johnson, D.W. Seldin, M. Muschel, et al., Circulation 76 (1987) 217.
[306] D.W. Seldin, L.L. Johnson, D.K. Blood, M.J. Muschel, K.F. Smith, R.M. Wall, et al., J. Nucl. Med. 30 (1989) 312.
[307] D.J. Meerdink, M. Thuber, S. Savage, et al., J. Nucl. Med. 29 (1988) 972.
[308] R.K. Narra, A.D. Nunn, B.L. Kuczynski, T. Feld, P. Wedeking, W.C. Eckelman, J. Nucl. Med. 30 (1989) 1830.
[309] Y. Ni, G. Marchal, P. Herijgers, W. Flameng, C. Petre, W. Ebert, et al., Acad. Radiol. 3 (1996) 395.
[310] D.M. Goldenberg, H. Goldenberg, R.M. Sharkey, R.E. Lee, E. Higgenbotham-Ford, J.A. Horowitz, Semin. Nucl. Med. 19 (1989) 262.
[311] D.M. Goldenberg, E.E. Kim, F.H. DeLand, S. Bennett, F.J. Primusl, Cancer Res. 40 (1980) 2984.
[312] A. Hertel, R.P. Baum, M. Lorenz, T. Baew-Christow, A. Encke, G. Hor, Br. J. Cancer 62 (1990) 34.

[313] D.M. Goldenberg, H. Goldenberg, E.H. Ford, et al., J. Nucl. Med. 30 (1989) 809.
[314] R. Sirisriro, D.A. Podoloff, Y.Z. Patt, S.A. Curley, L.P. Kasi, V.A. Bhadkamkar, et al., Nucl. Med. Commun. 17 (1996) 568.
[315] S.W. Young, Q. Fan, Invest. Radiol. 31 (1996) 280.
[316] R.W. Arnold, G. Sukamanian, J.G. McAfer, R.J. Blair, F.D. Thomas, J. Nucl. Med. 16 (1975) 357.
[317] M. Oginski, M. Rembelska, J. Nucl. Med. 15 (1976) 282.
[318] V.Y. Kuperman, G.S. Karczmar, M.J. Blomley, M.Z. Lewis, L.M. Lubich, M.J. Lipton, J. Magn. Reson. Imaging 6 (1996) 764.
[319] W.M. Burch, P.J. Sullivan, C.J. McLaren, Nucl. Med. Commun. 7 (1986) 865.
[320] P. Lind, H.J. Gallowitsch, P. Mikosch, E. Kresnik, I. Gomez, J. Omann, et al., Clin. Nucl. Med. 22 (1997) 30.
[321] C. Guckel, K. Schnabel, M. Deimling, W. Steinbrich, Radiology 200 (1996) 681.
[322] A. Martinez-Caballero, M.N. Martinez, J. Serrano, J. Verdu, M. Coronas, O. Caballero, Rev. Esp. Enferm. Dig. 89 (1997) 51.
[323] P.J. Mountford, A.G. Kettle, M.J. O'Doherty, et al., J. Nucl. Med. 31 (1990) 311.
[324] N. Kenna, M. Hayward, Clin. Radiol. 45 (1992) 331.