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REVIEW

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Nanoparticles for MRI-guided radiation therapy: a review

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Abstract

The development of nanoparticle agents for MRI-guided radiotherapy is growing at an increasing pace, with clinical trials now underway and many pre-clinical evaluation studies ongoing. Gadolinium and iron-oxide-based nanoparticles remain the most clinically advanced nanoparticles to date, although several promising candidates are currently under varying stages of development. Goals of current and future generation nanoparticle-based contrast agents for MRI-guided radiotherapy include achieving positive signal contrast on T1-weighted MRI scans, local radiation enhancement at clinically relevant concentrations and, where applicable, avoidance of uptake by the reticuloendothelial system. Exploiting the enhanced permeability and retention effect or the use of active targeting ligands on nanoparticle surfaces is utilised to promote tumour uptake. This review outlines the current status of promising nanoparticle agents for MRI-guided radiation therapy, including several platforms currently undergoing clinical evaluation or at various stages of the pre-clinical development process. Challenges facing nanoparticle agents and possible avenues for current and future development are discussed.

Keywords: Nanoparticles, RgRT, Nanotechnology, Cancer, Radiation therapy, Image-guided radiation therapy, MRI

Introduction

About half of all cancers are treated with radiation therapy, most commonly using megavoltage (MV) energy X-ray beams. Radiotherapy treatment involves the use of sophisticated approaches to accurately target radiation to tumours while sparing normal tissue to the maximum possible extent. In particular, the practice of image-guided radiation therapy (IGRT) utilises frequent imaging during a course of radiotherapy treatment to localise the tumour and update treatment accordingly, enabling more precise targeting of the tumour and sparing of healthy tissue (Grégoire et al. 2020; Jaffray et al. 2007; Sterzing et al. 2011). Typically, this is facilitated via kilovoltage (kV) imaging modalities such as computed tomography (CT) incorporated into radiotherapy treatment units.

An emerging paradigm in IGRT is replacing kV image guidance in the treatment workflow with magnetic resonance imaging (MRI) (Keall et al. 2022; Otazo et al. 2021). While MRI initially was only used to assist in radiotherapy treatment planning and treatment

response, magnetic resonance-guided radiation therapy (MRgRT) now includes integrated MRI-linac treatment units that enable MRI at the time of treatment (Otazo et al. 2021). Both CT and MRI routinely employ contrast agents to enhance the acquired images, by highlighting structures of interest on the basis of contrast uptake. In the case of CT, this involves administration of a contrast agent (usually iodine-based) that absorbs X-rays and hence appears as having a high X-ray attenuation. For MRI, contrast agents leverage different physical mechanisms based on differential spin relaxation of ^{1}H in surrounding water molecules (Matson and Wilson 2010). Typically, this is achieved with gadolinium-based agents. Parallel developments in the use of nanoparticles for MRI contrast and for radiotherapy (Schuemann et al. 2020) have raised the prospect of nanoparticle contrast agents as a potent modality for enhancing the effectiveness of MRgRT in two ways: (i) MRI contrast enhancement (enabling better visualisation and delineation of a tumour during planning, treatment and assessing response); and (ii) radiation dose enhancement, wherein increased local radiation dose increases damage to the tumour without increasing dose to surrounding healthy tissue, thereby improving treatment efficacy.

This review focuses on the use of nanoparticle-based agents for enhancing MRgRT. This is a timely issue given the rapidly growing uptake of MRgRT, facilitated by MRI-linac technology, and the reliance of MRI on contrast agents, of which several nanoparticle-based candidates present exciting opportunities for clinical translation. The principles of nanoparticle-based agents are discussed and existing nanoparticle candidates for clinical use are evaluated.

MRI-guided radiotherapy

The potential advantages of MRgRT are considerable. The soft-tissue contrast of MRI is superior to cone-beam CT and thus enables more accurate delineation of a tumour against surrounding tissue (Otazo et al. 2021). MRI scanners also do not use ionising radiation and so repeated MRI scans over the course of a radiotherapy treatment avoids radiation dose to healthy tissue. In doing so, MRgRT is better able to delineate daily changes in both the tumour and also organs at risk (OARs) than conventional X-ray-based imaging modalities (Corradini et al. 2019; Mittauer et al. 2018) (Fig. 1). This could potentially include real-time imaging of moving tumours (e.g. from respiratory movement), and imaging of anatomical changes over a course of treatment with treatment plan optimisation (Corradini et al. 2019).

Another technical advantage of MRgRT is the potential for functional imaging, wherein MRI is able to measure water diffusion or perfusion to tumours (Chin et al. 2020), or biological markers such as tumour hypoxia (Keall et al. 2022; Salem et al. 2019). This can potentially predict response to radiotherapy or identify areas for dose adjustment; in particular, dedicated MRI sequences may be deployed to assess markers of radiosensitivity and radioresistance, such as perfusion, cellularity or hypoxia. The clinical utility of such an approach would be to facilitate higher doses to be targeted to more radioresistant sections of a tumour (thereby limiting the risk of post-radiotherapy recurrence) and lower doses elsewhere, thereby increasing the prospect of long-term tumour control for an equivalent total dose (and associated risk of toxicity) (Brighi et al. 2022; Keall et al. 2022).

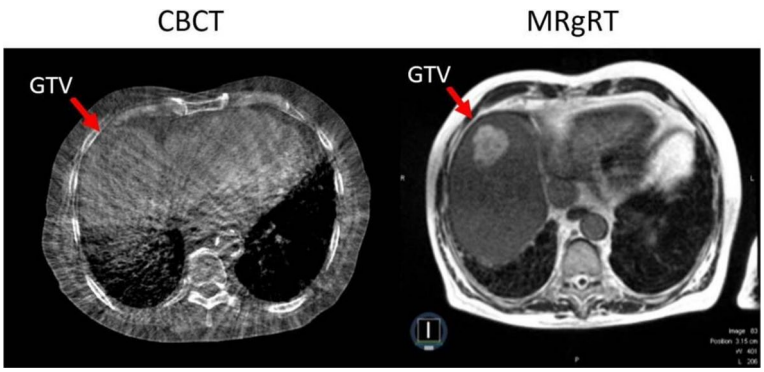

Fig. 1 Thoracic cone-beam CT (CBCT) image (left) compared to a contrast-enhanced T1-weighted MR image, demonstrating better identification of a liver tumour (hepatocellular carcinoma, red arrow) within the gross tumour volume (GTV) (Reprinted from Mittauer et al. (2018), licensed under the Creative Commons Attribution License)

Dynamic contrast-enhanced MRI involves scans before and after injection of a contrast agent (usually gadolinium based), which can quantify parameters such as blood volume and time to maximum enhancement, providing further opportunities to predict response to treatment (Chin et al. 2020). One current limitation of this is the impact of repeated contrast administration on patients, which has potential to cause toxicity due to gadolinium accumulation (Costa et al. 2018).

The technical challenges of incorporating MRI machines (which rely on high-strength magnetic fields) into the radiotherapy suite and training staff on new treatment techniques mean MRI-linac systems come at a higher price than traditional radiotherapy machines (Chin et al. 2020; Keall et al. 2022). While improved treatment efficiencies and reduced toxicity may offset these costs, solutions to address these technical challenges are under development,, including novel approaches such as ultra-low field MRI, which does not require superconducting magnets and hence enables smaller, cheaper, portable MRI units that can be deployed at point of care (Liu et al. 2021; Sarracanie et al. 2015).

Clinically, randomised controlled trial evidence quantifying the effectiveness of MRgRT compared to conventional IGRT is being obtained in prospective studies. The MIRAGE trial is an ongoing phase III trial of CT guidance vs MRI guidance for stereotactic radiotherapy in prostate cancer, wherein MRI guidance has the potential to identify at-risk structures such as the urethra and image prostate motion in real-time (Ma et al. 2021). Interim analysis published in February 2022 suggests that this translates to improved clinical outcomes, including a reduction in genitourinary and bowel toxicity from 47% in the CT-guided group to 22% in the MRI-guided group (Kishan et al. 2022). Future clinical experience with MRgRT is anticipated to provide additional evidence regarding its clinical utility, advantages and appropriate indications (Keall et al. 2022; Verkooijen and Henke 2021). Another ongoing registry study, the MOMENTUM study, intends to collect systematic outcome data on patients treated using an MRI-linac (de Mol van Otterloo et al. 2020).

Emerging roles for nanoparticles in MRI and radiotherapy

Due to nanoscale geometric confinement, nanoparticles possess unique physical properties compared to ordinary chemical agents. Their large surface-area-to-volume ratio enhances interaction rates (e.g. with surrounding biochemical species and charged particles) and enhances escape probabilities of secondary particles produced by radiation interactions, leading to greater biological effectiveness of radiation dose. Additionally, single-domain magnetisation of some nanoparticles enhances spin interactions with ^{1}H in surrounding water molecules, thereby enhancing MRI contrast (Wang 2011). There exists a multitude of different nanoparticles in various stages of pre-clinical development, however only a few are approved by regulatory agencies for clinical use, thus demonstrating the challenge of clinical translation (Hua et al. 2018).

Critical to the role of nanoparticles in MRI and radiotherapy is their ability to accumulate selectively within tumour deposits, for which a number of mechanisms exist. Applications that exploit this relevant to MRgRT include contrast enhancement in MRI and local enhancement of radiation, discussed below.

Selective tumour accumulation by nanoparticles

The potential for nanoparticles to improve clinical outcomes in cancer has usually focussed on improving the effectiveness of existing or novel therapeutic drugs by enhancing their delivery to target sites, thereby increasing the concentration of the drug that is delivered to its site of action while minimising its concentration elsewhere. A similar strategy is relevant for both MRI and radiotherapy. This can be achieved by passive targeting using the enhanced permeability and retention (EPR) effect, or via active targeting with targeting ligands (cf. Fig. 2).

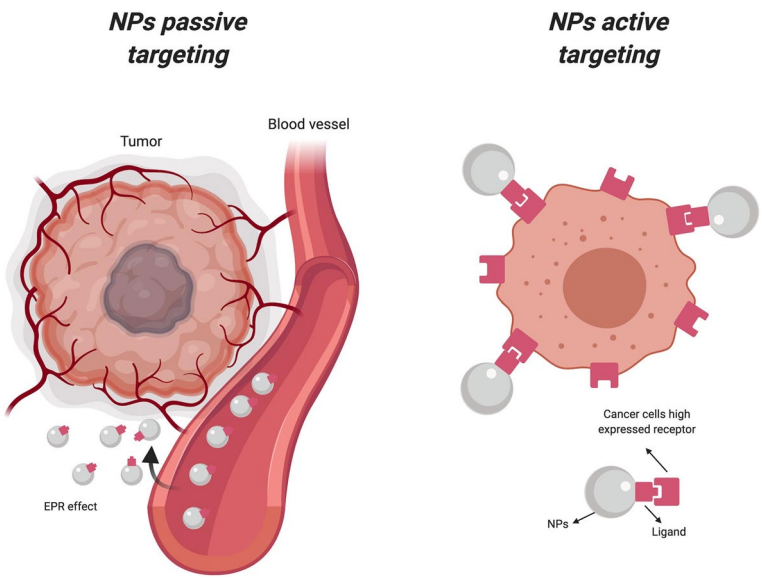

Fig. 2 Graphical depiction of passive targeting via the EPR effect (left) and active targeting (right) of nanoparticles (NPs) for tumour selectivity (Reproduced from Sanità et al. (2020), distributed under the terms and conditions of the Creative Commons Attribution [CC BY] license)

The EPR effect describes a tendency for nanoparticles (and macromolecules) to preferentially accumulate in cancerous tumours (Nakamura et al. 2015; Shi et al. 2020; Wu 2021). The proposed biological mechanism for the EPR effect is increased vascular permeability in the tumour environment (itself mediated by the need for tumours to induce new blood vessel formation to sustain blood supply), wherein the blood vessels in close proximity to the tumour have "leaky" walls that permit larger molecules to enter (Houston et al. 2020). A second component is a dysfunctional lymphatic drainage system from tumours, diminishing clearance of these same structures (Nakamura et al. 2015). This means particles of the appropriate size may be more likely to enter tumour cells and less likely to leave them, resulting in a higher intra-tumoural concentration of the particles, relative to surrounding tissue. If the particles are too small, they are usually cleared by the renal system too efficiently for any significant tumour uptake to occur, as well as accumulating in healthy tissues (Nakamura et al. 2015). Most particles that exploit the EPR effect are roughly 10–100 nm in diameter (Fang et al. 2020).

While the EPR effect relies on an imbalance between vascular uptake and lymphatic drainage in tumour deposits, active targeting relies on functionalising nanoparticles to have an affinity for the cancerous cells. The two main forms of active targeting are (Bi et al. 2016): (i) directed targeting, or nanoparticles that bind to targetable molecules or structures (e.g. receptors or proteins) that may be expressed exclusively or to a disproportionately high extent by the tumour cells (Pearce and O'Reilly 2019); and (ii) tumour microenvironment targeting, where nanoparticles respond to the physiochemical environment expressed inside the tumour, such as hypoxia or low pH. Among the most established active targeting strategies is the use of antibodies, which demonstrate high levels of specificity for their target antigen (Attia et al. 2019; Bazak et al. 2015; Clemons et al. 2018). Antibody-conjugated iron oxide nanoparticles that target the HER-2 receptor overexpressed in breast cancer cells, for instance, can improve the detectability of HER-2-positive cancers on MRI (Oghabian et al. 2011).

MRI contrast enhancement

MRI scans operate by utilising a magnetic field to align nuclear spins (most commonly hydrogen protons in water molecules). The time taken for the ^{1}H nuclei to relax to their original alignment is termed the "spin–lattice" or T1 relaxation time and is exploited in T1-weighted scan protocols. The time for the ^{1}H (which upon excitation are in a coherent phase) to decohere with one another is termed the "spin–spin" or T2 relaxation time (Matson and Wilson 2010).

Clinically, MRI scans often rely on contrast agents based on gadolinium, which is paramagnetic due to seven unpaired electrons in its 4f subshell. Importantly, in its most common oxidation state, Gd^{III}, this paramagnetism is preserved upon chelation as the 4f electrons are not involved in bonding. MRI contrast is enhanced by shortening the T1 relaxation time of surrounding protons (Naseri et al. 2018) causing them to appear hyperintense (bright) on T1-weighted images. While chemical gadolinium chelators are widely used clinically, nanoparticle-based contrast agents that incorporate gadolinium can also be utilised, which appear hyperintense on T1-weighted images also.

In comparison, shortening T2 relaxation times causes hypointensity (dark contrast) on T2-weighted scans (Matson and Wilson 2010). T2 contrast can be induced by

ferromagnetic materials, or superparamagnetism in single-domain particles, referred to as superparamagnetic iron oxide nanoparticles (SPIONs) (Wei et al. 2017). Due to their nanoscale size, SPIONs may be able to preferentially accumulate within tumours using the mechanisms described above, thereby improving tumour identification in MRI scans (Matson and Wilson 2010). As shall be discussed, some SPIONs also work on the principle of accumulation in healthy tissue, suppressing the T2 signal there, while leaving tumour deposits illuminated (Vogl et al. 1996). Although this may not be as straightforward to interpret clinically as increased intensity on T1 images, it nevertheless has potential applications for specialised imaging purposes.

Although T2 contrast images may be more difficult to interpret than T1 contrast images, SPIONs are attracting growing interest as an alternative to Gd-based contrast agents, due to the risk of the rare but serious complication of nephrogenic systemic fibrosis (NSF), mostly seen with linear-chelating Gd agents, predominantly in patients with reduced renal function (Rudnick et al. 2021). Although the risk of NSF has been reduced significantly by macrocyclic chelating agents and restrictive policies around the use of gadolinium in patients with reduced renal function, it is still recommended that the risks and benefits of gadolinium-based contrast agents be weighed against the risk of harm in those with acute kidney injury or reduced renal function (Weinreb et al. 2021). This could indicate an alternative agent that does not predispose to NSF would be of use in these patients. Also of concern is the more controversial diagnosis of "gadolinium deposition disease", which relates to purported cognitive and neurological symptoms associated with administration of Gd-based contrast agents (Layne et al. 2020).

Dual-mode imaging (PET–MRI)

A potential opportunity also exists for nanoparticles in multi-modal PET–MR imaging, which combines the high-sensitivity physiological imaging of positron emission tomography (PET) with the high spatial resolution soft tissue anatomical imaging of MRI. PET images biological function using a trace amount of positron-emitting radioisotope conjugated to a chemical agent (most commonly FDG). Labelling SPIONs or Gd-based nanoparticles with PET tracers would enable the nanoparticles to be detectable to both imaging modalities simultaneously, thereby allowing more accurate delineation for further diagnosis, staging and treatment response monitoring, as well as providing important information on nanoparticle uptake, biodistribution and clearance (Gholami et al. 2020; Pellico et al. 2021). Nanoparticles under development for this strategy (Abadjian et al. 2016; Thakare et al. 2019) are further discussed below.

Radio-enhancement

In radiotherapy, the potential for nanoparticles to locally enhance radiation dose and improve treatment efficacy is being actively investigated (Choi et al. 2020; Jin and Zhao 2020; Kuncic and Lacombe 2018; Schuemann et al. 2020). When irradiated with a photon beam, high atomic number (high-Z) nanoparticles can produce an excess of secondary electrons (Choi et al. 2020; Jin and Zhao 2020; Kuncic and Lacombe 2018). At kilovoltage X-ray energies, interactions with high-Z nanoparticles produce short-ranged photoelectrons and copious Auger electrons, which may enhance radiation damage in a highly localised region, on the order of a few cell diameters or less (Choi et al. 2020). This

manifests as an effective increase in local physical radiation dose, typically by a factor of 2 at kilovoltage energy ranges (Kuncic and Lacombe 2018). Unfortunately, this effect is negligible at the megavoltage (MV) X-ray energies used in clinical radiotherapy, Nevertheless, studies have reported nanoparticle-enhanced effects using clinical MV beams, which has been attributed to molecular biology-driven radiosensitisation (e.g. oxidative stress, immune responses, as well as DNA damage and repair responses) rather than an enhancement in physical radiation dose (Butterworth et al. 2012; Jain et al. 2011; Schuemann et al. 2020). Furthermore, nanoparticles radiolabelled with therapeutic isotopes commonly used in nuclear medicine may offer a more promising strategy for radio-enhancement effects given the relatively low-energy (kV) regime of emitters commonly used in internal radionuclide therapy (Gholami et al. 2019; Maschmeyer et al. 2020).

The role for theranostic nanoparticles

The principle of theranostic nanoparticles usually refers to the prospect of a single nanoparticle system incorporating both diagnostic and therapeutic properties (Chen et al. 2014; Maniglio et al. 2018; Verry et al. 2020). This concept has clear advantages, in that uptake of the system in the target of interest (usually a tumour) may be directly assessed during treatment, whilst simultaneously assessing the tumour's extent and potential response to treatment. This concept is being utilised clinically in CT-guided radiation therapy by NBTXR3, which is a functionalised hafnium nanoparticle currently in clinical trials for multiple sites (Hoffmann et al. 2021). On treatment imaging of NBTXR3 can be utilised to monitor tumour uptake and retention of the nanoparticle and for dose enhancement (Bagley et al. 2022).

For MRI diagnostics, SPIONs or Gd-based nanoparticles could be labelled with a therapeutic radioisotope (e.g. ^{223}Ra, ^{90}Y) or even a theranostic radioisotope (e.g. ^{64}Cu, ^{177}Lu) for additional imaging with PET or SPECT in a radionanomedicine theranostic strategy (Pratt et al. 2016). In radiation oncology and particularly MRgRT, nanoparticles may have intrinsic theranostic properties, in that the nanoparticles are detectable to MRI and also act as a radio-enhancer in their own right. As such, the uptake of these nanoparticles in target sites could be confirmed with imaging. The use of an MRI-linac permits image acquisition immediately prior to treatment and while the treatment beam is on, enabling real-time imaging acquisition and modification to the treatment plan (Byrne et al. 2020; Keall et al. 2014).

Nanoparticles in MRI-guided radiotherapy

Nanoparticles developed for MRgRT can be broadly classified into two categories: gadolinium-based nanoparticles (GdNPs) and SPIONs. In addition to enhancing T1 and/or T2-weighted contrast, studies have investigated the potential for additional benefits due to local radio-enhancement and active targeting. Specific agents in each category are discussed herein.

Gadolinium-based nanoparticles

Gadolinium has been the clinical workhorse of MRI contrast since the first gadolinium-based contrast agent was approved by the United States Food and Drug Administration in 1988 and is in widespread use across the world. Being a toxic heavy metal (of the

lanthanide series), free gadolinium is not used clinically; instead, it is combined within an organic chelating agent.

Given its established use as an MRI contrast agent, it is perhaps not surprising that gadolinium could serve as a basis for nanoparticles to improve contrast for image-guided radiotherapy. Indeed, several GdNPs are in various stages of development, incorporating both gadolinium's advantages as an image contrast agent, and also its potential for dose contrast enhancement.

AGuIX

The GdNP "Activation and Guidance of Irradiation by X-ray", or AGuIX, is a polysiloxane nanoparticle with chelated gadolinium (Bort et al. 2020; Detappe et al. 2015; Luchette et al. 2014; Lux et al. 2019; Verry et al. 2021) and as of 2022, is arguably the furthest-advanced nanoparticle in terms of clinical development for MRgRT. It was initially developed for MRI contrast enhancement in cancer and non-cancer imaging. An example of the latter is inhaled AGuIX for imaging pulmonary fibrosis via MRI (Tassali et al. 2016). Most of its clinical studies to date, however, have been in cancer imaging and radiotherapy, which is the focus of this review.

The total size of AGuIX is about 4–6 nm with a molecular weight of 10 kDa; in spite of this small size, the nanoparticles are able to accumulate in tumour models via the EPR effect (Bort et al. 2020). Each GdNP contains an average of 10 gadolinium chelates (Fig. 3). AGuIX has been evaluated in early-stage clinical studies in humans in tumours metastatic to the central nervous system (CNS), with trials underway in other anatomical sites (Lux et al. 2019). The neurotoxicity of AGuIX was compared with the DOTAGA chelator agent by Borisova et al., who found that at medically used concentrations (0.25 mM, equivalent to 0.25 g/L gadolinium), neither agent showed significant effects on presynaptic neurotransmission (Borisova et al. 2021). At higher concentrations (1.25 to 6 mM), AGuIX showed little effect on neurotransmission, which was inhibited by DOTAGA over the same range of concentrations (Borisova et al. 2021). There is currently little convincing evidence of chronic toxicity from AGuIX in terms of gadolinium

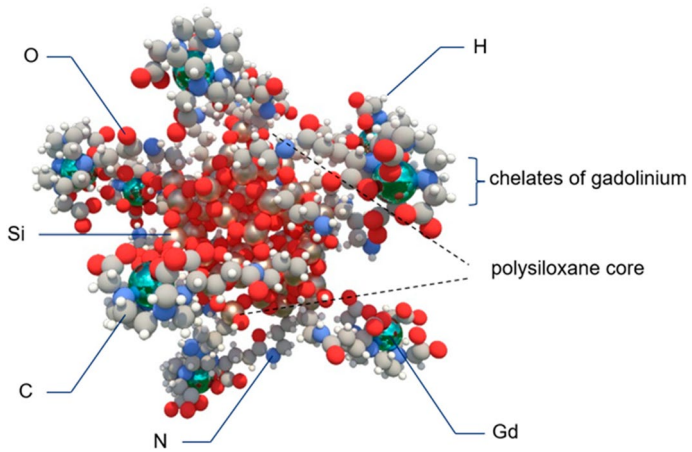

Fig. 3 Schematic representation of the AGuIX nanoparticle (Reproduced from Gawel et al. (2022), distributed under the Creative Commons Attribution License)

deposition disease or nephrogenic systemic fibrosis, with animal studies reporting only transient reductions in renal function occurring after it is administered systemically (Kotb et al. 2016; Sancey et al. 2015).

Clinically, AGuIX nanoparticles have been evaluated in humans as part of the NANORAD-1 study, which was a phase I study to evaluate the safety and tolerability of AGuIX as a radiosensitisation agent for whole-brain radiotherapy brain metastases from a range of primary tumours (Verry et al. 2020, 2021). As part of NANORAD-1, patients were administered AGuIX as a single intravenous dose and underwent imaging with MRI 2 h after administration and serial follow-up scans with the existing DOTAREM contrast agent (Fig. 4). All patients had multiple brain metastases, although they were from four different primary sites (melanoma, lung, breast and colon) (Verry et al. 2020). Whole-brain radiotherapy was delivered as 30 Gy total dose, with the first fraction being delivered 4 h after AGuIX administration, with 10 sessions in total delivered over 2 weeks.

MRI signal enhancement in NANORAD-1 was linearly correlated to the amount of AGuIX administered, up to a maximum dose of 100 mg/kg (Verry et al. 2020). Signal enhancement comparable to that attained with DOTAREM was observed in tumours 2 h post-injection for the equivalent gadolinium ion content to the DOTAREM injection and remained detectable for at least a week. No signal enhancement outside tumours was observed with AGuIX. It was also possible to quantify the uptake and concentration of AGuIX in the tumour deposits using their MRI signal enhancement, which may prove of value in predicting response to radiotherapy (Verry et al. 2020). No dose-limiting toxicity was observed for AGuIX at a dose of up to 100 mg/kg.

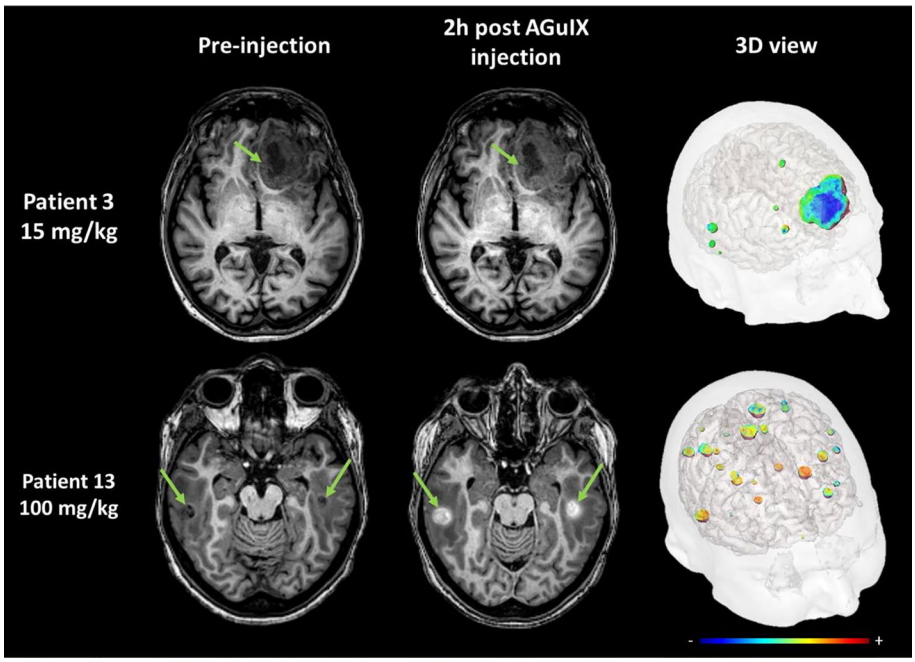

Fig. 4 T1-weighted MRI scans (3 T field strength) for 2 patients in the NANORAD-1 trial, taken prior to injection of AGuIX (left) and 2 h later (right) (green arrows point to metastatic tumour deposits), that demonstrate AGuIX accumulation post-injection via T1 contrast enhancement, most visible for the higher dose case. The 3D view demonstrates digital reconstruction of contrast uptake (colour bar) (Reprinted with permission from Verry et al. (2021), copyright 2021, Elsevier)

With the completion of NANORAD-1, clinical trials of AGuIX for a number of other indications are currently underway or in preparation (Table 1) (AGuIX 2021). According to the manufacturer, clinical trials of AGuIX are also being planned in glioblastoma and cervical cancer, as well as pancreatic and lung cancers as of 2021 (AGuIX). Most of these trials relate to the use of AGuIX as a radiosensitiser, although NANORAD-2 and NANOSMART also explore its potential for MRgRT.

NANORAD-2 will enrol approximately 100 patients, randomised to receive either whole-brain radiotherapy alone or whole-brain radiotherapy plus AGuIX delivered before the first and sixth sessions of treatment (equivalent to once-weekly treatment) (University Hospital, Grenoble 2021). It only incorporates MRI prior to treatment as

Table 1 Currently active or planned trials incorporating AGuIX, as of June 2022

Name and location	Status	Clinical site	Details
NANORAD-2, France	Phase II recruiting	CNS metastases	Whole-brain radiotherapy plus AGuIX (experimental group) vs whole-brain radiotherapy alone 3 injections of AGuIX given, within 7 days of commencement of therapy, before 1st fraction and before 6th fraction, in experimental arm
NANOCOL, France	Phase I recruiting	Locally advanced cervical cancer	AguIX (up to 50 mg/kg) plus cisplatin plus external beam radiotherapy plus brachytherapy AGuIX delivered on 1st and 11th days of radiotherapy. MRI performed after AGuIX
NANOSMART	Phase I/II recruiting	Lung cancer and pancreatic cancer	Stereotactic radiotherapy plus AGuIX vs stereotactic radiotherapy alone AGuIX given 7 or 14 days before radiotherapy, then with 1st fraction and 4th fraction in those with radiation over 2 weeks Both groups receive MRI-guided stereotactic radiotherapy
NANOBRAINMETS, United States	Phase II recruiting	CNS metastases	Stereotactic radiotherapy plus AGuIX, vs stereotactic radiotherapy plus placebo Experimental arm will receive AGuIX 3–5 days before irradiation, before first fraction, and on third day of irradiation *if* more than 4 days of radiation therapy
NANO-GBM	Phase I/II recruiting	Glioblastoma multiforme	60 Gy radiation therapy plus AGuIX plus chemotherapy (temozolomide) vs 60 Gy radiation without AGuIX plus chemotherapy (temozolomide) Radiotherapy delivered as 60 Gy over 6 weeks, with four injections of AGuIX

opposed to imaging during treatment or real-time adjustment of treatment plans. At present, only NANOSMART incorporates MRgRT during treatment delivered using an MRI-linac. NANOSMART is a phase I/II study of approximately 100 patients with either lung or locally advanced pancreatic cancer, consisting of a dose escalation phase I component to determine safe doses of AGuIX, and a phase II randomised component comparing stereotactic MRgRT with AGuIX (of the dose determined in phase I), or with placebo (Leeman 2021). The primary outcome of the phase II component is local control at 12 months with AGuIX plus radiotherapy, vs radiotherapy alone.

Pre-clinical animal studies of AGuIX-enhanced radiotherapy of 9L-gliosarcoma bearing rats were performed by Le Duc et al. (2014). This study compared the effects of AGuIX on image contrast and clinical survival, compared to DOTAREM, a gadolinium chelate contrast agent. Both AGuIX and DOTAREM facilitated enhanced MRI contrast. However, AGuIX conferred a survival benefit compared to radiotherapy with no contrast, whereas DOTAREM did not (median survival was 102 days with AGuIX plus radiotherapy, 32–43 days with DOTAREM plus radiotherapy and 44 days with radiotherapy without contrast).

Byrne et al. evaluated AGuIX for MRI contrast enhancement and radiosensitisation also in 9L-gliosarcoma bearing rats, but using a 1-T MRI-linac research facility (Byrne et al. 2020). Rats in this study demonstrated marked T1 contrast enhancement with AGuIX at 20 min after administration. Residual uptake of gadolinium in normal brain tissue in rats administered AGuIX was similar to that for ordinary contrast agents (Byrne et al. 2020). Importantly, the study by Liney et al. using the same MRI-linac facility indicated that MRI acquisition at time of treatment was possible and indeed that MRI acquisition could take place while the radiation beam was turned on, with no effect on image quality (Liney et al. 2019).

Other animal experiments with AGuIX have explored its role in the augmentation of radiotherapy at other anatomical sites such as the liver. Hu et al. inoculated nude mice with hepatic HepG2 tumour models with MRI performed 1, 3 and 6 h after systemic administration of AGuIX, which showed signal enhancement in the tumour model maximised at 1 h post-administration (Hu et al. 2019). Fries et al. compared AGuIX to conventional DOTAREM contrast agents with high-strength (9.4 T) MRI, finding that the contrast between tumour and normal liver tissue was higher with AGuIX than DOTAREM by a factor of 2–3. Unlike in CNS tumours, however, AGuIX also enhances MRI contrast of normal tissue (indeed more than DOTAREM), which is believed to result from the endothelial structure of the liver permitting larger molecules, including nanoparticles, to escape the vascular system (Fries et al. 2015).

AGuIX with modified ligands

The structure of AGuIX involves, as discussed, a polysiloxane core with multiple chelator molecules attached. This structure readily allows the addition of other ligands via "grafting" onto the DOTA molecule, or amine groups on the nanoparticle (Dentamaro et al. 2016). This enables additional functionalisation of the AGuIX nanoparticle to support further clinical applications, including additional imaging modalities (including PET and CT), active targeting or its use for applications outside of conventional radiotherapy (Detappe et al. 2020; Plissonneau et al. 2016; Thakare et al. 2019). Most of these

applications are still in pre-clinical evaluation, but open the possibility for the development of customisable contrast agents using the AGuIX platform.

It is possible to make AGuIX visible to additional imaging modalities as well as MRI, which can be done either by adding an additional chelation molecule to amine groups on the AGuIX particle, or by changing the metal ion contained within the DOTA chelator. For instance, it is relatively straightforward to functionalise AGuIX with the NODAGA chelator, which can be labelled with gallium-68, or the DFO chelator for zirconium-89, to facilitate dual-mode PET–MRI imaging (Bouziotis et al. 2017) (Fig. 5). Similarly, incubating AGuIX with copper-64 chloride in solution produces ^{64}Cu-radiolabelled AGuIX, visible to PET scanners at lower concentrations than visible on MRI alone (Hu et al. 2017). Another radiolabelled AGuIX variant involves grafted zirconium-89, with a longer half-life than gallium-68 (Truillet et al. 2016). Huclier-Markai et al. investigated the effects of radiolabelling AGuIX with different radionuclides, including copper-64, scandium-44 and gallium-67. Yields of 60–100% were identified, with the average size of the modified AGuIX being approximately 3.5 nm (similar to traditional AGuIX) (Huclier et al. 2019).

For CT image enhancement with AGuIX, Detappe et al. combined gadolinium AGuIX nanoparticles with an additional bismuth chelator. The CT contrast enhancement of this agent was 4.26 HU/mM, which is similar to existing iodine-based CT contrast agents (Detappe et al. 2017). In the setting of IGRT, these approaches could enable modified AGuIX to be incorporated into existing clinical workflows, as well as enabling dual-mode imaging with both MRI and other modalities. Further developments in this field are likely, with "trimodal" AGuIX nanoparticles containing radiotracers and optical tracer molecules under development (Thakare et al. 2019).

Another potential adaptation of AGuIX, again in the research stage, involves modification to facilitate active targeting. In the case of peptide-based conjugation, most studies to date have evaluated tumour specific peptides conjugated to AGuIX for photodynamic therapy, in which the AGuIX nanoparticle contains a peptide to facilitate targeting and a photosensitising molecule. This includes peptides with an affinity for NRP-1 (expressed on glioblastoma cells), along with a photosensitiser (Gries et al. 2020). A recently developed variant of AGuIX, termed "CuPRIX", has approximately 40% of DOTAGA molecules on the AGuIX particle being "free" (without gadolinium—cf. Fig. 6) (Rocchi et al. 2022). The role of the free DOTAGA is to chelate copper from cancer cells, which is believed to impair the ability of these cells to metastasise. In vitro studies suggest it may facilitate this by inhibition of the LOX enzyme involved in metastasis (Rocchi et al.

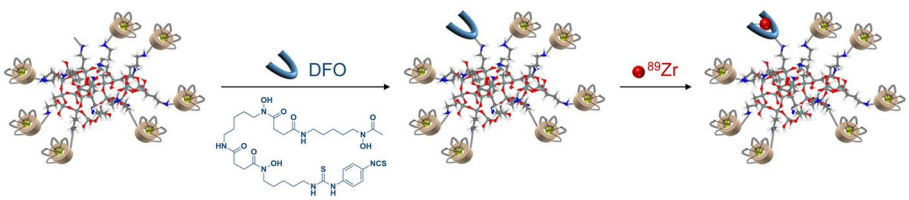

Fig. 5 AGuIX conjugated with DFO-zirconium 89, facilitating PET–MRI (Reprinted with permission from Truillet et al. (2016). Copyright 2016, American Chemical Society)

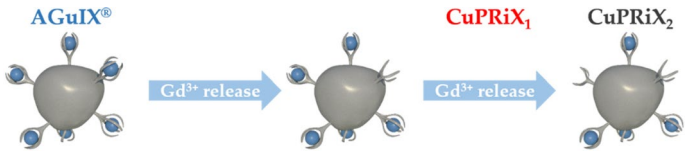

Fig. 6 Formation of the CuPRiX nanoparticle by gadolinium release from AGuIX (From Rocchi et al. (2022), distributed under the terms and conditions of the Creative Commons Attribution [CC BY] license)

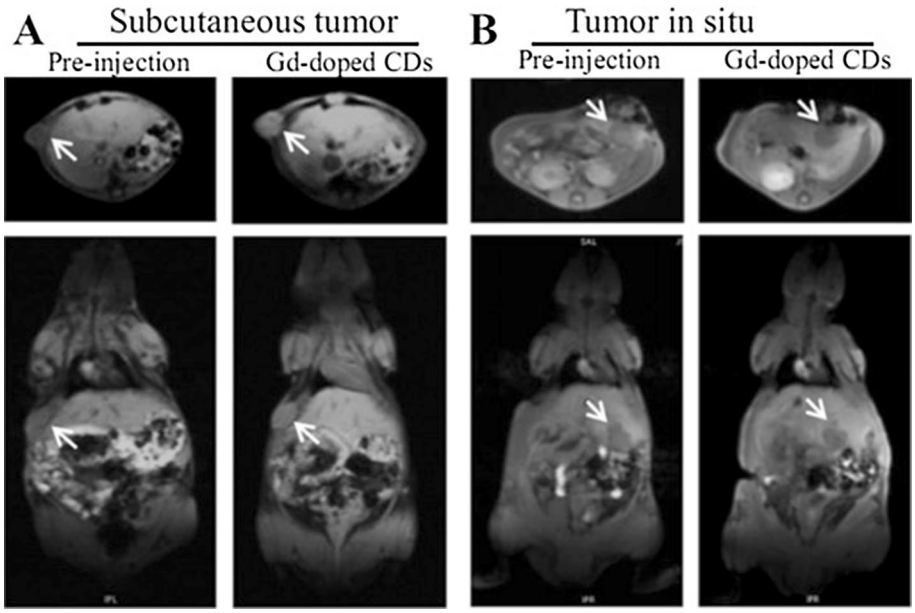

Fig. 7 T1-MRI enhancement (field strength 3 T) post-injection with gadolinium-doped carbon nanodots (CDs) in Herps-flank tumour-bearing mice (Reprinted with permission from Du et al. (2017), copyright 2017, Elsevier)

2022). CuPRIX still retains MRI contrast and radiotherapy enhancement properties similar to AGuIX (Rocchi et al. 2022).

At present, none of these modified AGuIX variants have progressed beyond animal testing, although as the original AGuIX proceeds into human trials, the possibility exists that modified AGuIX will be able to serve additional MRI and radiotherapy needs as a customisable platform.

Other gadolinium-based nanoparticles

Although AGuIX is, as of 2022, the most clinically advanced GdNP candidate for MRgRT, other candidates are currently under development at pre-clinical stages. Du et al. synthesised gadolinium-doped quantum carbon dots, which formed quasi-spherical nanoparticles approximately 18 nm in diameter (Du et al. 2017). This was evaluated in Hep2G cell colonies and in in vivo models in Herps flank tumour-bearing mice. Tumour uptake was readily apparent on T1-weighted MRI with resultant signal enhancement (Fig. 7). In mice that received the nanodots (dose 10 mg/kg) prior to radiotherapy (total dose 9 Gy over one week), tumour volume reduced 53% and median

survival was 32 days, whereas in mice that received radiotherapy alone, tumour volume reduced 12% and median survival was 24 days.

Similar results were obtained by Wu et al. who synthesised hyaluronic acid- functionalised gadolinium oxide nanoparticles. These nanoparticles, also tested in HEPG2 cell lines and subcutaneous heps tumour-bearing mice, were approximately 105 nm in diameter. In addition to the EPR effect, the functionalisation with hyaluronic acid was intended to facilitate active targeting against cells expressing an excess of hyaluronic acid receptors (e.g. CD44) (Wu et al. 2020). The addition of the functionalised nanoparticles had little effect on tumour volume compared to control mice, but when combined with radiotherapy, resulted in nearly 60% reduction in tumour volume, compared to 38% with radiotherapy alone. Survival times were not reported.

The impact of these GdNPs is anticipated to be further demonstrated in future preclinical and eventual clinical studies and may serve as an alternate source of GdNPs for MRgRT. Other nanoparticles with similar properties to GdNPs, such as manganese-based nanoparticles, are discussed further below.

Superparamagnetic iron oxide nanoparticles (SPIONs)

SPIONs are iron oxide nanoparticles under consideration for applications in MRI contrast enhancement (Waddington et al. 2020) and magnetically induced hyperthermia (Dulińska-Litewka et al. 2019). Some SPION-based agents have been approved for clinical use in humans, albeit not for MRI specifically.

The iron oxide content of SPIONs can take several forms, including magnetite (Fe_3O_4) and maghemite (Fe_2O_3). For clinical use, they are coated with a biocompatible material (Dulińska-Litewka et al. 2019), dextran being the most commonly used coating (McCarthy and Weissleder 2008) (Fig. 8). Free SPIONs are readily taken up by the reticuloendothelial system in the liver (Janko et al. 2019) and also by macrophages, which has enabled their use as contrast-enhancement agents for liver lesions (one of their approved indications), and potentially for imaging of infection/inflammation by direct imaging of macrophage influx into inflamed areas (Neuwelt et al. 2015).

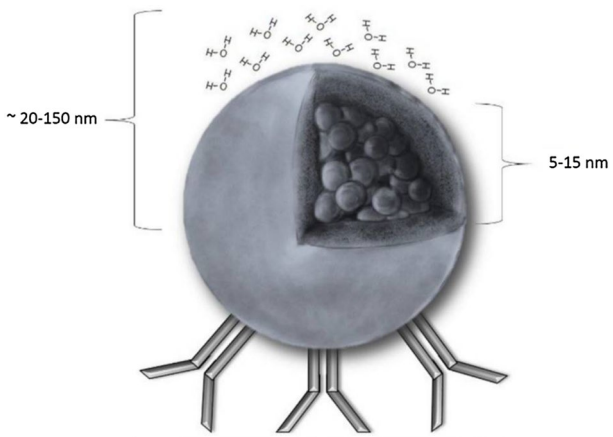

Fig. 8 Schematic diagram of a SPION, showing the iron oxide core and surrounding hydrophobic shell and antibodies that may be added to the shell to promote active targeting (Reprinted from Dulińska-Litewka et al. (2019) under the terms and conditions of the Creative Commons Attribution [CC BY] license)

The size of SPIONs varies depending on the production method used and the coating and can range from < 10 nm to over 100 nm (Nelson et al. 2020). SPIONs have a large magnetic moment and cause localised magnetic field inhomogeneity. This suppresses their signal on T2-weighted images (causing the SPIONs to appear dark) (Bakhtiary et al. 2016; Neuwelt et al. 2015; Shan 2004; Wei et al. 2017), although smaller SPIONs can also induce positive contrast (appear brighter) on T1-weighted images (Wei et al. 2017).

As of 2022, SPION products that have been developed for use in humans include (Janko et al. 2019):

- Ferumoxytol (FeraHeme): for iron deficiency anaemia (currently approved).
- Ferumoxides (Feridex IV): intravenous contrast agent for MRI imaging of liver lesions (discontinued).
- Ferumoxsil (GastroMark): oral contrast agent for MRI (discontinued).
- Ferumoxtran-10 (Combidex): for imaging of metastatic cancer in lymph nodes (discontinued).

Unfortunately, most of these SPION agents have been discontinued from clinical use, mostly due to a number of limitations that newer generations of SPION products are intended to overcome. Chief among these limitations is the issue of negative contrast, in that the presence of the SPIONs reduces, rather than increases, signal intensity (Wei et al. 2017; Yin et al. 2018). Other limitations include the relatively large size of some SPIONs, impairing renal clearance and hence causing prolonged retention (which can interfere with subsequent scans) (Shen et al. 2017). Some earlier SPION formulations are associated with anaphylactoid reactions, prompting FDA warnings. To address this, newer SPION formulations such as "SPIONdex" are under development which incorporate cross-linked dextran coating to reduce the risk of anaphylactoid reactions (Unterweger et al. 2017).

The use of SPIONs as radiosensitisers is another potential role in addition to MRI contrast enhancement. Although this application has not been as extensively evaluated, it has been evaluated in cell lines and animal models (Russell et al. 2021). Russell et al. evaluated 5-nm magnetite SPIONs in multiple cell lines, with radiation exposure to 2 Gy causing increased radiosensitivity in the presence of the SPION (Russell et al. 2021). In the same study, intra-tumoral injection of SPIONs (23.5 μg/ml magnetite SPIONs in solution, total volume 50 μl injected) in immunosuppressed mice with orthoptic H460 cell tumours showed significant reduction in tumour growth (24 days to reach maximum tumour size with SPIONs plus radiotherapy, compared to 12 days with radiotherapy alone) (Russell et al. 2021).

At present, SPIONs are used for a number of MRI applications with some radiotherapy applications, to be discussed herein.

Traditional contrast agents incorporating SPIONs

The potential for SPIONs to shorten T2 relaxation times of nearby water molecules has been recognised since the 1970s, which led to SPION-based contrast agents including ferumoxide (dextran coated, 120–180 nm) and ferucarbotran (carboxydextran coated, 45–60 nm) being approved for hepatic imaging (Shen et al. 2017). When administered

intravenously, these agents are readily taken up by macrophages, the reticuloendothelial system and Kupffer cells in the liver, suppressing T2 signal intensity there. This permits a number of applications including imaging of liver lesions, lymph nodes, the spleen, and blood pool-imaging (Bashir et al. 2015).

In the case of the liver, Kupffer cell uptake permits enhanced differentiation of various liver lesions based on relative difference in SPION uptake compared to normal liver parenchyma (Wang 2011). In particular, malignant liver lesions like hepatocellular carcinoma have reduced Kupffer cell activity and are less likely to uptake SPIONs, meaning the relative signal suppression of these lesions is less than surrounding liver parenchyma (thereby increasing the relative signal intensity of the lesion) (Fig. 9). As such, these agents were proposed as a sensitive mechanism for differentiating benign lesions from malignant (Vogl et al. 1996).

Of the "traditional" SPIONs, currently only ferumoxytol is readily available commercially, solely as a treatment for iron deficiency anaemia. It does, however, see continued off-label use as an MRI contrast agent, which was indeed its original intended purpose (Bashir et al. 2015; Nguyen et al. 2019). Ferumoxytol is approximately 17–30 nm in size and coated with dextran (core size is approximately 7–8 nm). It is used as a potential alternative to gadolinium-based contrast agents for vascular imaging, and also has potential roles for imaging liver lesions (based on selective uptake by Kupffer cells in the liver parenchyma), lymph nodes, or other lesions that demonstrate macrophage uptake (including arterial plaques and intracranial tumours) (Castaneda et al. 2011; Normandin et al. 2015). Ferumoxytol demonstrates a longer intravascular half-life than gadolinium, which makes it a useful agent for imaging of vascular structures and perfusion of various structures (Fig. 10). It does however, like most traditional SPIONs, persist in some structures including the liver, spleen and bone marrow for weeks to months, potentially interfering with subsequent scans (Toth et al. 2017).

In the context of MRgRT, ferumoxytol is also currently being evaluated as a contrast agent for liver tumours (primary and metastatic) (Kirichenko 2021). Patients with liver cirrhosis and liver tumours amenable to liver stereotactic body radiation therapy (SBRT) will receive untargeted ferumoxytol on the day of radiotherapy planning and undergo

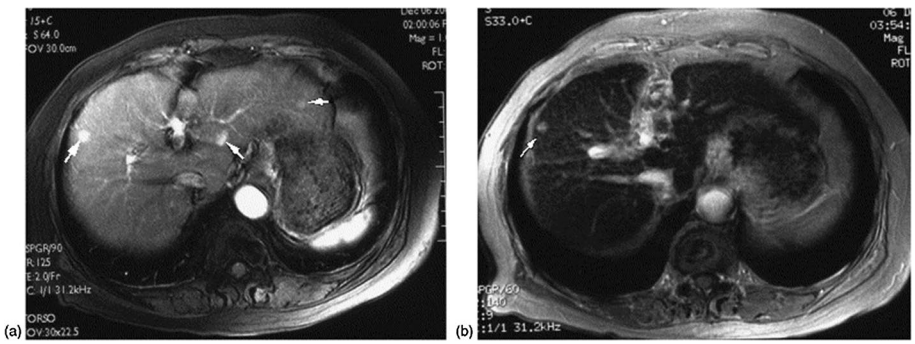

Fig. 9 Dynamic MRI (left) vs SPION-enhanced MRI (right) in a patient with hepatocellular carcinoma (SPION type not specified). On the dynamic MR image, a number of enhancing lesions (arrows) are seen. On the SPION-enhanced MRI, all but one of these are suppressed, with only the hepatocellular carcinoma with reduced SPION uptake being apparent. At surgery, only the lesion present on the SPION-enhanced sequence was found to be malignant (Reprinted with permission from Tanimoto and Kuribayashi (2006), copyright Elsevier, 2006 [arrows enhanced from original])

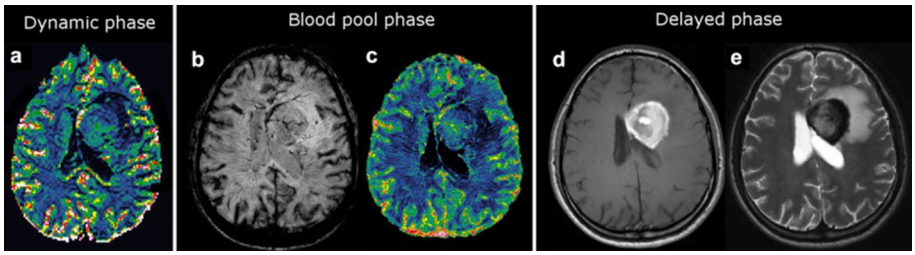

Fig. 10 Perfusion and MRI sequences of a patient with CNS lymphoma after ferumoxytol administration. Part **a** shows dynamic-phase cerebral blood volume with slightly increased uptake in the tumour. Part **b** shows abnormal vasculature on susceptibility-weighted imaging. Part **c** shows increased blood flow in the tumour. Parts **d** and **e** show T1 hyperintensity and T2 hypointensity, respectively (Reprinted with permission from Toth et al. (2017), copyright Elsevier 2017)

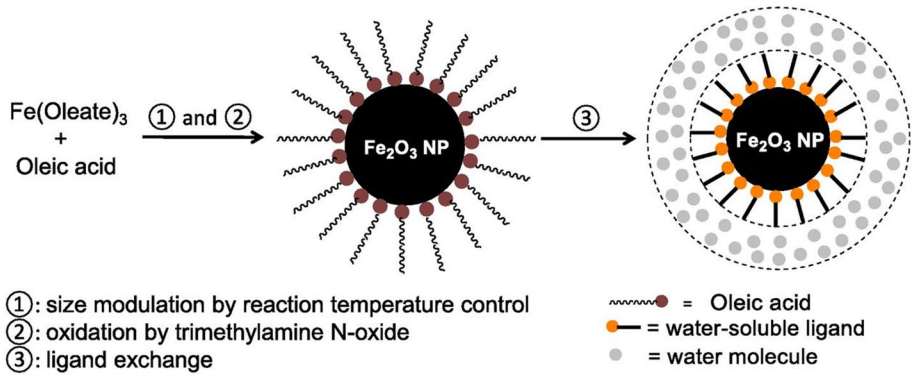

Fig. 11 Synthesis of ultrasmall zwitterion-coated SPIONs (Reprinted from Wei et al. (2017), copyright 2017, National Academy of Sciences)

imaging on an MRI-linac. SPION accumulation in this setting will be used to identify active liver parenchyma to avoid during radiotherapy treatment. Results of this study are pending although if successful would represent the first case of successful deployment of SPIONs for MRgRT specifically (Lee et al. 2022).

Ultrasmall SPIONs

SPIONs with a hydrophobic diameter of less than 10 nm, categorised here as "ultrasmall", are under development as the next-generation of SPION-based contrast agents (Shen et al. 2017). The properties of these SPIONs are intended to address some of the limitations of traditional SPION-based contrast agents. In particular, their smaller size permits renal clearance (meaning they should not accumulate in the liver or other organs), and reduces longitudinal relaxation time of nearby protons (Shen et al. 2017; Wei et al. 2017). This has the effect of reducing the ratio of transverse to longitudinal relaxivity, thereby showing up hyperintense (appearing brighter) on T1-weighted MRI sequencies (Wei et al. 2017). At present, these SPIONs are not yet approved for human use although a number of candidates are under development.

Wei et al. developed zwitterion-coated exceedingly small superparamagnetic iron oxide nanoparticles (ZES-SPIONs) as a gadolinium-free T1 contrast agent (Fig. 11; Wei et al. 2017). ZES-SPIONs have a hydrodynamic diameter of only 5.5 nm and clearance

by the renal system was confirmed in animal studies, in which over 87% of ZES-SPIONs administered to mice were cleared via urine within the first 3 h. As such multiple scans are possible without iron accumulation or retention of the nanoparticle in target organs.

Polyethylene glycol (PEG) coated SPIONs were developed by Tromsdorf et al. (2009). These SPIONs had a hydrophobic diameter of 10–15 nm. This size permitted positive T1 contrast enhancement, although was slightly beyond the size at which efficient renal clearance was possible. The presence of the PEG coating, however, reduced uptake by macrophages (Tromsdorf et al. 2009). As such, the authors hypothesised that ultrasmall SPIONs could serve as blood pool-imaging agents, although clearance at the specific size tested may be delayed.

Nevertheless, the development of ultrasmall SPIONs may serve to overcome the existing limitations of SPION-based contrast agents and permit novel gadolinium-free contrast agents. The possibility of blood pool-imaging may also serve as another possible approach for tumour imaging and radiotherapy planning in future studies.

Targeted SPIONs

Another potential approach to facilitate SPION-based imaging, outside the liver or reticuloendothelial system, is to functionalise SPIONs with various targeting moieties (Bakhtiary et al. 2016). This can involve a number of different molecules depending on the target, with most focusing on either antibodies/aptamers, or small molecules targeted to receptors over-expressed on cancer cells. Several SPIONs are under development for this purpose.

Yoo et al. evaluated folate-expressing SPIONs (approx. 18.5 nm size) for lung cancer imaging, which demonstrated increased uptake in mouse models, but this uptake could be suppressed by administration of folic acid before administering the nanoparticle, suggesting overexpression of folic acid receptors was responsible for the uptake (Yoo et al. 2012). Similarly increased uptake in MTT cells was observed by Liao et al. (2011). Lee et al. developed antibody-conjugated SPIONs conjugated to trastuzumab, which demonstrated uptake in mouse models, facilitating imaging of tumours as small as 50 mg in mass (Lee et al. 2007).

Antibody-conjugated SPIONs include antibodies to prostate-specific membrane antigen (PSMA) conjugated to polyethylene glycol-coated iron oxide nanoparticles (110 nm size), developed by Tse et al. (2015). These nanoparticles, when evaluated in prostate cancer cell lines, caused no significant toxicity. In orthotopic prostate cancer models in mice, they caused signal suppression on T2 MRI (Fig. 12).

Novel and emerging nanoparticle candidates

Of the general classes of nanoparticles discussed thus far for MRgRT, GdNPs and SPIONs are as of 2022 the most clinically advanced. Nevertheless, other candidates remain under development, mostly in pre-clinical stages. Individual candidates may exhibit specific properties of clinical use for defined indications, which will hopefully be demonstrated further in pre-clinical and eventual clinical trials.

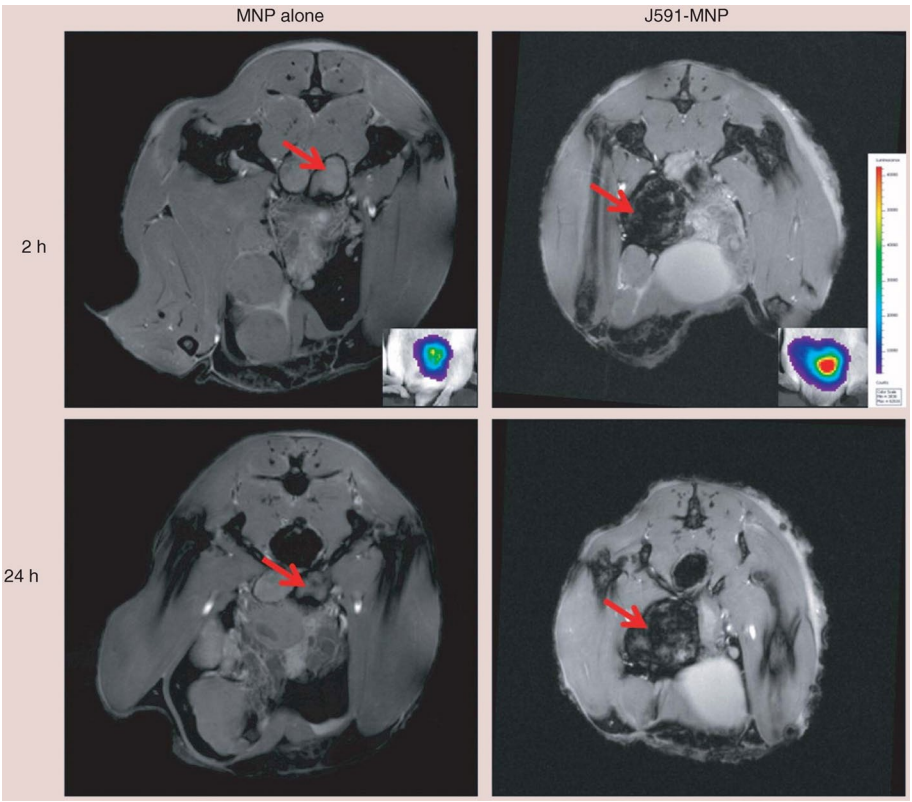

Fig. 12 Systemic administration of antibody-conjugated SPIONs (J591-MNP) against PSMA in mice, compared to unconjugated SPIONs (MNP alone), measured on a T2 MRI scan. Injection was performed when tumour size (measured by bioluminescence, shown in the figure inserts) reached target values antibody-mediated uptake in the conjugated example enables greater total uptake in the tumour (red arrows) (Reproduced with permission from Tse et al. (2015), copyright 2015, Future Medicine Ltd)

Manganese dioxide

Manganese oxide nanoparticles have been developed previously as contrast agents for MRI (Cai et al. 2019). The toxicity of manganese, a potential challenge for these nanoparticles, can be mitigated somewhat with coating the nanoparticle in polyethylene glycol (PEG) (Cai et al. 2019). Similarly, polymer-coated manganese dioxide nanoparticles have been reported as having modulating effects on the tumour environment (specifically tumour hypoxia) with a radiosensitisation effect in animal models (Abbasi et al. 2016). Preliminary evaluation of these nanoparticles is underway for their suitability as a theranostic (MRI and radiotherapy enhancement) agent, with positive results (Yen et al. 2021). In animal models, the nanoparticles were retained in tumour deposits for about 4 h and cleared from normal organs within 72 h. Although positive results on survival in animal studies have been determined including improved survival and reduced tumour volumes in animals treated with these nanoparticles in combination with radiotherapy, human trials are yet to commence.

Liu et al. developed manganese dioxide nanoparticles approximately 125–150 nm across, containing the chemical radiosensitiser acridine orange (Liu et al. 2020). These nanoparticles degraded in the acidic tumour environment, releasing free oxygen and manganese ions (Fig. 13). The intention is to reverse the hypoxic environment of

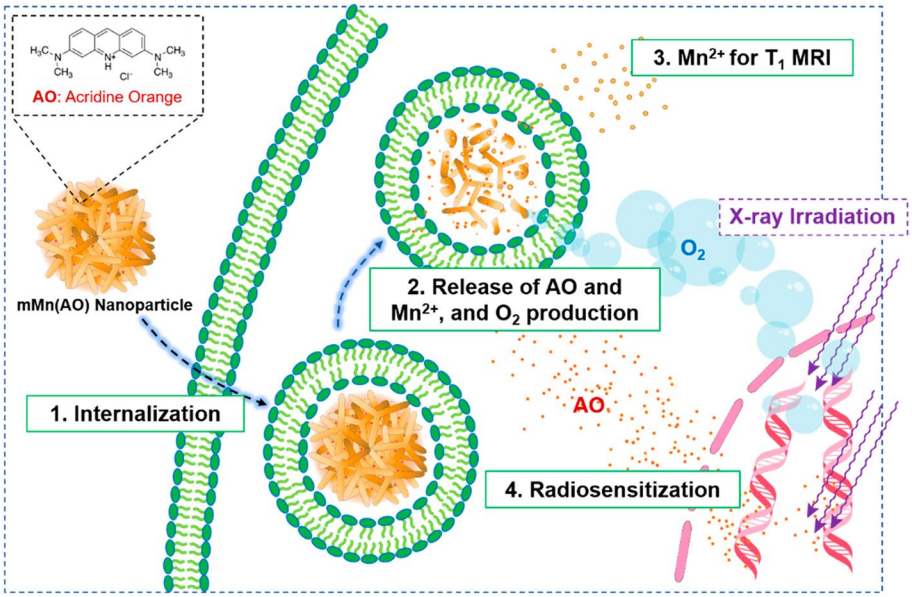

Fig. 13 Manganese dioxide nanoparticles, with T1-MRI contrast enhancing properties, loaded with Acridine Orange (AO), degrading inside hypoxic tumour cells to release oxygen and enhance sensitivity to radiotherapy (Reprinted with permission from Liu et al. (2020), copyright 2020, American Chemical Society)

tumour cells, increasing response to radiotherapy. Meanwhile the release of manganese enhances T1 contrast on MRI scans. Animal studies with intra-tumoral injection followed by radiotherapy showed positive results, with significant suppression of tumour volume compared to controls; future studies are planned to evaluate the effects of systemic administration (Liu et al. 2020).

Nanoparticles with multiple active elements

The following details a number of nanoparticles with multiple active elements contained within to facilitate dual imaging and radiotherapy enhancement within a single particle. In particular, elements that facilitate MRI contrast may be combined with high-Z elements to facilitate radiotherapy enhancement.

Combined gold manganese nanoparticles were synthesised by Wang et al., in which a gold shell was applied to a manganese dioxide core, surrounded by hyaluronic acid (Wang et al. 2019). These nanoparticles, evaluated in vivo in 4T1 orthoptic tumour models, inhibited tumour growth in conjunction with radiotherapy, and lead to tumour regression with radiotherapy and phototherapy, to a significantly greater extent than untreated or radiotherapy-only controls (Wang et al. 2019).

Kuang et al. developed combined gadolinium–hafnium nanoparticles loaded with the chemotherapy agent cisplatin. With a total size of 5 nm, within the range of renal clearance, these nanoparticles were visible in T1-weighted MRI scans (Kuang et al. 2020). The nanoparticles were intended to facilitate multi-modal treatment including slow-release chemotherapy, phototherapy and radiotherapy in resistant tumours. As such, it serves as a potential platform for MRgRT, a concept demonstrated in animal models (Kuang et al. 2020).

Nanoparticles incorporating bismuth, selenium and manganese oxide on a bovine serum albumin template were created by Yao et al. (2021). Intended as a multimodal platform for image contrast and radiotherapy enhancement, the manganese oxide component is intended to catalyse the conversion of hydrogen peroxide (present at increased concentration in tumour cells) to oxygen, overcoming radioresistance in hypoxic tumour cells. The presence of high-Z bismuth also facilitated increased local radiation effects. The nanoparticle induced positive T1 contrast on MRI scans and considerably reduced tumour growth in combination with radiotherapy (Fig. 14).

An additional combined nanoparticle formulation in the pre-clinical stage was developed by Maniglio et al., which incorporates both iron oxide and gold (Maniglio et al. 2018). Similar to pure SPIONs, it exploits the superparamagnetic property of iron oxide as an MRI contrast agent. Consequently, it appears dark on T2-weighted MRI sequences. The core of this nanoparticle is gold, whose higher atomic number is intended to enable an enhanced radiosensitisation effect, thus suitable for MRgRT (Maniglio et al. 2018). These hydrophobic nanoparticles demonstrated limited intrinsic cytotoxicity and were taken up by osteosarcoma cells in in vitro assays.

Li et al. developed a core–shell nanoparticle platform incorporating a gold core with a manganese sulfide inner shell, a zinc sulfide outer shell and a PEG outer coating, with a hydrodynamic diameter of approximately 100 nm (Li et al. 2016). The intended structure was for the gold core to provide local radiation enhancement, the manganese shell providing T1 image contrast and the zinc shell protecting against oxidation, respectively. This nanoparticle, intended specifically for MRgRT, showed little intrinsic toxicity but considerably inhibited tumour growth in combination with 6 Gy radiotherapy in a 4T1 breast cancer model.

Damasco et al. synthesised ultrasmall nanoparticles containing ytterbium and gadolinium as a multifunctional imaging and radiosensitisation platform (Damasco et al. 2021).

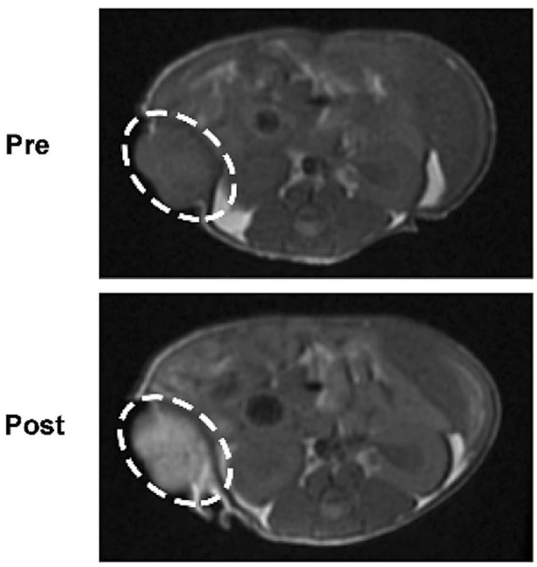

Fig. 14 Tumour MRI contrast enhancement in a mouse model after injection of bismuth–manganese albumin templated nanoparticles (Reprinted with permission from (Yao et al. 2021), copyright 2021 American Chemical Society)

These nanoparticles were conjugated with folate, aiming to facilitate active targeting of glioma cell lines. In rats, the conjugation of these nanoparticles increased penetration of the blood–brain barrier from 5% in untargeted nanoparticles, to 17% in folate-conjugated nanoparticles. In in vitro studies, irradiation of C6 rat glioma cells with 2 Gy of X-ray photons reduced colony survival by 20%, compared to 60% reduction in the presence of the nanoparticles. No intrinsic toxicity was reported from the presence of the nanoparticles (Damasco et al. 2021).

Challenges and opportunities for nanoparticles in MRI-guided radiotherapy

Arguably the biggest challenge faced by the field of cancer nanomedicine has been clinical translation. In the specific context of MRgRT, the subject of this review, GdNPs and SPIONs face a similar challenge, albeit somewhat subdued by the promising clinical trials of AGuIX and the history of clinical use of SPIONs. Nevertheless, as imaging agents, these nanoparticles must compete with small-molecule agents for whom pharmacokinetic evaluation may be more straightforward (Kiessling et al. 2014). For many earlier-generation agents, particularly SPION-based agents, much of the imaging potential has, as discussed, focused on blood pool-imaging or uptake in the reticuloendothelial system; in the case of blood pool-imaging, competition with techniques such as time-of-flight MRI (which requires no contrast) may limit the application of this approach in certain indications (Kiessling et al. 2014).

In the case of cancer imaging, next-generation nanoparticle products need to reduce clearance by the reticuloendothelial system, whilst still being taken up by tumour deposits (Chapman et al. 2013). This is increasingly being overcome with smaller nanoparticle sizes, targeting ligands and optimisation of nanoparticle properties including surface charge. Shielding nanoparticles with polyethylene glycol (PEG) may limit reticuloendothelial uptake at a potential cost of somewhat reduced tumour uptake (although this may be offset by increased circulation time). As such, combination with active targeting ligands, or optimising size and surface charge to maximise the EPR effect, have been considered (Chapman et al. 2013). The emergence of nanoparticles with positive T1 contrast is also a welcome development that is likely to make these agents more widely accepted among radiologists for imaging purposes.

In contrast, tumour microenvironment targeting, another approach for active targeting, exploits the chemical and physical properties that differentiate them from normal tissue, including hypoxia, acidity and increased concentrations of specific enzymes (Fernandes et al. 2018; Uthaman et al. 2018). While such an approach may be advantageous for promoting specificity uptake of anti-cancer agents into tumour cells, it is less likely to promote retention of nanoparticles in tumour deposits, and so it is not considered for radiotherapy or MRI contrast enhancement.

Similarly, for nanoparticle agents that use the EPR effect, challenges for targeting very small tumour deposits (< 1 mm minimum dimension) may occur as the development of "leaky" vasculature may not occur at this stage; targeting ligands may be effective at overcoming this (Chapman et al. 2013). Challenges with targeting ligands do also exist, particularly in that their presence may tend to reduce total circulation half-life (as targeting ligands may make nanoparticles more amenable to clearance). This can potentially reduce total uptake compared to passively targeted nanoparticles (Chen et al. 2012).

It is also recognised that the EPR effect is not entirely homogenous and appears to be influenced by factors such as the tumour histological subtype (Wang 2015), size and vascular infiltration (Maeda 2015; Pasut 2019). Some authors have proposed the development of radiolabelled nanoparticles to enable in vivo confirmation of the EPR effect in individual patients in whom they are administered. This could be done by administering nanoparticles labelled with a PET or SPECT radioisotope to determine quantitatively, the extent to which EPR-mediated nanoparticle uptake occurs and where it does so (Wang 2015). This would then justify irradiation of nanoparticle-rich tumours to exert a radiosensitisation and dose enhancement effect.

Other generalised challenges with nanoparticle agents include the risk of toxicity and the need for specialised approaches to evaluate the potential toxic effects of the nanoparticles. In particular, a need exists for nanoparticles to accumulate in tumour deposits to a sufficient extent to enhance radio-therapeutic efficacy, whilst not inducing clinically significant toxicity (Schuemann et al. 2020; Wilhelm et al. 2016). It has been proposed that increasing standardisation of nanoparticle design and evaluation will help in the identification of toxic effects associated with particular nanoparticle components, enabling reduced toxicity in subsequent generations (Hofmann-Amtenbrink et al. 2015). To help reduce the risk of toxic effects in future generations of nanoparticle products, the application of versatile, standardised platforms (such as that used by AGuIX) with limited intrinsic toxicity may be effective. This would enable customisation to given clinical indications by way of addition of specific ligands to a standardised structure, may facilitate a lower risk of toxicity.

A final challenge for nanoparticle agents in their clinical translation is ensuring their cost-effectiveness and ability to remain financially competitive against other agents (Chapman et al. 2013). Given their relative complexity compared to certain small-molecule agents, and the need for specialist expertise in their manufacture and characterisation, the cost of developing nanoparticle-based contrast agents is potentially high. In the MRI contrast context, this has made it difficult for traditional SPION-based agents to find widespread clinical use (Chapman et al. 2013). However, the increasing advantage of ultrasmall SPION agents, or the theranostic potential of nanoparticles for MRgRT, offering clinical advantages not readily achieved by standard small molecules, may present clinical justifications for nanoparticle agents and support their clinical utilisation. Furthermore, expansion of the imaging applications of nanoparticle agents may further justify their commercialisation; in the case of SPIONs, a notable example is the development of SPION agents as contrast agents for portable low-field MRI (Stein 2022; Waddington et al. 2020), substantially increasing their overall clinical utility.

Conclusion

A number of nanoparticle agents at varying stages of development present exciting opportunities for synergistic effects in MRI-guided radiotherapy, potentially enhancing both image contrast and radiation dose contrast. As of 2022, gadolinium-based nanoparticle agents are now in human clinical trials for MRI-guided radiotherapy. At the pre-clinical stage, newer iron oxide nanoparticle solutions and novel labelling and functionalisation approaches to existing nanoparticles are under development. The authors contend that nanoparticle-enhanced MRI-guided radiotherapy is on the verge of rapid

uptake into clinical use and that it is an ideal time to consider the potential applications of such agents into clinical radiotherapy workflows. Furthermore, the nanoparticle platforms currently undergoing clinical evaluation in humans both demonstrate the potential for further adaptation and functionalisation with future nanoparticles under development with additional properties. It is anticipated that the promise of nanoparticles and MRI guidance will further enhance the clinical utility of radiotherapy and further improve outcomes for cancer patients.

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Author contributions
LS wrote the main manuscript text. DW contributed to the content of the section "Superparamagentic Ion Oxide Nanoparticles". HB and ZK reviewed the main manuscript text and made a number of recommendations incorporated into the manuscript. All authors reviewed the final manuscript prior to publication. All authors read and approved the final manuscript.

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References

Abadjian M-C, Latoche J, Thomas E, Foley L, Day K, Lux F et al (2016) PET and MR imaging with 64Cu/68Ga-labeled AGuIX ultra-small nanoparticles in tumor-bearing mice. J Nucl Med 57(supplement 2):1181–1181

Abbasi AZ, Gordijo CR, Amini MA, Maeda A, Rauth AM, DaCosta RS et al (2016) Hybrid manganese dioxide nanoparticles potentiate radiation therapy by modulating tumor hypoxia. Cancer Res 76(22):6643–6656

AGuIX (2021) Clinical trial cancer drugs, AGuIX® evaluation. NH TherAguix. https://nhtheraguix.com/pipeline/. Accessed 26 Sept 2021

Attia MF, Anton N, Wallyn J, Omran Z, Vandamme TF (2019) An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. J Pharm Pharmacol 71(8):1185–1198

Bagley AF, Ludmir EB, Maitra A, Minsky BD, Li Smith G, Das P et al (2022) NBTXR3, a first-in-class radioenhancer for pancreatic ductal adenocarcinoma: report of first patient experience. Clin Transl Radiat Oncol 33:66–69

Bakhtiary Z, Saei AA, Hajipour MJ, Raoufi M, Vermesh O, Mahmoudi M (2016) Targeted superparamagnetic iron oxide nanoparticles for early detection of cancer: possibilities and challenges. Nanomed Nanotechnol Biol Med 12(2):287–307

Bashir MR, Bhatti L, Marin D, Nelson RC (2015) Emerging applications for ferumoxytol as a contrast agent in MRI. J Magn Reson Imaging 41(4):884–898

Bazak R, Houri M, Achy SE, Kamel S, Refaat T (2015) Cancer active targeting by nanoparticles: a comprehensive review of literature. J Cancer Res Clin Oncol 141(5):769–784

Bi Y, Hao F, Yan G, Teng L, Lee RJ, Xie J (2016) Actively targeted nanoparticles for drug delivery to tumor. Curr Drug Metab 17(8):763–782

Borisova T, Pozdnyakova N, Krisanova N, Pastukhov A, Dudarenko M, Paliienko K et al (2021) Unique features of brain metastases-targeted AGuIX nanoparticles vs their constituents: a focus on glutamate-/GABA-ergic neurotransmission in cortex nerve terminals. Food Chem Toxicol 149:112004

Bort G, Lux F, Dufort S, Crémillieux Y, Verry C, Tillement O (2020) EPR-mediated tumor targeting using ultrasmall-hybrid nanoparticles: from animal to human with theranostic AGuIX nanoparticles. Theranostics 10(3):1319–1331

Bouziotis P, Stellas D, Thomas E, Truillet C, Tsoukalas C, Lux F et al (2017) 68Ga-radiolabeled AGuIX nanoparticles as dual-modality imaging agents for PET/MRI-guided radiation therapy. Nanomed 12(13):1561–1574

Brighi C, Verburg N, Koh E-S, Walker A, Chen C, Pillay S et al (2022) Repeatability of radiotherapy dose-painting prescriptions derived from a multiparametric magnetic resonance imaging model of glioblastoma infiltration. Phys Imaging Radiat Oncol 23:8–15
Butterworth KT, McMahon SJ, Currell FJ, Prise KM (2012) Physical basis and biological mechanisms of gold nanoparticle radiosensitization. Nanoscale 4(16):4830–4838
Byrne HL, Le Duc G, Lux F, Tillement O, Holmes NM, James A et al (2020) Enhanced MRI-guided radiotherapy with gadolinium-based nanoparticles: preclinical evaluation with an MRI-linac. Cancer Nanotechnol 11(1):9
Cai X, Zhu Q, Zeng Y, Zeng Q, Chen X, Zhan Y (2019) Manganese oxide nanoparticles as MRI contrast agents in tumor multimodal imaging and therapy. Int J Nanomed 14:8321–8344
Castaneda RT, Khurana A, Khan R, Daldrup-Link HE (2011) Labeling stem cells with ferumoxytol, an FDA-approved iron oxide nanoparticle. J vis Exp 57:e3482
Chapman S, Dobrovolskaia M, Farahani K, Goodwin A, Joshi A, Lee H et al (2013) Nanoparticles for cancer imaging: the good, the bad, and the promise. Nano Today 8(5):454–460
Chen WC, Zhang AX, Li S-D (2012) Limitations and niches of the active targeting approach for nanoparticle drug delivery. Eur J Nanomed 4(2–4):89–93
Chen F, Ehlerding EB, Cai W (2014) Theranostic nanoparticles. J Nucl Med 55(12):1919–1922
Chin S, Eccles CL, McWilliam A, Chuter R, Walker E, Whitehurst P et al (2020) Magnetic resonance-guided radiation therapy: a review. J Med Imaging Radiat Oncol 64(1):163–177
Choi J, Kim G, Cho SB, Im H-J (2020) Radiosensitizing high-Z metal nanoparticles for enhanced radiotherapy of glioblastoma multiforme. J Nanobiotechnol 18(1):122
Clemons TD, Singh R, Sorolla A, Chaudhari N, Hubbard A, Iyer KS (2018) Distinction between active and passive targeting of nanoparticles dictate their overall therapeutic efficacy. Langmuir 34(50):15343–15349
Corradini S, Alongi F, Andratschke N, Belka C, Boldrini L, Cellini F et al (2019) MR-guidance in clinical reality: current treatment challenges and future perspectives. Radiat Oncol 14(1):92
Costa AF, van der Pol CB, Maralani PJ, McInnes MDF, Shewchuk JR, Verma R et al (2018) Gadolinium deposition in the brain: a systematic review of existing guidelines and policy statement issued by the Canadian association of radiologists. Can Assoc Radiol J 69(4):373–382
Damasco JA, Ohulchanskyy TY, Mahajan S, Chen G, Singh A, Kutscher HL et al (2021) Excretable, ultrasmall hexagonal NaGdF4:Yb50% nanoparticles for bimodal imaging and radiosensitization. Cancer Nanotechnol 12(1):4
de Mol van Otterloo SR, Christodouleas JP, Blezer ELA, Akhiat H, Brown K, Choudhury A et al (2020) The MOMENTUM study: an international registry for the evidence-based introduction of MR-guided adaptive therapy. Front Oncol 10:1328. https://doi.org/10.3389/fonc.2020.01328
Dentamaro M, Lux F, Vander Elst L, Dauguet N, Montante S, Moussaron A et al (2016) Chemical and in vitro characterizations of a promising bimodal AGuIX probe able to target apoptotic cells for applications in MRI and optical imaging. Contrast Media Mol Imaging 11(5):381–395
Detappe A, Kunjachan S, Rottmann J, Robar J, Tsiamas P, Korideck H et al (2015) AGuIX nanoparticles as a promising platform for image-guided radiation therapy. Cancer Nanotechnol 6(1):4
Detappe A, Thomas E, Tibbitt MW, Kunjachan S, Zavidij O, Parnandi N et al (2017) Ultrasmall silica-based bismuth gadolinium nanoparticles for dual magnetic resonance-computed tomography image guided radiation therapy. Nano Lett 17(3):1733–1740
Detappe A, Mathieu C, Jin C, Agius MP, Diringer M-C, Tran V-L et al (2020) Anti-MUC1-c antibody-conjugated nanoparticles potentiate the efficacy of fractionated radiation therapy. Int J Radiat Oncol 108(5):1380–1389
Du F, Zhang L, Zhang L, Zhang M, Gong A, Tan Y et al (2017) Engineered gadolinium-doped carbon dots for magnetic resonance imaging-guided radiotherapy of tumors. Biomaterials 121:109–120
Dulińska-Litewka J, Łazarczyk A, Hałubiec P, Szafrański O, Karnas K, Karewicz A (2019) Superparamagnetic iron oxide nanoparticles—current and prospective medical applications. Materials 12(4):617
Fang J, Islam W, Maeda H (2020) Exploiting the dynamics of the EPR effect and strategies to improve the therapeutic effects of nanomedicines by using EPR effect enhancers. Adv Drug Deliv Rev 157:142–160
Fernandes C, Suares D, Yergeri MC (2018) Tumor microenvironment targeted nanotherapy. Front Pharmacol 9:1230
Fries P, Morr D, Müller A, Lux F, Tillement O, Massmann A et al (2015) Evaluation of a gadolinium-based nanoparticle (AGuIX) for contrast-enhanced MRI of the liver in a rat model of hepatic colorectal cancer metastases at 9.4 Tesla. ROFO Fortschr Geb Rontgenstr Nuklearmed 187(12):1108–1115
Gawel AM, Singh R, Debinski W (2022) Metal-based nanostructured therapeutic strategies for glioblastoma treatment—an update. Biomedicines 10(7):1598
Gholami YH, Maschmeyer R, Kuncic Z (2019) Radio-enhancement effects by radiolabeled nanoparticles. Sci Rep 9(1):14346
Gholami YH, Yuan H, Wilks MQ, Maschmeyer R, Normandin MD, Josephson L et al (2020) A radio-nano-platform for T1/T2 dual-mode PET-MR imaging. Int J Nanomed 15:1253–1266
Grégoire V, Guckenberger M, Haustermans K, Lagendijk JJW, Ménard C, Pötter R et al (2020) Image guidance in radiation therapy for better cure of cancer. Mol Oncol 14(7):1470–1491
Gries M, Thomas N, Daouk J, Rocchi P, Choulier L, Jubréaux J et al (2020) Multiscale selectivity and in vivo biodistribution of NRP-1-targeted theranostic AGuIX nanoparticles for PDT of glioblastoma. Int J Nanomed 15:8739–8758
Hoffmann C, Calugaru V, Borcoman E, Moreno V, Calvo E, Liem X et al (2021) Phase I dose-escalation study of NBTXR3 activated by intensity-modulated radiation therapy in elderly patients with locally advanced squamous cell carcinoma of the oral cavity or oropharynx. Eur J Cancer 146:135–144
Hofmann-Amtenbrink M, Grainger DW, Hofmann H (2015) Nanoparticles in medicine: current challenges facing inorganic nanoparticle toxicity assessments and standardizations. Nanomed Nanotechnol Biol Med 11(7):1689–1694
Houston ZH, Bunt J, Chen K-S, Puttick S, Howard CB, Fletcher NL et al (2020) Understanding the uptake of nanomedicines at different stages of brain cancer using a modular nanocarrier platform and precision bispecific antibodies. ACS Cent Sci 6(5):727–738

Hu P, Cheng D, Huang T, Banizs AB, Xiao J, Liu G et al (2017) Evaluation of novel 64Cu-labeled theranostic gadolinium-based nanoprobes in HepG2 tumor-bearing nude mice. Nanoscale Res Lett 12(1):523
Hu P, Fu Z, Liu G, Tan H, Xiao J, Shi H et al (2019) Gadolinium-based nanoparticles for theranostic MRI-guided radiosensitization in hepatocellular carcinoma. Front Bioeng Biotechnol 7:368
Hua S, de Matos MBC, Metselaar JM, Storm G (2018) Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization. Front Pharmacol 9:790
Huclier S, Ntsiba E, Thomas E, Alliot C, Cutler S, Lux F et al (2019) Multimodal AGuIX® nanoparticles: size characterization by HF5 and optimization of the radiolabeling with various SPECT/PET/theranostic tracers. Int J Med Nano Res. https://doi.org/10.23937/2378-3664.1410027
Jaffray D, Kupelian P, Djemil T, Macklis RM (2007) Review of image-guided radiation therapy. Expert Rev Anticancer Ther 7(1):89–103
Jain S, Coulter JA, Hounsell AR, Butterworth KT, McMahon SJ, Hyland WB et al (2011) Cell-specific radiosensitization by gold nanoparticles at megavoltage radiation energies. Int J Radiat Oncol Biol Phys 79(2):531–539
Janko C, Ratschker T, Nguyen K, Zschiesche L, Tietze R, Lyer S et al (2019) Functionalized superparamagnetic iron oxide nanoparticles (SPIONs) as platform for the targeted multimodal tumor therapy. Front Oncol 9:59
Jin J, Zhao Q (2020) Engineering nanoparticles to reprogram radiotherapy and immunotherapy: recent advances and future challenges. J Nanobiotechnol 18(1):75
Keall PJ, Barton M, Crozier S, Australian MRI-Linac Program, including contributors from Ingham Institute, Illawarra Cancer Care Centre, Liverpool Hospital, Stanford University, Universities of Newcastle (2014) The Australian magnetic resonance imaging-linac program. Semin Radiat Oncol 24(3):203–206
Keall PJ, Brighi C, Glide-Hurst C, Liney G, Liu PZY, Lydiard S et al (2022) Integrated MRI-guided radiotherapy—opportunities and challenges. Nat Rev Clin Oncol 19:1–13
Kiessling F, Mertens ME, Grimm J, Lammers T (2014) Nanoparticles for imaging: top or flop? Radiology 273(1):10–28
Kirichenko A (2021) Adaptive stereotactic radiotherapy with superparamagnetic iron oxide nanoparticles (SPION) cellular magnetic resonance imaging on MR-linac (MR-L-SPION) for primary and metastatic hepatic malignancies with assessment of treatment response. clinicaltrials.gov. Report No. NCT04682847. https://clinicaltrials.gov/ct2/show/NCT04682847
Kishan AU, Lamb J, Casado M, Wang X, Ma TM, Low D et al (2022) Magnetic resonance imaging-guided versus computed tomography-guided stereotactic body radiotherapy for prostate cancer (MIRAGE): interim analysis of a phase III randomized trial. J Clin Oncol 40(6_suppl):255
Kotb S, Piraquive J, Lamberton F, Lux F, Verset M, Di Cataldo V et al (2016) Safety evaluation and imaging properties of gadolinium-based nanoparticles in nonhuman primates. Sci Rep 6(1):35053
Kuang Y, Zhang Y, Zhao Y, Cao Y, Zhang Y, Chong Y et al (2020) Dual-stimuli-responsive multifunctional Gd2Hf2O7 nanoparticles for MRI-guided combined chemo-/photothermal-/radiotherapy of resistant tumors. ACS Appl Mater Interfaces 12(32):35928–35939
Kuncic Z, Lacombe S (2018) Nanoparticle radio-enhancement: principles, progress and application to cancer treatment. Phys Med Biol 63(2):02TR01
Layne KA, Wood DM, Dargan PI (2020) Gadolinium-based contrast agents—what is the evidence for 'gadolinium deposition disease' and the use of chelation therapy? Clin Toxicol 58(3):151–160
Le Duc G, Roux S, Paruta-Tuarez A, Dufort S, Brauer E, Marais A et al (2014) Advantages of gadolinium based ultrasmall nanoparticles vs molecular gadolinium chelates for radiotherapy guided by MRI for glioma treatment. Cancer Nanotechnol 5(1):4
Lee J-H, Huh Y-M, Jun Y, Seo J, Jang J, Song H-T et al (2007) Artificially engineered magnetic nanoparticles for ultra-sensitive molecular imaging. Nat Med 13(1):95–99
Lee D, Oh S, Hwang M-S, McCauley M, Pavord D, Kyung Lim Y et al (2022) Application of super-paramagnetic iron oxide nanoparticle to improve tumour visualization for MR-guided SBRT using elekta unity MR-linac, London
Leeman J (2021) Nano-SMART: an adaptive phase I–II trial of AGuIX gadolinium-based nanoparticles with stereotactic magnetic resonance-guided adaptive radiation therapy for centrally located lung tumors and locally advanced unresectable pancreatic ductal adenocarcinoma. clinicaltrials.gov. Report No. NCT04789486. https://clinicaltrials.gov/ct2/show/NCT04789486
Li M, Zhao Q, Yi X, Zhong X, Song G, Chai Z et al (2016) Au@MnS@ZnS core/shell/shell nanoparticles for magnetic resonance imaging and enhanced cancer radiation therapy. ACS Appl Mater Interfaces 8(15):9557–9564
Liao Z, Wang H, Lv R, Zhao P, Sun X, Wang S et al (2011) Polymeric liposomes-coated superparamagnetic iron oxide nanoparticles as contrast agent for targeted magnetic resonance imaging of cancer cells. Langmuir 27(6):3100–3105
Liney GP, Jelen U, Byrne H, Dong B, Roberts TL, Kuncic Z et al (2019) Technical note: the first live treatment on a 1.0 Tesla inline MRI-linac. Med Phys 46(7):3254–3258
Liu J, Zhang W, Kumar A, Rong X, Yang W, Chen H et al (2020) Acridine orange encapsulated mesoporous manganese dioxide nanoparticles to enhance radiotherapy. Bioconjug Chem 31(1):82–92
Liu Y, Leong ATL, Zhao Y, Xiao L, Mak HKF, Tsang ACO et al (2021) A low-cost and shielding-free ultra-low-field brain MRI scanner. Nat Commun 12(1):7238
Luchette M, Korideck H, Makrigiorgos M, Tillement O, Berbeco R (2014) Radiation dose enhancement of gadolinium-based AGuIX nanoparticles on HeLa cells. Nanomed Nanotechnol Biol Med 10(8):1751–1755
Lux F, Tran VL, Thomas E, Dufort S, Rossetti F, Martini M et al (2019) AGuIX® from bench to bedside—transfer of an ultrasmall theranostic gadolinium-based nanoparticle to clinical medicine. Br J Radiol 92(1093):20180365
Ma TM, Lamb JM, Casado M, Wang X, Basehart TV, Yang Y et al (2021) Magnetic resonance imaging-guided stereotactic body radiotherapy for prostate cancer (mirage): a phase iii randomized trial. BMC Cancer 21(1):538
Maeda H (2015) Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity. Adv Drug Deliv Rev 91:3–6
Maniglio D, Benetti F, Minati L, Jovicich J, Valentini A, Speranza G et al (2018) Theranostic gold-magnetite hybrid nanoparticles for MRI-guided radiosensitization. Nanotechnology 29(31):315101

Maschmeyer RT, Gholami YH, Kuncic Z (2020) Clustering effects in nanoparticle-enhanced β^- emitting internal radionuclide therapy: a Monte Carlo study. Phys Med Biol 65(12):125007
Matson ML, Wilson LJ (2010) Nanotechnology and MRI contrast enhancement. Future Med Chem 2(3):491–502
McCarthy JR, Weissleder R (2008) Multifunctional magnetic nanoparticles for targeted imaging and therapy. Adv Drug Deliv Rev 60(11):1241–1251
Mittauer K, Paliwal B, Hill P, Bayouth JE, Geurts MW, Baschnagel AM et al (2018) A new era of image guidance with magnetic resonance-guided radiation therapy for abdominal and thoracic malignancies. Cureus 10(4):e2422
Nakamura H, Jun F, Maeda H (2015) Development of next-generation macromolecular drugs based on the EPR effect: challenges and pitfalls. Expert Opin Drug Deliv 12(1):53–64
Naseri N, Ajorlou E, Asghari F, Pilehvar-Soltanahmadi Y (2018) An update on nanoparticle-based contrast agents in medical imaging. Artif Cells Nanomed Biotechnol 46(6):1111–1121
Nelson NR, Port JD, Pandey MK (2020) Use of superparamagnetic iron oxide nanoparticles (SPIONs) via multiple imaging modalities and modifications to reduce cytotoxicity: an educational review. J Nanotheranostics 1(1):105–135
Neuwelt A, Sidhu N, Hu C-AA, Mlady G, Eberhardt SC, Sillerud LO (2015) Iron-based superparamagnetic nanoparticle contrast agents for MRI of infection and inflammation. Am J Roentgenol 204(3):W302–W313
Nguyen K-L, Yoshida T, Kathuria-Prakash N, Zaki IH, Varallyay CG, Semple SI et al (2019) Multicenter safety and practice for off-label diagnostic use of ferumoxytol in MRI. Radiology 293(3):554–564
Normandin MD, Yuan H, Wilks MQ, Chen HH, Kinsella JM, Cho H et al (2015) Heat-induced radiolabeling of nanoparticles for monocyte tracking by PET. Angew Chem Int Ed 54(44):13002–13006
Oghabian MA, Jeddi-Tehrani M, Zolfaghari A, Shamsipour F, Khoei S, Amanpour S (2011) Detectability of Her2 positive tumors using monoclonal antibody conjugated iron oxide nanoparticles in MRI. J Nanosci Nanotechnol 11(6):5340–5344
Otazo R, Lambin P, Pignol J-P, Ladd ME, Schlemmer H-P, Baumann M et al (2021) MRI-guided radiation therapy: an emerging paradigm in adaptive radiation oncology. Radiology 298(2):248–260
Pasut G (2019) Grand challenges in nano-based drug delivery. Front Med Technol 1:1
Pearce AK, O'Reilly RK (2019) Insights into active targeting of nanoparticles in drug delivery: advances in clinical studies and design considerations for cancer nanomedicine. Bioconjug Chem 30(9):2300–2311
Pellico J, Gawne PJ, de Rosales RTM (2021) Radiolabelling of nanomaterials for medical imaging and therapy. Chem Soc Rev 50(5):3355–3423
Plissonneau M, Pansieri J, Heinrich-Balard L, Morfin J-F, Stransky-Heilkron N, Rivory P et al (2016) Gd-nanoparticles functionalization with specific peptides for ß-amyloid plaques targeting. J Nanobiotechnol 14(1):60
Pratt EC, Shaffer TM, Grimm J (2016) Nanoparticles and radiotracers: advances toward radionanomedicine. Wires Nanomed Nanobiotechnol 8(6):872–890
Rocchi P, Brichart-Vernos D, Lux F, Morfin I, David L, Rodriguez-Lafrasse C et al (2022) A new generation of ultrasmall nanoparticles inducing sensitization to irradiation and copper depletion to overcome radioresistant and invasive cancers. Pharmaceutics 14(4):814
Rudnick MR, Wahba IM, Leonberg-Yoo AK, Miskulin D, Litt HI (2021) Risks and options with gadolinium-based contrast agents in patients with CKD: a review. Am J Kidney Dis 77(4):517–528
Russell E, Dunne V, Russell B, Mohamud H, Ghita M, McMahon SJ et al (2021) Impact of superparamagnetic iron oxide nanoparticles on in vitro and in vivo radiosensitisation of cancer cells. Radiat Oncol 16(1):104
Salem A, Little RA, Latif A, Featherstone AK, Babur M, Peset I et al (2019) Oxygen-enhanced MRI is feasible, repeatable, and detects radiotherapy-induced change in hypoxia in xenograft models and in patients with non-small cell lung cancer. Clin Cancer Res 25(13):3818–3829
Sancey L, Kotb S, Truillet C, Appaix F, Marais A, Thomas E et al (2015) Long-term in vivo clearance of gadolinium-based AGuIX nanoparticles and their biocompatibility after systemic injection. ACS Nano 9(3):2477–2488
Sanità G, Carrese B, Lamberti A (2020) Nanoparticle surface functionalization: how to improve biocompatibility and cellular internalization. Front Mol Biosci 7:587012. https://doi.org/10.3389/fmolb.2020.587012
Sarracanie M, LaPierre CD, Salameh N, Waddington DEJ, Witzel T, Rosen MS (2015) Low-cost high-performance MRI. Sci Rep 5(1):15177
Schuemann J, Bagley AF, Berbeco R, Bromma K, Butterworth KT, Byrne HL et al (2020) Roadmap for metal nanoparticles in radiation therapy: current status, translational challenges, and future directions. Phys Med Biol 65(21):21RM02
Shan L (2004) Superparamagnetic iron oxide nanoparticles (SPION) stabilized by alginate. Mol. Imaging Contrast Agent Database MICAD. Bethesda: National Center for Biotechnology Information (US). http://www.ncbi.nlm.nih.gov/books/NBK23636/. Accessed 18 July 2022
Shen Z, Wu A, Chen X (2017) Iron oxide nanoparticle based contrast agents for magnetic resonance imaging. Mol Pharm 14(5):1352–1364
Shi Y, van der Meel R, Chen X, Lammers T (2020) The EPR effect and beyond: strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. Theranostics 10(17):7921–7924
Stein J (2022) Evaluation of hyperfine low field strength portable point-of-care magnetic resonance imaging system in patients receiving ferumoxytol infusions. clinicaltrials.gov. Report No. NCT04721262. https://clinicaltrials.gov/ct2/show/NCT04721262
Sterzing F, Engenhart-Cabillic R, Flentje M, Debus J (2011) Image-guided radiotherapy. Dtsch Ärztebl Int 108(16):274–280
Tanimoto A, Kuribayashi S (2006) Application of superparamagnetic iron oxide to imaging of hepatocellular carcinoma. Eur J Radiol 58(2):200–216
Tassali N, Bianchi A, Lux F, Raffard G, Sanchez S, Tillement O et al (2016) MR imaging, targeting and characterization of pulmonary fibrosis using intra-tracheal administration of gadolinium-based nanoparticles. Contrast Media Mol Imaging 11(5):396–404
Thakare V, Tran V-L, Natuzzi M, Thomas E, Moreau M, Romieu A et al (2019) Functionalization of theranostic AGuIX® nanoparticles for PET/MRI/optical imaging. RSC Adv 9(43):24811–24815
Toth GB, Varallyay CG, Horvath A, Bashir MR, Choyke PL, Daldrup-Link HE et al (2017) Current and potential imaging applications of ferumoxytol for magnetic resonance imaging. Kidney Int 92(1):47–66

Tromsdorf UI, Bruns OT, Salmen SC, Beisiegel U, Weller H (2009) A highly effective, nontoxic T1 MR contrast agent based on ultrasmall PEGylated iron oxide nanoparticles. Nano Lett 9(12):4434–4440
Truillet C, Thomas E, Lux F, Huynh LT, Tillement O, Evans MJ (2016) Synthesis and characterization of 89Zr-labeled ultrasmall nanoparticles. Mol Pharm 13(7):2596–2601
Tse BW-C, Cowin GJ, Soekmadji C, Jovanovic L, Vasireddy RS, Ling M-T et al (2015) PSMA-targeting iron oxide magnetic nanoparticles enhance MRI of preclinical prostate cancer. Nanomedicine 10(3):375–386
University Hospital, Grenoble (2021) Radiotherapy of multiple brain metastases using AGuIX® gadolinium-chelated polysiloxane based nanoparticles: a prospective randomized phase II clinical trial. clinicaltrials.gov. Report No. NCT03818386. https://clinicaltrials.gov/ct2/show/NCT03818386
Unterweger H, Janko C, Schwarz M, Dézsi L, Urbanics R, Matuszak J et al (2017) Non-immunogenic dextran-coated superparamagnetic iron oxide nanoparticles: a biocompatible, size-tunable contrast agent for magnetic resonance imaging. Int J Nanomed 12:5223–5238
Uthaman S, Huh KM, Park I-K (2018) Tumor microenvironment-responsive nanoparticles for cancer theragnostic applications. Biomater Res 22(1):22
Verkooijen HM, Henke LE (2021) Sensible introduction of MR-guided radiotherapy: a warm plea for the RCT. Front Oncol 11:652889
Verry C, Dufort S, Lemasson B, Grand S, Pietras J, Troprès I et al (2020) Targeting brain metastases with ultrasmall theranostic nanoparticles, a first-in-human trial from an MRI perspective. Sci Adv 6(29):eaay5279
Verry C, Dufort S, Villa J, Gavard M, Iriart C, Grand S et al (2021) Theranostic AGuIX nanoparticles as radiosensitizer: a phase I, dose-escalation study in patients with multiple brain metastases (NANO-RAD trial). Radiother Oncol 160:159–165
Vogl TJ, Hammerstingl R, Schwarz W, Mack MG, Müller PK, Pegios W et al (1996) Superparamagnetic iron oxide-enhanced versus gadolinium-enhanced MR imaging for differential diagnosis of focal liver lesions. Radiology 198(3):881–887
Waddington DEJ, Boele T, Maschmeyer R, Kuncic Z, Rosen MS (2020) High-sensitivity in vivo contrast for ultra-low field magnetic resonance imaging using superparamagnetic iron oxide nanoparticles. Sci Adv 6(29):eabb0998
Wang Y-XJ (2011) Superparamagnetic iron oxide based MRI contrast agents: current status of clinical application. Quant Imaging Med Surg 1(1):35–40
Wang AZ (2015) EPR or no EPR? The billion-dollar question. Sci Transl Med 7(294):294ec112
Wang S, You Q, Wang J, Song Y, Cheng Y, Wang Y et al (2019) MSOT/CT/MR imaging-guided and hypoxia-maneuvered oxygen self-supply radiotherapy based on one-pot MnO_2-$mSiO_2$@Au nanoparticles. Nanoscale 11(13):6270–6284
Wei H, Bruns OT, Kaul MG, Hansen EC, Barch M, Wiśniowska A et al (2017) Exceedingly small iron oxide nanoparticles as positive MRI contrast agents. Proc Natl Acad Sci 114(9):2325–2330
Weinreb JC, Rodby RA, Yee J, Wang CL, Fine D, McDonald RJ et al (2021) Use of intravenous gadolinium-based contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. Radiology 298(1):28–35
Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF et al (2016) Analysis of nanoparticle delivery to tumours. Nat Rev Mater 1(5):1–12
Wu J (2021) The enhanced permeability and retention (EPR) effect: the significance of the concept and methods to enhance its application. J Pers Med 11(8):771
Wu C, Cai R, Zhao T, Wu L, Zhang L, Jin J et al (2020) Hyaluronic acid-functionalized gadolinium oxide nanoparticles for magnetic resonance imaging-guided radiotherapy of tumors. Nanoscale Res Lett 15(1):94
Yao Y, Li P, He J, Wang D, Hu J, Yang X (2021) Albumin-templated Bi_2Se_3–MnO_2 nanocomposites with promoted catalase-like activity for enhanced radiotherapy of cancer. ACS Appl Mater Interfaces 13(24):28650–28661
Yen C, Abbasi AZ, He C, Amini MA, Lip H, Rauth M et al (2021) Abstract PO-100: Theragnostic tumor-targeted manganese dioxide-loaded polymer-lipid nanoparticles for magnetic resonance image-guided radiation therapy. Clin Cancer Res 27(8_Supplement):PO-100
Yin X, Russek SE, Zabow G, Sun F, Mohapatra J, Keenan KE et al (2018) Large T1 contrast enhancement using superparamagnetic nanoparticles in ultra-low field MRI. Sci Rep 8(1):11863
Yoo M-K, Park I-K, Lim H-T, Lee S-J, Jiang H-L, Kim Y-K et al (2012) Folate-PEG-superparamagnetic iron oxide nanoparticles for lung cancer imaging. Acta Biomater 8(8):3005–3013

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