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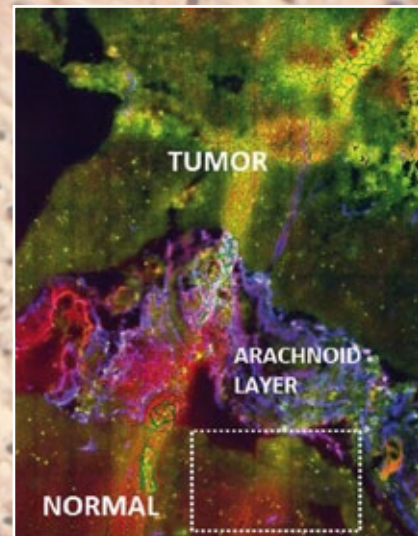
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Applications of Multifunctional Nanoparticles in Malignant Brain Tumours

Costas G Hadjipanayis¹, Alexandros Bouras¹, Susan Chang²

Abstract: Malignant brain tumours are one of the most devastating human cancers associated with high mortality and morbidity rates. Clinical management of these tumours remains challenging despite recent advances in current treatment strategies. Difficulties in early detection, local recurrence, and resistance to conventional therapies are the major reasons for failure in malignant brain tumour treatment. Nanoparticles have drawn increased interest in treating malignant

brain tumours due to their potential to act as a vector for brain delivery and to provide tumour-specific detection and treatment. Multitasking nanoparticles can be engineered into a single nanoplatform and hold great promise for brain tumour diagnosis and treatment. Currently, magnetic nanoparticles are being used for the imaging and treatment of malignant brain tumours in humans. This review article summarizes different types of multifunctional nanoparticles that have

been used both preclinically and in humans for nanoparticle-based brain tumour imaging and therapy. *Eur Assoc NeuroOncol Mag* 2014; 4 (1): 9–15.

Key words: malignant brain tumours, nanoparticles, drug delivery, magnetic resonance imaging, thermotherapy, theranostics, glioblastoma

■ Introduction

Malignant brain tumours remain a major clinical problem despite improvements in surgery and multimodal adjuvant therapies. Malignant gliomas represent the most common and aggressive malignant brain tumours. The median survival of malignant glioma patients ranges between 3 and 16 months and has virtually remained unchanged during the last 3 decades [1, 2]. Management of malignant gliomas poses a surgical challenge due to their proximity to eloquent anatomical structures within the brain and also their diffuse infiltrative nature which precludes complete surgical resection. The therapy of malignant gliomas is further limited by the inadequate delivery of therapeutic agents to the brain due to the presence of the blood-brain barrier (BBB) as well as non-specificity targeting. The application of novel therapeutic agents for the treatment of malignant brain tumours is urgently needed.

Among different therapeutic approaches, nanotechnology appears to be a promising tool for advancing cancer therapies. Nanotechnology is defined as the manufacturing and construction of materials in the nanometer scale size range of 1–100 nm [3, 4]. Nanomedicine is the use of nanotechnology in medicine and health care [3, 4]. Cancer nanotechnology is the application of nanotechnology toward various aspects of detection, imaging, treatment, and monitoring of cancer [5]. Current innovations in nanotechnology hold great promise in changing the foundations of cancer diagnosis and therapy. The potential application of nanoparticles (NP) to the diagnosis and treatment of malignant brain tumours is now being explored. Various nanotechnology platforms have been used for improving malignant brain tumour imaging, drug delivery to brain tumours, and therapeutic efficacy. One of the most promising aspects of NP-based cancer therapy is multi-

functionality. NPs can be attached to different types of small molecules such as targeting ligands, imaging, and therapeutic agents to serve as diagnostic and therapeutic agents simultaneously [6–12]. The integrated diagnostic and therapeutic capability of nanotechnology has attracted particular attention for diagnosing and treating brain tumours. This review article focuses on different types of multifunctional NPs that have been studied in the management of brain tumours in preclinical models as well as human patients.

■ NPs and Brain Tumours

The unique properties of NPs offer several advantages over conventional malignant brain tumour therapeutic agents. One advantage may be more effective delivery of compounds to the brain tumour site in comparison to conventional drug delivery systems [13–15]. The flow of NPs through blood capillaries and uptake by cancer cells can be facilitated by their small size [13, 14]. The NPs can be engineered to contain small molecules such as contrast agents and drugs [13]. Multiple types of small ligands with different functions, such as MRI contrast enhancement or therapeutic agents, can be incorporated into a nanoparticle and delivered to the brain tumour site. The specificity of the delivery can be achieved by adding targeting ligands, such as monoclonal antibodies, to the nanoparticle surface in order to ensure targeted delivery of the agents to the brain tumour site. The ability of nanoplatform-based targeted delivery of imaging or therapeutic regimens to the brain tumour site at effective concentrations is the fundamental principle of multifunctionality of NPs and the key factor for efficient cancer diagnosis and therapy.

Another advantage of nanotechnology compared to conventional imaging and therapeutic agents is the tendency of NPs to accumulate within the brain tumour site via the enhanced permeability and retention effect (EPR). The growth of the tumour results in neoangiogenesis in order to provide cancer cells with oxygen and nutrients for rapid proliferation [16]. The defective architecture of the neovascularization resulting in leaky vasculature, along with the expression of vascular mediators of extravasation (eg, nitric oxide, VEGF) are thought to be responsible for the EPR effect and selective retention of NPs at the brain tumour site [17–19]. In con-

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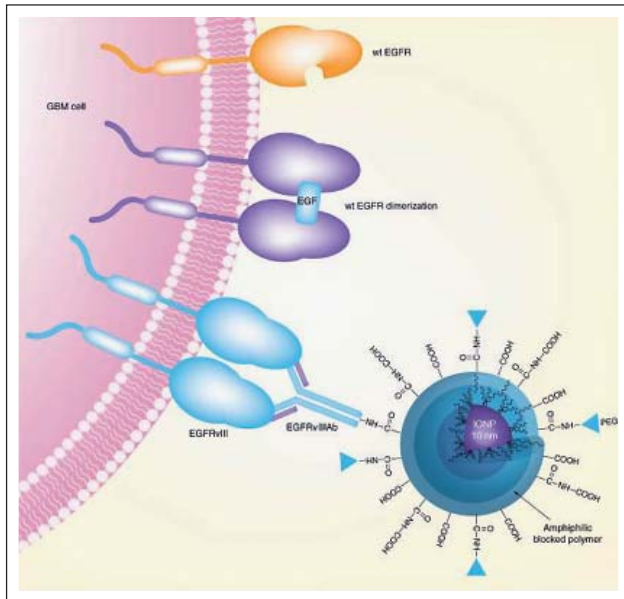


Figure 1. Illustration of an EGF receptor VIII-expressing glioblastoma cell bound by an EGF receptor VIII antibody-conjugated magnetic nanoparticle construct. Reproduced from [Expert Review of Clinical Pharmacology, March 2012, vol 5, no 2, pp 173–86] with permission from Expert Reviews Ltd. The wt EGFR dimerizes upon ligand binding. The truncated EGFRvIII deletion mutant, which does not require a ligand for activation, is bound by an EGFRvIII antibody-conjugated magnetic nanoparticle conjugate (EGFRvIIIAb-iron oxide nanoparticle). The EGFRvIIIAb-iron oxide nanoparticle is comprised of a 10-nm iron oxide core surrounded by an amphiphilic triblock copolymer, which is covalently conjugated to the EGFRvIIIAb. Ab: antibody; EGFR: EGF receptor; GBM: glioblastoma; IONP: iron oxide nanoparticle; wt: wild-type.

trast, small molecules, such as conventional chemotherapeutic agents, diffuse freely across the tissues and the EPR effect is not observed.

In regards to treatment toxicity, the payload of the NPs can be isolated from the surrounding normal tissues by the addition of biocompatible polymers, preventing the release of the loaded agents within those normal tissues. The result is increased maximum tolerated dose of the therapeutic agent and reduced systemic toxicity. Moreover, targeted delivery of therapeutic agents encapsulated into NPs in conjunction with retention of NPs within the brain tumour site can lead to higher localized concentrations of the agents within the tumour mass, while preventing the undesired systemic consequences of the therapeutic agents [20, 21].

Taking into account the above advantages of nanotechnology, many different types of NPs have been examined in malignant brain tumour research. These include magnetic iron oxide (Fe_3O_4) NPs [22–33], gadolinium (Gd) NPs [34, 35], gold NPs (AuNPs) [36], quantum dots (QDs) [37, 38], dendrimers [39–42], carbon nanotubes (CNTs) [43–45] and polymer-based NPs [46–61].

■ Magnetic NPs

MRI Contrast Effect

Magnetic NPs (MNPs) have been studied as potential diagnostic and therapeutic tools in malignant brain tumours. The unique paramagnetic properties of MNPs enable their detection by magnetic resonance imaging (MRI), and have been

used as both T_1 and T_2 MRI contrast agents [62–65]. Most MNP formulations are comprised of iron-oxide nanoparticles (IONPs). Superparamagnetic iron-oxide NPs (SPIOs) have most commonly been used as MRI contrast agents [66, 67]. Ultrasmall SPIOs (USPIOs) with size < 50 nm have also been examined as potential MRI contrast agents [68]. The MRI contrast effect can occur in both T_2 -weighted MRI sequences, where they produce a hypointense (dark) signal (negative contrast enhancement), and in T_1 -weighted images, where they produce a hyperintense (bright) signal (positive contrast enhancement) [69–71]. The major advantage of USPIOs, compared to conventional Gd- (gadolinium-) based contrast agents, is their prolonged MRI contrast effect due to uptake by tumour cells and microglia (reactive phagocytic cells in the brain) and retention within the brain [72]. Administration of USPIOs leads to an observed peak enhancement for approximately 24 hours that can persist for up to 72 hours in contrast to Gd-based contrast agents which are rapidly cleared by the kidneys [34, 73–75]. In an attempt to overcome the rapid elimination of conventional Gd and increase its retention within brain tumours, Gd NPs have also been reported. Incorporation of Gd into therapeutic NPs has been utilized to track them by using MRI [76]. Functionalized Gd NPs have also been reported as radiosensitizing agents [77]. Gd NPs can be better visualized in T_1 -weighted MRI sequences [35]. SPIOs and USPIOs have been shown to have a relatively safe toxic profile with no evidence of brain toxicity [67, 78]. These agents can be served as an alternative in patients at high risk for Gd-induced nephrogenic systemic fibrosis [79, 80].

Tumour Targeting

MNPs specifically targeted to tumour cells can further increase their imaging benefits by enhancement of their uptake by the targeted tumour cells [81]. Multiple types of compounds, such as peptides and antibodies, have been reported as potential MNP targeting ligands [82].

Chlorotoxin, a peptide derived from scorpion venom, has been described as a targeting motif for brain tumour cells. Chlorotoxin inhibits tumour infiltration by specific binding and inhibition of matrix metalloproteinase-2 (MMP-2), which is over-expressed on the surface of glioma cells and responsible for the degradation of extracellular matrix during tumour invasion [83–85]. Conjugation of chlorotoxin to MNPs has been reported as a method for targeted brain tumour imaging [24] by MRI in addition to inhibition of tumour cell invasion [86]. Furthermore, incorporation of the fluorescent Cy5.5 molecule to the conjugated chlorotoxin-MNPs allows for simultaneous MRI and intraoperative optical imaging [22, 25, 87]. Chlorotoxin-labelled MNPs have also been utilized for targeted gene delivery to glioma cells [32].

Attachment of another small peptide, called F3, to the MNP surface has also been used for the targeting of brain tumours. F3 targets endothelial cells by specific binding to nucleolin, which is over-expressed on the surface of proliferating vascular endothelial cells of tumour-associated vasculature [88]. Intravenous injection of IONPs coated with F3 has provided more persistent and profound MRI contrast enhancement of intracranially implanted rodent tumours compared to identical non-F3-targeted IONPs [48].

Polymer-coated IONPs have been conjugated to a purified antibody that selectively binds to the epidermal growth factor receptor deletion mutant, EGFRvIII (Figure 1), which is a tumour-specific mutation present on the surface of glioblastoma (GBM) cells. The bioconjugated IONPs can provide simultaneous MRI contrast enhancement, as well as targeted therapy of intracranial human GBM xenografts implanted in rodents after convection-enhanced delivery (CED) [26]. Recent toxicity testing of cetuximab-conjugated IONPs has been reported in healthy canines after CED in the brain [89].

Conjugation of a tumour-specific monoclonal antibody known as L6 to IONPs can provide targeted MRI enhancement of the neovasculature of malignant brain tumours after their uptake by tumour cells [90]. Dextran-coated SPIOs functionalized with an antibody against an insulin-like growth factor domain have also been used for targeted MRI and fluorescent imaging of the GBM vasculature [91].

Cytokines can be utilized for the targeted imaging of malignant brain tumours. Gd-containing metallofullerenes functionalized and conjugated to IL-13 peptides have the ability to specifically bind to glioma cells over-expressing the IL-13 receptor providing targeted imaging of these cells in vitro [92].

Neural Stem Cells

MNPs can also be used for tracking stem cell tropism to malignant gliomas in vivo. Neural stem cells are brain tumour targeting tools as they exhibit tropism for GBM tumours after intracranial administration [93]. This striking characteristic makes neural stem cells a potential candidate for tumour-targeted gene delivery and therapy [94, 95]. IONPs can label neural stem cells enabling visualization of their migration into the brain [96, 97].

Chemotherapeutics and MNPs

MNPs can also be utilized to deliver chemotherapeutic agents to the brain tumour site while simultaneously tracking them by MRI. IONPs coated with a polymer have been used for both delivery of the chemotherapeutic agent epirubicin and monitoring of their distribution in vivo by MRI [29]. Paclitaxel-loaded MNPs have been utilized to deliver the chemotherapeutic agent paclitaxel in a rat glioma model. Increased drug uptake by the brain tumour cells resulted in enhanced therapeutic efficacy and effective MRI contrast enhancement [30].

Magnetic Targeting and Focal Ultrasound

In an attempt to enhance the delivery of MNPs to malignant brain tumours after systemic administration, magnetic targeting has been described. Magnetic targeting is the application of a magnetic field to enhance accumulation of MNPs within the brain tumour site [98–100]. Another concept that has been described in an effort to increase the systemic delivery and deposition of MNPs into malignant brain tumours is disruption of the BBB. Many strategies have been examined in order to facilitate opening of the BBB. Focal ultrasound is a non-invasive technique that can be utilized for selective BBB disruption in a targeted brain region [101–103]. The synergistic effect of focal ultrasound and magnetic targeting has been demonstrated in a study where both systemic delivery and deposi-

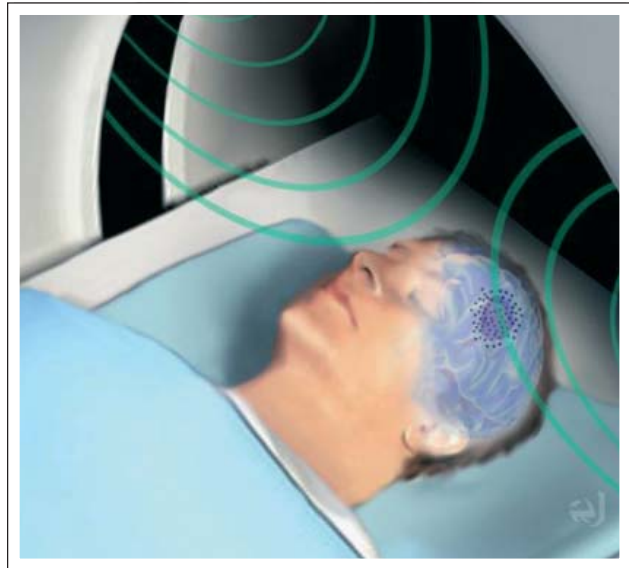


Figure 2. Intratumoural thermotherapy of a malignant brain tumour with magnetic nanoparticles. Reproduced from [Expert Review of Clinical Pharmacology, March 2012, vol 5, no 2, pp 173–86] with permission from Expert Reviews Ltd. A patient who has undergone intratumoural implantation of magnetic nanoparticles is depicted undergoing an alternating magnetic field session for treatment of his malignant brain tumour by thermotherapy.

tion of epirubicin-loaded MNPs into tumour-bearing animals were significantly increased [29].

Thermotherapy

Another function of MNPs is their ability to produce heat with the application of an alternating magnetic field (AMF). Use of hyperthermia for the treatment of cancer, known as thermotherapy, has been demonstrated in patients with human GBM [104, 105] (Figure 2). Temperatures above 41 °C cause heat stress with resultant protein denaturation and DNA cross-linking within the cell, leading to cell apoptosis [106]. Alterations of the tumour microenvironment can also occur [107]. The above changes have a synergistic effect when combined with chemotherapy and radiation [108]. Engineering of MNPs plays a crucial role in maximizing the hyperthermia response [109, 110]. MNPs that can be used for thermotherapy are combinations of various metals such as manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), zinc (Zn), and magnesium (Mg) [111–114]. Iron oxide-based MNPs have been extensively examined for thermotherapy application in brain tumours due to their biocompatibility and safe toxicity profile [115, 116]. Animal models and human patients with malignant brain tumours have been used to evaluate feasibility and safety of MNP-based thermotherapy [104, 105, 117]. Safety and efficacy have been demonstrated holding great promise of this cancer treatment modality.

■ Polymer-Based NPs

A vast amount of research has been made exploring polymer-based NPs in brain tumour diagnosis and therapy. Varying core polymer compositions have been examined with the most popular being the polysorbate 80-coated poly(butyl cyanoacrylate) and poly(ϵ caprolactone) [46, 50, 51, 53, 54]. Drug delivery to brain tumours is the main application of polymer-based NPs

with doxorubicin, paclitaxel, and camptothecin being used [46, 50, 51, 53, 57, 58, 118]. Polymer-based NPs have been used in clinical trials as vehicles for drug delivery, but the results were discouraging as 1 % or even less of the injected dose was delivered to the brain with most of the nanoparticle-drug conjugate being trapped in the liver [119]. The incorporation of a small peptide sequence known as angiopep has been used for improved targeted delivery to brain tumours [55]. Dual targeting by using 2 different moieties has also been reported. Incorporation of both a small peptide accounting for BBB targeting and an additional small aptamer targeting cancer cells onto a polymer-based nanoparticle has been described [59]. Dual targeting resulted in enhanced tumour distribution of the dual targeted NPs [59]. Furthermore, polymer-based NPs have been successfully used for gene therapy of brain tumours [49, 120]. In one study, incorporation of the integrin-binding motif RDG into a polymer-based nanoparticle enabled efficient targeted delivery of a plasmid expressing an apoptosis ligand in a rat glioma model resulting in increased survival [120]. Moreover, polymer-based NPs have also been utilized for both MRI and drug delivery by loading of both a magnetic contrast agent and a fluorescent drug [48]. Polymer-based NPs can also be encapsulated by both iron oxide and photodynamic therapy (PDT) drugs for both MRI contrast enhancement and PDT of brain tumours, respectively [48].

■ Gold NPs

Gold NPs comprised of a silica core and coated with a gold shell have received increased attention as potential vehicles for delivery of therapeutic agents to the brain, as well as for imaging. Their small size, surface chemistry available for functionalization, and biocompatibility make them strong candidates for biological and medical applications [36, 121–125]. Gold NPs with sizes up to 50 nm are able to cross through the disrupted blood-brain tumour barrier [121, 123, 124, 126]. Gold NPs have been utilized to deliver gadolinium for enabling preoperative detection and surgical planning through MRI, as well as to simultaneously deliver photoacoustic and Raman imaging agents for tumour margin delineation during surgery [127]. Fluorescent imaging agents can also be incorporated into gold NPs for purely diagnostic purposes [36]. Another application of gold NPs is phototherapy. Gold NPs can be designed as nanoshells enabling light absorption in the near-infrared range of the light spectrum which has minimal absorption by water, thus allowing for passage deep into tissues with minimal energy loss. Design of these gold NPs has been achieved and their activation by light has enabled killing of medulloblastoma and glioma cells *in vitro* by phototherapy [128]. Loading of gold nanoshells into macrophages can lead to efficient delivery of the NPs to gliomas and their subsequent activation by near infrared light can result in growth inhibition [129].

■ Quantum Dots

QDs are nanocrystals made of semiconductors with unique optical and electronic properties [130]. They are advantageous for *in vivo* imaging due to the fact that they can emit fluorescence light from 400–2000 nm. Their increased fluorescence emission spectrum allows for enhanced brightness and simul-

taneous multicolour detection [131]. Due to their heavy metal content, toxicity issues are a concern with normal surrounding tissues [131]. QDs can be loaded with contrast agents, such as gadolinium, in order to provide further imaging capabilities in addition to inherent fluorescent properties [37, 132]. However, the above capabilities have not been applied to brain tumours at this point. QDs have also been used for targeted delivery of siRNA for selective inhibition of EGFRvIII expression in human GBM cells [38]. Conjugation of epidermal growth factor (EGF) or EGF receptor antibody to QDs has been attempted and has led to successful specific labelling of human glioma cells *in vitro*, glioma mouse models, and in human brain tumour biopsies by the fluorescent emission of QDs [133].

■ Dendrimers

Dendrimers have been examined as NPs with the potential of delivering agents to brain tumours by crossing the BBB. It has been shown that dendrimers with size < 20 nm can cross the BBB [41]. Dendrimers are spherical molecules formed from repetitively monomeric or oligomeric organic molecule branching units. Their structure, specifically the degree of branching, allows for encapsulation of molecules in the interior as well as on the surface [39, 40, 42]. Dual targeting can be performed with dendrimers [40, 134]. A dendrimer-based nanoprobe has been labelled with both angiopep-2, for higher BBB transcytosis efficacy, and RGD peptides for targeting of the brain tumour vasculature [40]. The near-infrared fluorophore Cy5.5 and rhodamine were added to the dendrimer in order to create a multifunctional nanoprobe allowing for non-invasive preoperative localization of brain tumours, as well as possible intraoperative image-guided tumour resection [40]. A tolerable toxicity after using dendrimers has been reported [39, 40].

■ Carbon Nanotubes

CNTs are formed of graphite sheets assuming a cylinder-shaped configuration. They possess electrical properties and heat conductivity [135]. They have been used as nanovectors for targeted drug and gene delivery into tumours. CNTs can be packaged with siRNA molecules for targeting tumour cells by exerting RNA interference on target gene expression and suppressing tumour growth [136]. CNTs can potentially be used as a nanovector delivery system for targeted delivery of agents into phagocytic cells *in vivo* for modulating macrophage function in brain tumours. Selective uptake by tumour macrophages labelled with non-toxic hydrophobic fluorescent dye multi-walled CNTs has been shown in a murine glioma model [45]. In another study, conjugation of an immunopotent oligodeoxynucleotide to single-walled CNTs has been described. Enhanced targeted delivery and uptake of the immunopotent compound by glioma cells both *in vitro* and *in vivo* has been demonstrated resulting in potentiation of anti-glioma immunity and inhibition of glioma tumour growth [44]. CNTs can also be utilized for thermal ablation therapy. Photothermolysis of GBM stem-like cells by CNTs targeted with CD133 monoclonal antibody has been reported [43]. Both GBM-CD133⁺ and GBM-CD133⁻ cells were treated *in vitro* with single-walled CNTs functionalized with a CD133 monoclonal antibody (CD133Ab-CNT) and subsequent irradiation with near-infrared laser light. The GBM-CD133⁺

cells were selectively targeted and eradicated, whereas GBM-CD133⁻ cells were unaffected [43]. Moreover, GBM-CD133⁺ cells pre-treated *in vitro* with the CD133Ab-CNTs were injected subcutaneously into mice and then near-infrared laser-induced photothermolysis was applied. Significant inhibition of both tumour growth rate and tumour progression was observed [43]. This study has demonstrated the potential utilization of CNTs as a thermal-coupling agent for effective targeting and inhibition of growth of GBM stem-like cells.

■ Human Clinical Translation of NPs

Although the benefits of NPs in cancer diagnosis and therapy have been widely explored, their potential effects in humans are still unclear. The translation of NPs into clinical use remains challenging. Various issues, such as pharmacokinetics, biodistribution, side effects, potential toxicity, and the immune system reaction to NPs, remain to be addressed and are of great importance in order to establish whether and which NPs can be used in humans. The recent advances of cancer nanotechnology are necessary to proceed in parallel with bioactivity and toxicity assessment studies before clinical application. Numerous nanoparticle platforms are currently under different stages of preclinical and clinical development. However, in the brain tumour field, investigation of potential clinical use of NPs remains limited. MNPs, specifically IONPs, are the most advanced NPs in terms of translation into clinical application for brain tumours. Ferumoxytol, a USPIO that targets phagocytic cells, has been used in the imaging of patients with malignant brain tumours. Patients underwent serial MRI up to 72 hours after a single dose of ferumoxytol and the time course of enhancement was compared with baseline Gd scan [73]. Maximal ferumoxytol-induced enhancement intensity was observed at 24–28 hours after administration and enhancement was expanded into non-Gd enhancing regions of infiltrating brain [73]. The use of IONPs as MRI contrast agents can provide visualization of brain tumours that is not apparent with conventional Gd. Furthermore, the delayed peak enhancement provided after IONP administration compared to Gd can allow for assessment of postoperative residual tumour without the need of re-administration of a contrast agent. In another study, intraoperative MRI (iMRI) with ferumoxtran-10, also a USPIO, was used in patients who underwent malignant brain tumour surgical resection [137]. Less confounding (non-tumoural) contrast enhancement was observed during iMRI compared to iMRI after Gd administration [137]. IONPs have also been used for hyperthermia-induced tumour ablation, known as thermotherapy, in patients with recurrent GBM. In a phase-II clinical trial, aminosaline-coated IONPs have been used for hyperthermia induction after intratumoural injection in patients with recurrent GBM and application of AMF in combination with fractionated external beam radiotherapy (EBRT) [104, 105]. Direct inoculation of IONPs into tumours using stereotactic-guided injections was used, followed by multiple thermotherapy sessions, demonstrating safety and efficacy in combination with EBRT [104, 105].

■ Conclusion

Effective treatment of malignant brain tumours poses a significant challenge. Recent advances in microsurgery and mul-

timodal adjuvant therapy have only resulted in a modest improvement in patient prognosis. Novel technologies are therefore needed to be applied to the management of malignant brain tumours. Nanotechnology has quickly emerged as a promising tool having the potential to change multiple aspects of malignant brain tumour diagnosis and treatment. Several types of NPs have been described providing MRI contrast enhancement, intra-operative tumour delineation, and targeted delivery of chemotherapy or gene therapy, as well as thermotherapy. Currently, NPs are being used in humans for imaging and thermotherapy of malignant brain tumours. Multifunctional NPs, which have the potential for simultaneous targeted cancer cell delivery, imaging, and therapy, form the basis for new approaches combating malignant brain tumours. Additional improvements in the design and surface chemistry of NPs will permit better delivery and penetration within brain tumours. The comprehensive assessment of the toxicological effects of NPs remain to be further determined in the future management of brain tumour patients.

■ Conflict of Interest

The authors report no conflict of interest with the material presented in this manuscript.

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