Review

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Magnetic nanoparticles for cancer therapy

Abstract: Cancer is one of the biggest challenges facing the medical research in our time. The goals are to improve not only the therapeutic outcome, even in the cases of advanced and metastatic cancer, but also the methods of treatment, which often have considerable adverse effects. In addition, the current developments, such as demographic change, population growth, and increasing healthcare costs, have to be taken into consideration. In all likelihood, nanotechnology and, in particular, the use of magnetic nanoparticles consisting of the elements nickel, cobalt, and iron can make a significant contribution. The greatest potential can be ascribed to the drug delivery systems: magnetic nanoparticles are functionalized by binding them to various substances, including chemotherapeutic agents, radionuclides, nucleic acids, and antibodies. They can then be guided and accumulated using a magnetic field. Hyperthermia can be induced with an alternating magnetic field, providing another therapeutic option. Magnetic nanoparticles may be useful in overcoming cancer drug resistance. They also contribute to realizing a combination of diagnostic investigation and therapy in the field of "theranostics". The multifaceted and promising results of research in the recent years offer the prospect of a real advance in cancer therapy in the near future.

Keywords: cancer drug resistance; cancer therapy; drug delivery; hyperthermia; magnetic nanoparticles.

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1 Introduction

Despite the intensive efforts within the last 50 years, it has only been possible to slightly, but not substantially, lower the mortality of cancer. On the other hand, considerable advances have been achieved for the other medical conditions, including the cardiovascular and cerebrovascular diseases and pneumonia [1]. At the present time, there are three basic approaches for treating cancer: surgery, radiotherapy, and chemotherapy. However, all of these procedures have considerable side effects and often are not sufficient for the curative treatment of metastatic cancer. The tumor-specific drugs, such as the tyrosine kinase inhibitors, have now been in use for several years with good results in certain types of cancer (e.g., Imatinib for chronic myeloid leukemia) [2]. The antibodies are also increasingly being used in oncology, although the antibody therapy sometimes has adverse systemic effects and often is expensive. For a subgroup of breast cancer patients, for example, the Her2-targeting antibodies are used successfully in treatment [3]. However, the approval of some previous indications for the antibody therapy has even been withdrawn recently (the British National Institute for Health and Clinical Excellence refused Avastin® (Bevacizumab) in colorectal carcinomas) [4]. There has not yet been a real breakthrough in cancer therapy, in general.

According to the estimates by the US National Cancer Institute, nanomedicine will prove to be trailblazing in the future prevention, diagnostic investigation, and treatment of cancer [5]. Nanotechnology has already found uses in many medical specialties, e.g., in otorhinolaryngology [6]. It is widely used in the different disciplines, from imaging to regenerative medicine. Before being used for medical purposes, however, those substances have to be investigated closely to determine their effects on the organism. This field of research is called nanotoxicology. It investigates the effects of both the nanoparticles that occur naturally (in the environment) and those that are created by industry and traffic. Although a wide variety of materials are being used in medicine, the magnetic nanoparticles

seem to hold the greatest potential of success. They are already established in clinical use as contrast media for magnetic resonance imaging (MRI), e.g., Resovist® and Sinerem® [7]. In addition, these particles can be guided non-invasively (drug delivery) [8] and have the ability to be heated (hyperthermia) [9] by external magnetic fields. A combination of diagnostic investigation and therapy, as "theranostics", is, thus, possible. Therefore, magnetic nanoparticles have excellent potential to improve the treatment of cancer.

This review article presents and summarizes the current developments regarding magnetic nanoparticles in cancer therapy.

2 Relevance of nanotechnology to cancer therapy

Cancer is a huge burden not only to the healthcare system but also to the economy, in general. As the second most common cause of death in Europe, it generates annual costs of approximately 120 billion euro [10]. This does not merely include the direct costs of hospital treatment, nursing care, and medication; this also includes the expenses for information and loss of production. The costs for the treatment alone account for about 36% of the total, while the early mortality and morbidity are responsible for another 36% [11]. Considering the fact that the incidence of cancer increases with age, an escalation could be expected due to the present demographic trends. Irrespective of the dimension of the problem, the costs for healthcare *per se* are progressively increasing, which means that paying for the adequate treatment will become appreciably more difficult. The European Commission is assuming an increase in age-related public expenditure (healthcare and long-term nursing care, as well as pensions) by some five percentage points of the EU gross domestic product by the year 2060 [12]. Therefore, a considerable reduction in the costs of cancer therapy is needed. This reduction would also make it possible to provide better care in the poorer countries of the developing world, where only the upper echelons of society can afford the costly surgeries, radio- or chemotherapy at the moment. Besides infectious diseases, cancer is the second biggest challenge in healthcare that these countries have to face. Finally, the treatment of cancer should not be so time-consuming and complicated that it is only possible to be carried out in a few highly specialized centers, accessible to just a restricted circle of patients. The smaller facilities must be able to provide this care as well, as only in this way sufficient healthcare provision can be guaranteed to the population. The treatment in the local centers would also have the advantage of reducing the costs for transportation, which are sometimes considerable and often not covered by the health insurance (or only under very specific conditions). Apart from these structural problems, it is essential that the existing forms of treatment will be improved, not only in terms of outcome and expenditure but also in terms of tolerability. Surgery, radio- and chemotherapy often have considerable side effects. These adverse effects often affect the patients more than the disease itself. The initial approach certainly consists of improving the existing methods and/or supplementing and combining them with the new procedures. The long-term goal has to be that everyone will have access to cancer therapy that is simple, cost-effective, and well-tolerated. With the help of nanotechnology, nowadays, this seems to be possible to achieve.

A multitude of new potential is opening up. Efforts are being made to simultaneously measure a wide range of known laboratory parameters, like tumor markers and biomarkers *in vitro*, using simple and cheap methods, as well as to discover further parameters with novel techniques. The nanoparticles are already being used as contrast agents in medical imaging, to visualize tumors more accurately, with respect not only to the margins and extent but also to distinguish between the active and inactive regions. Therewith, treatment such as radiotherapy can be planned and carried out more easily and efficiently. In addition, nanomedicine is being used to refine the monitoring of the disease progression so that the patient's management can be adjusted promptly, if necessary. This review will focus more closely on the drug delivery, hyperthermia, and overcoming drug resistance as means of improvement of cancer therapy.

3 Cancer therapy with magnetic nanoparticle drug delivery

3.1 Background

As the conventional chemotherapy is administered systemically, it often causes considerable adverse reactions such as nausea, hair loss, and bone marrow suppression, as well as liver and kidney toxicity. These aspects determine the dose of the chemotherapeutic agents and limit their effects on the tumor. Therefore, in the recent years, it has been a trend in cancer pharmacotherapy to identify substances with higher specificity. Although considerable

success has already been achieved (e.g., Herceptin®), the limits of this strategy have become clear. The targeted blockage of a specific signaling pathway has led to the emergence of genetically mutated cancer cells that are able to circumvent this blockage by upregulation of an effective parallel, alternative, or overlapping pathway [13]. That leads to broad-spectrum medicinal products being used again. The biodistribution of these substances is of particular relevance to targeted therapy. This is where nanotechnology comes in. It can be used to transport medicinal products very precisely to the intended site of action.

Magnetic nanoparticle drug delivery opens the possibility of using local enhancement methods, so that the drug can accumulate and act in a previously determined area. This method was first described in 1978 [14]. It is based on the usage of three elements: iron (Fe), cobalt (Co), and nickel (Ni). All are ferromagnetic under physiological conditions, although they do not exhibit the same magnetization: Ni 55 emu/g, Co 160 emu/g, and Fe 218 emu/g. Mostly, they are used as hybrids with other metal ions, oxygen, or carbon dioxide. There are innumerable possibilities for such combinations [13]. The iron compounds are predominantly used because of their biocompatibility. They show the lowest toxicity and are even used therapeutically for iron substitution [15]. The nanoparticles are coated in order to prevent agglomeration, ensure stability, and provide a positive effect on biodistribution. A wide variety of materials, including fatty acids, polyethylene glycol (PEG), dextran, and chitosan may be used [16]. Magnetic nanoparticles can transport various different substances and molecules, such as chemotherapeutic agents, antibodies, nuclear acids, radionuclides, etc. In principle, this approach can be used for any tumor, irrespective of its size, differentiation, or site.

3.2 Administration and biodistribution

The mode of administration is essential when using magnetic nanoparticles in cancer therapy. Depending on the purpose and target structure, the nanoparticles can be applied parenterally (intravenously or intra-arterially), by mouth, as an aerosol, or interstitially, i.e., directly into the tissue. Intravenous injection is usually preferred though. Many of these particles, however, are being trapped in the liver and spleen and get excreted via the kidneys [17]. So, clearance from the bloodstream by metabolism and excretion might be a problem. Despite this, Chao et al. were able to reduce the tumor growth significantly in mice with hepatocellular carcinomas induced by subcutaneous injection. They administered doxorubicin-coupled magnetic nanoparticles intravenously and used a magnet to achieve local enhancement [18]. Although the intra-arterial route is being used much less frequently, it has a greater potential. Working with rats and applying an external magnetic field, Chertok et al. increased the accumulation of the iron oxide nanoparticles in brain tumors by a factor of 1.8 after intra-arterial compared to intravenous injection [19]. Magnetic nanoparticles can be administered as an aerosol in the treatment of lung cancer. Verma et al. developed a formulation (Fe_3O_4 magnetic nanoparticles coated with a polymer poly(lactic-co-glycolic acid (PGLA)) that has been well tolerated in both cell culture and animal studies (mice) [20]. Hiraiwa et al. injected various magnetic nanoparticle formulations subcutaneously into the chest wall of rats and investigated whether there was any accumulation in the axillary lymph nodes [21]. In contrast, Remsen et al. did not find any significant difference of enhancement in human lung cancer tissue after intravenous, intra-arterial, or intratumoral administration in a rat model [22]. The direct instillation into the tumor is particularly used in hyperthermia [23].

The distribution of magnetic nanoparticles can be an active or passive process. Passive distribution occurs mainly by diffusion, after parenteral injection. The greater permeability of the tumor blood vessels is, thereby, useful, although it is often counteracted by the high pressure in the interstitial tissue of cancer. The nanoparticles can also be transported actively to the tumor by coupling them with appropriate tumor-specific ligands (e.g., antibodies). Magnetic nanoparticles, in particular, can be guided by means of a magnetic field. Coupling active substances with nanoparticles or encapsulating them into nanocarriers should improve their solubility, distribution, and stability. This should facilitate the crossing of biological barriers, as well as their uptake into cells, and an increase in the general tolerance.

Table 1 summarizes the actual use of magnetic nanoparticles in cancer therapy *in vivo*. For the sake of clarity, it does not include studies that were aimed only at imaging or demonstrating the practical enhancement of nanoparticle constructs without any therapeutic aspects (Table 1).

3.3 Magnets

The nanoparticles consisting of nickel, cobalt, and/or iron can be guided by a magnetic field due to their ferromagnetism. In biomedicine, particularly, iron oxide nanoparticles are being used. However, the magnetic force on these particles decreases very rapidly with the increasing

Table 1 *In vivo* application of magnetic nanoparticles in cancer therapy.

Reference	Application	Nanoparticles	Therapy	Tumour entity (origin)/organ	Animal
Agemy et al. 2011 [24]	Intravenous	Iron oxide nanoparticles with PEG coating	Apoptosis inducing peptide	Glioblastoma cell line U87 (human) brain	Mouse
Alexiou et al. 2000 [25]	Intra-arterial	Iron oxide nanoparticles with starch coating	Mitoxantrone	Squamous cell carcinoma VX-2 (rabbit) subcutaneous (hind limb)	Rabbit
Alphandery et al. 2011 [26]	Intratumoral	Iron oxide nanoparticles with either citrate or PEG coating	Hyperthermia (alternating magnetic field)	Breast cancer cell line MDA-MB-231 (human) mamma	Mouse
Balivada et al. 2010 [27]	Intravenous/ intratumoral	Iron oxide nanoparticles (Fe_3O_4)	Hyperthermia (alternating magnetic field)	Melanoma cell line B16-F10 (mouse) subcutaneous (rear limb above stifle)	Mouse
Bruners et al. 2010 [28]	Intratumoral	Iron oxide nanoparticles (Fe_2O_3, Fe_3O_4)	Hyperthermia (alternating magnetic field)	Squamous cell carcinoma VX-2 (rabbit) kidney	Rabbit
Chao et al. 2012 [18]	Intravenous	Iron oxide nanoparticles (Fe_3O_4)/gold	Doxorubicin	Hepatoma cell line H22 (mouse) subcutaneous (right flank)	Mouse
Chen et al. 2006 [29]	Intratumoral	Iron oxide nanoparticles (Fe_3O_4) with dextran coating	Anti-VEGF monoclonal antibody ^{131}Iod	Liver cancer cell line HepG2 (human) intradermal (right flank)	Mouse
DeNardo et al. 2007 [30]	Intravenous	Iron oxide nanoparticles with dextran coating and ^{111}In-marked L6 monoclonal antibody	Hyperthermia (alternating magnetic field)	Breast cancer cell line HBT3477 (human) subcutaneous (abdomen)	Mouse
Dutz et al. 2011 [31]	Intratumoral	Iron oxide nanoparticles with dextran coating	Hyperthermia (alternating magnetic field)	Breast cancer cell line MDA-MB-231 (human) subcutaneous (between the shoulder blades)	Mouse
Fang et al. 2010 [32]	Intravenous	Iron oxide nanoparticles with PEG coating	Arginine-glycine-aspartic acid or chlorotoxin	Glioblastoma cell line U87 (human) subcutaneous	Mouse
Hilger et al. 2002 [33]	Intratumoral	Iron oxide nanoparticles (Fe_3O_4)	Hyperthermia (alternating magnetic field)	Breast cancer cell line (human) subcutaneous (abdomen)	Mouse
Kumar et al. 2010 [34]	Intravenous	Iron oxide nanoparticles with dextran coating and binding for tumor-specific antigen uMUC-1	siRNA against BIRC5	Breast cancer cell line BT-20 (human) subcutaneous	Mouse
Li et al. 2007 [35]	Intravenous	Iron oxide nanoparticles (Fe_3O_4) coated with poly lactic acid	Arsenic trioxide	Osteosarcoma cell line MG-63 (human) subcutaneous (flank)	Mouse
Li et al. 2009 [36]	Intravenous	Iron oxide nanoparticles with polylysine coating	NM23-H1 gene (an anti-metastatic gene)	Melanoma cell line B16F10 (mouse) intravenous	Mouse
Plank et al. 2011 [37]	Intratumoral	Iron oxide nanoparticles with polyethylenimine coating	Plasmid DNA comprising a cytokine gene	Fibrosarcoma	Cat

(**Table 1** Continued)

Reference	Application	Nanoparticles	Therapy	Tumour entity (origin)/organ	Animal
Rainov et al. 1995 [38]	Intra-arterial	Iron oxide nanoparticles with dextran coating	Herpes simplex virus vector	Gliosarcoma cell line 9L (rat) brain	Rat
Remsen et al. 1996 [22]	Intravenous, intra-arterial, intratumoral	Iron oxide nanoparticles	L6 IgG monoclonal antibody	Lung carcinoma cell line LX-1 (human) brain	Rat
Shen et al. 2010 [39]	Intratumoral	Iron oxide nanoparticles with dextran coating	Human adenovirus type 5 early region 1A (E1A)	Cervix carcinoma cell line HeLa (human) subcutaneous (lower limbs)	Mouse
Tanaka et al. 2005 [40]	Intratumoral	Iron oxide nanoparticles (Fe_3O_4) within liposomes	Hyperthermia (alternating magnetic field) combined with dendritic cells	Melanoma cell line B16 (mouse) subcutaneous (right flank)	Mouse
Tang et al. 2011 [41]	Intravenous	$Mn_xZn_{1-x}Fe_2O_4$ coated with human albumin and folate	Radionuclide ^{188}Rhenium cisplatin (hyperthermia possible)	Ovarian cancer cell line SKOV3 (human) subcutaneous (right side)	Mouse
Toraya-Brown et al. 2013 [42]	Intraperitoneal	Iron oxide nanoparticles coated with starch, dextran or mannan for uptake in tumor-associated immunosuppressive phagocytes	Hyperthermia (alternating magnetic field)	Ovarian cancer cell line ID8-Defb29/Vegf-a (mouse) intraperitoneal	Mouse
Tresilwised et al. 2010 [43]	Intratumoral	Iron oxide nanoparticles (Fe_3O_4)	Adenoviruses	Pancreatic carcinoma cell line 181RDB-fLuc (human) subcutaneous (right flank)	Mouse
Wang et al. 2012 [44]	Intratumoral	Iron oxide nanoparticles	Hyperthermia (alternating magnetic field)	Pancreatic carcinoma cell line 181RDB-fLuc (human) subcutaneous (armpit)	Mouse
Wu et al. 2011 [45]	Intratumoral	Gold-coated iron nanoparticles (non-oxidized!)	Non-oxidized iron nanoparticles	Buccal pouch carcinoma HCDB1 (hamster) buccal pouch	Hamster
Reference	**Application**	**Nanoparticles**	**Therapy**	**Tumour**	**Human**
Johannsen et al. 2007 [46]	Intratumoral	Iron oxide nanoparticles (Fe_3O_4) with aminosilane coating	Hyperthermia (alternating magnetic field)	Prostate cancer	Human
Maier-Hauff et al. 2011 [47]	Intratumoral	Iron oxide nanoparticles (Fe_3O_4) with aminosilane coating	Hyperthermia (alternating magnetic field)	Glioblastoma	Human

distance. As a result, it is hard to accumulate magnetic nanoparticles in tumors deep within the body by using an external magnetic field, making therapy difficult. Namiki et al., therefore, implanted magnets in mice before carrying out the treatment [48]. Besides such implantation, it is also conceivable that the magnets can be put in preformed body cavities, which would make it possible to concentrate magnetic nanoparticles in deeper regions as well.

3.4 Active substances

3.4.1 Chemotherapeutic agents

There are many reports on chemotherapeutic agents attached to magnetic nanoparticles. Some of the latest studies are presented here. Shanta Singh et al. treated cancer cells lines using silicate nanoparticles with an yttrium, vanadium, or europium core and the anticancer drug doxorubicin, which was released in a pH-dependent manner. After adding iron oxide nanoparticles, an additional cytotoxic effect could be achieved by applying an alternating magnetic field [49]. Fang et al. presented a formulation with iron oxide nanoparticles, poly-β-amino-ester-copolymer and doxorubicin, with which they managed to get a higher uptake and greater toxicity in the treatment of glioma cells than with the pure medication [50]. By coating magnetic iron particles with β-cyclodextrin and F127 polymer, Yallapu et al. also modified the release of the encapsulated drug, resulting in a better therapeutic efficacy against cancer [51]. Guo et al. used nickel-based magnetic nanoparticles, furnishing daunorubicin with a greater cytotoxicity against leukemia cells *in vitro* [52].

Magnetic drug targeting (MDT) to treat cancer is a specific form of drug delivery, being developed at our center that uses chemotherapeutic agents directly associated with superparamagnetic iron oxide nanoparticles. The resulting suspension (ferrofluid) is injected into an artery, directly supplying the tumor. The particles and, hence, the attached drug are concentrated in the tumor by means of an external magnetic field (Figure 1) [8]. These iron oxide nanoparticles have also been tested *in vitro*. Therapeutically relevant concentrations showed no toxicity [53]. An electromagnet with a strong magnetic field gradient of up to 72 T/m at the pole tip and a high magnetic flux density was developed especially for this purpose [54]. The flow and distribution of the nanoparticles were investigated in detail under the different experimental conditions in an *ex vivo* arterial model [55, 56]. Studies in rabbits demonstrated the accumulation of the

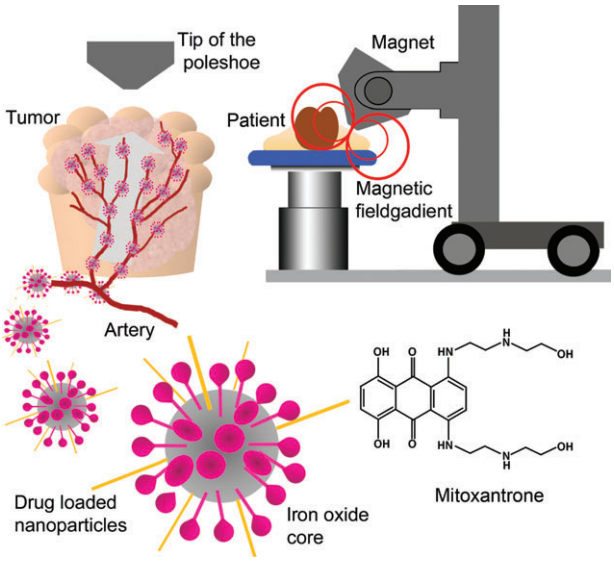

Figure 1 The principle of magnetic drug targeting. Magnetic iron oxide nanoparticles are functionalized with a chemotherapeutic agent and injected directly into the arterial supply of the tumor. The application of an external magnetic field brings about their enhancement in the tumor.

nanoparticles with the anticancer drug mitoxantrone on histology, MRI, X-ray microtomography (μCT), and high-performance liquid chromatography (HPLC) [57–59]. The application of an external magnetic field increased the nanoparticle enhancement per gram of tissue by a factor of 114 in the tumor and surrounding tissue, as shown by a quantitative analysis with ^{59}Fe-labeled ferrofluids [60]. Detailed imaging of the vascular supply is crucial for intra-arterial injection at an appropriate site. An interventional angiography system (Artis zee floor™, Siemens AG Healthcare Sector, Forchheim) which can provide both 2D and 3D images is most suited for this purpose (Figure 2). The complete regression of both the blood vessels supplying the tumor and of the tumor itself, has been reported after successful treatment [61]. MDT can be used for all solid tumors, which has basically been demonstrated in an earlier animal study [25].

3.4.2 Antibodies

As sometimes there are considerable limitations to antibody therapy, efforts have been made to improve this type of treatment with the help of the drug delivery. By coupling antibodies with magnetic iron oxide nanoparticles, Wang et al. detected cancer cells circulating in the blood of patients with non-small-cell carcinomas of the lung [62]. Another method uses nanoimmunoliposomes.

Figure 2 The procedures room with angiography system and magnet.
The precise imaging before and after the intervention is needed to perform and record magnetic drug targeting effectively. It requires an interventional angiography system (Artis zee floor™, Siemens AG Healthcare Sector, Forchheim) that provides both 2D and 3D images. A specially developed electromagnet is used to concentrate the drug in the tumor.

Superparamagnetic iron oxide nanoparticles are encapsulated by nanosized cationic liposomes with surface fragments of an antibody to the transferrin receptor, which shows an increased expression in cancer cells [63]. These methods are not directly therapeutic approaches, but might enable the early diagnosis and prevention of recurrence.

3.4.3 Radiotherapy

Klein et al. used iron oxide nanoparticles to sensitize cancer cells to radiotherapy, *in vitro*. After the incorporation of the nanoparticles, a higher concentration of reactive oxygen species (ROS) was found in the cells, improving the response to irradiation [64].

3.4.4 Gene therapy

Gene therapy holds a great potential in the treatment of cancer. The malignancy of a cell can ultimately be attributed to "dysfunctional genes." Gene therapy can interfere at the origin of the tumor occurrence [65]. The greatest obstacle is in applying "genetic medication," i.e., getting the genetic material into the mutated cells. There is a lack of suitable and efficient transport agents, known as vectors, but magnetic nanoparticles can also be used here. The method is often referred to as magnetofection, meaning, the targeted transfection of cells with nucleic acids conjugated to magnetic nanoparticles, with the aid of a magnetic field [37]. Qi et al. employed magnetic iron oxide nanoparticles to transport siRNA directly into cancer cells. Combining the technique with a magnet, they demonstrated a considerably higher efficacy of gene delivery than with other transfection reagents [66]. Magnetofection has already been used in numerous studies *in vivo*; for example, Muthana et al. used magnetic nanoparticles to improve the uptake of transfected monocytes into tumors. They found considerably greater enhancement in cell cultures and in mice bearing the solid tumors [67]. Plank et al. injected plasmid DNA (encoding a cytokine), associated with magnetic nanoparticles, directly into the tumor (fibrosarcoma in cats) and fixed it there by means of a magnet. Thereby, they activated the immune system against the tumor and reduced the probability of recurrence after surgery. They called the procedure Magnetovax® (Figure 3) [37]. In a recent study, cobalt carbide nanoparticles were used. These cobalt nanoparticles, encapsulated in carbon shells, showed a good biotolerability and provided another tool for target-specific gene delivery [68].

4 Cancer therapy using hyperthermia with magnetic nanoparticles

4.1 Background

Hyperthermia is certainly one of the oldest forms of cancer therapy. Up until the middle of the twentieth century, it was the standard treatment for inoperable tumors. The patients were given bacterial toxins to induce high body temperatures [69]. Hyperthermia is used in many different forms – combined with other procedures such as radiotherapy or chemotherapy (temperature: 40°C–44°C), or used alone for thermal ablation (temperature: >60°C) [70]. It is already well established as an adjuvant to radiotherapy in humans [71] and is also used in combination with chemotherapy in clinical practice [72].

4.2 Magnetic nanoparticles

As magnetic nanoparticles can be heated by the application of an alternating magnetic field, they can be used for local hyperthermia. Gilchrist et al. carried out the first investigations of this treatment method in 1957, when

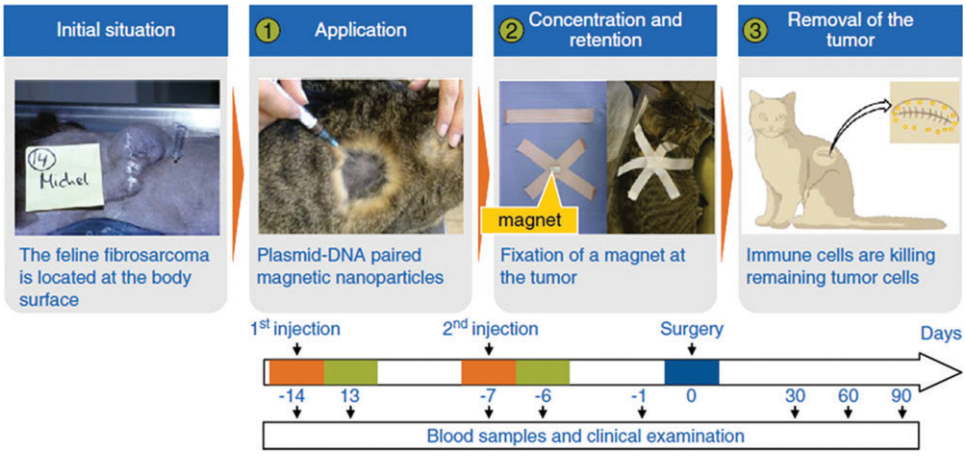

Figure 3 The treatment of fibrosarcomas in cats with Magnetovax® [37]; reprinted with permission from Elsevier.
Magnetic nanoparticles functionalized with DNA are injected directly into the tumor and fixed there by a magnet. After the uptake into the cancer cells, a specific gene is expressed. This gene activates the animal's immune system against the tumor, preventing any recurrence once the tumor has been excised.

they heated iron oxide particles in lymph nodes of dogs [73]. The idea was applied within the following years and further developed in many studies. The heating rate of magnetic iron oxide nanoparticles depends not only on strength and frequency of the alternating field applied but also on the size of the particles used [74].

4.3 Types of hyperthermia

There are various possibilities for increasing the temperature in a particular area of the body. When using magnetic nanoparticles, increasing the temperature can be induced by an alternating magnetic field. Xu et al. studied hyperthermia with the assistance of cobalt nanoparticles, although they did not apply an alternating magnetic field. This research group heated the particles by ultrasonic sound (350 kHz) and showed that the effects of the nanoparticles *in vitro* depended on the exposure time and the nanoparticle concentration [75]. However, as Rodriguez-Luccioni et al. demonstrated in a comparative study, the viability of cells *in vitro* was affected significantly more by magnetic hyperthermia than by heating in a water bath, which implicates that magnetic hyperthermia might have additional effects on tumor cell viability [76]. In their study, Hedayati et al. defined the minimum size of a tumor for efficient hyperthermia with an alternating magnetic field. They determined a minimum tumor volume of 1 mm^3 consisting of cells that had incorporated magnetic nanoparticles to facilitate hyperthermia effects [77]. It is of interest to note that Asin et al. found no increase in temperature with the application of an alternating magnetic field *in vitro*. Even so, there was more cell death. The authors assumed that the alternating magnetic field caused mechanical cell damage by actuating intracellular iron oxide nanoparticles [78].

4.4 Release of active substances

Hyperthermia can also serve to release active substance from a nanoparticle/drug construct, which means that the site and the timing of the drug's action can be determined precisely. Using an alternating magnetic field, Oliveira et al. increased the release of doxorubicin from a polymersome containing iron oxide nanoparticles, thus, achieving a greater toxicity in cell cultures [79]. Using the same method, Li et al. also demonstrated a greater release of doxorubicin *in vitro* [80]. In 2012, Koppolu et al. presented polymer-coated iron oxide nanoparticles, which likewise released doxorubicin in a temperature-dependent manner [81].

4.5 Thermal ablation

Kale et al. were able to heat in-house-produced nickel nanoparticles up to 75°C within 2 min *in vitro*, which is a very promising result regarding their use in hyperthermia or thermal ablation [82]. Balivada et al. found an anticancer effect in mice after injecting magnetic nanoparticles either directly into the tumor or intravenously, followed by the exposure to an alternating magnetic field [27].

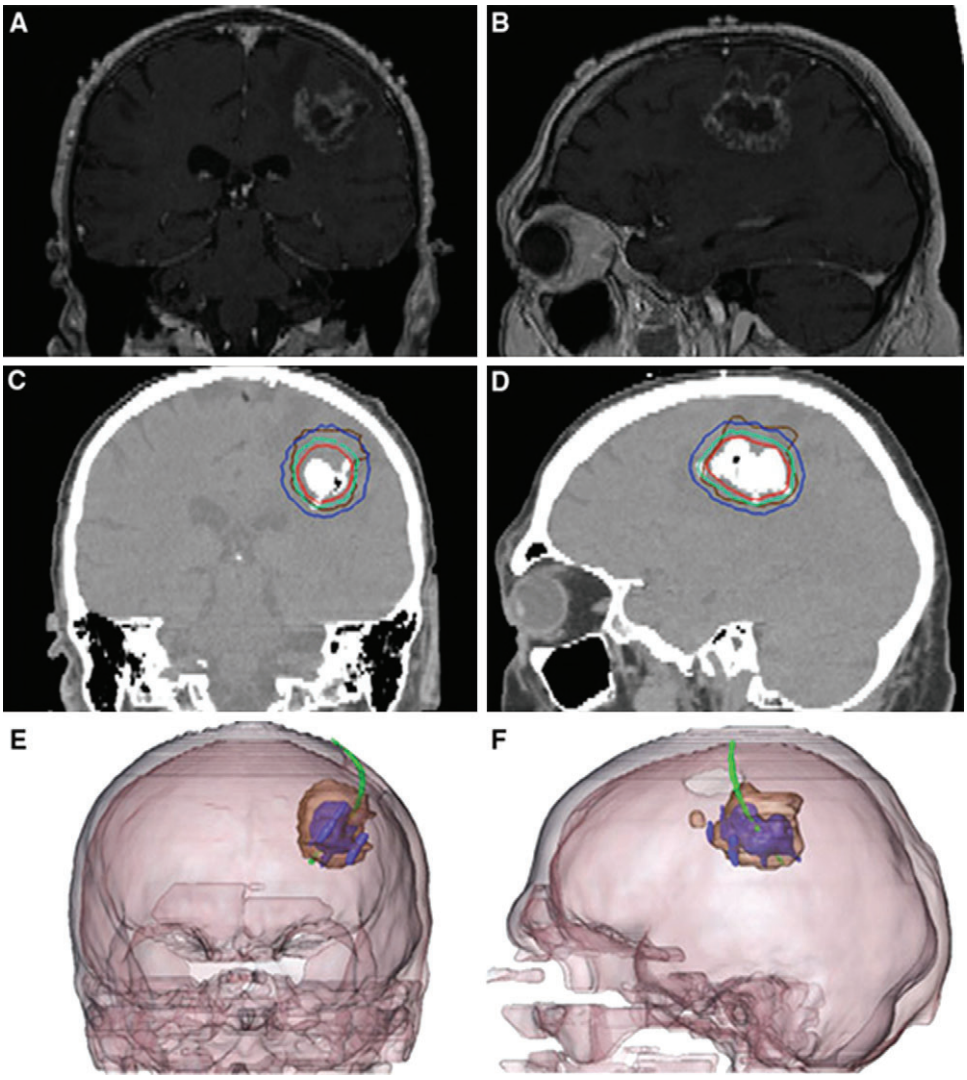

Figure 4 The treatment of a glioblastoma with hyperthermia [47]; reprinted with permission from Elsevier.
Baseline situation on MRI (A: coronal; B: sagittal). Computer tomography after the installation of the particles, which can be seen as hyperdense spots. The brown line depicts the extent of the tumor, the other lines show the calculated temperature from 40°C (blue) to 50°C (red) (C: corona; D: sagittal). The 3D reconstructions showing the tumor (brown), the administered magnetic nanoparticles (blue), and the thermometry catheter (green) (E: corona; D: sagittal).

Hyperthermia alone, with superparamagnetic iron oxide nanoparticles heated by an alternating magnetic field, is already being used for cancer treatment. This thermotherapy has been used in a phase I clinical trial to treat patients with a recurrence of prostate cancer [46]. Combined with radiotherapy, hyperthermia has also been used in patients with recurrent glioblastoma (Figure 4) [47].

In principle, hyperthermia is conceivable with all magnetic nanoparticles. The first uses in patients are very promising, so a further improvement in cancer therapy is to be expected in the future.

5 Overcoming cancer drug resistance with the help of magnetic nanoparticles

5.1 Causes of drug resistance

Surgery is still the gold standard of treatment for most solid tumors. At the time of cancer diagnosis, the disease is no longer confined to the local growth but has already metastasized is in 50% of the patients. [83]. Surgery can,

therefore, no longer offer a curative treatment. Radiotherapy and chemotherapy, which are now the available options, also have their limitations. The tumor may be located in sites that are difficult to reach for the medication or are protected by other mechanisms such as a high hydrostatic pressure in the tissue or an unfavorable vascular supply. In addition, certain types of cancer are not sensitive to irradiation or anticancer drugs. One of the biggest problems, however, is the resistance to a particular therapy developing during the course of treatment. This is usually the cause of recurrence after radio- or chemotherapy. The ATP-binding cassette (ABC) transporters are of particular importance in here. They are responsible for the simultaneous resistance to several different chemotherapeutic agents (multidrug resistance), as they transport these toxic substances out of the cells [84]. Other mechanisms include the augmented DNA repair, effects on the cell cycle, and altered intracellular drug metabolism [85, 86].

5.2 Magnetic nanoparticles against cancer drug resistance

Nanotechnology allows the combination of a wide variety of substances and mechanisms of action, as well as their targeted use. Magnetic nanoparticles are coated with biocompatible materials and functionalized with one or more different active substances. It is, therefore, possible to use different therapeutic mechanisms concomitantly in one place, which greatly reduces the probability of resistance. For example, Tang et al. used magnetic nanoparticles with a manganese, zinc, and iron oxide core, as well as human albumin, folic acid, cisplatin, and the radionuclide ^{188}rhenium. In this way, a triple effect of radiotherapy, chemotherapy, and hyperthermia could be achieved. They tested the pharmacokinetics and biodistribution *in vivo* in a tumor-bearing nude mouse model (human ovarian cancer SKOV3 cells in 21 BALB/C nude mice) [41]. Another possibility is to increase the concentration of the anticancer drug to a level at which no malignant cell survives. A magnetic field for the tissue-specific enrichment of the magnetic nanoparticles and the attached drug is of great value for this purpose. This strategy is employed, for example, in MDT, as described previously. Even tumors that are already resistant to treatment can be more efficiently accessed by magnetic nanoparticles. One strategy is, for example, the simultaneous coupling of an anticancer drug and a medicinal product targeted against the mechanism of resistance. With this approach, Cheng et al. were successful in using magnetic nanoparticles loaded with a chemotherapeutic agent and an ABC transporter inhibitor. Testing the cytotoxicity of doxorubicin on K562/A02 cells (human chronic myeloid leukemia-resistant cell line) *in vitro*, they found a significantly enhanced effect on the cells compared to the antineoplastic agent bound to the nanoparticles without the ABC transporter inhibitor [87]. Substances can be used that are not affected by the relevant mechanism of resistance or that target it directly (e.g., antibodies to ABC transporters) [88]. Besides its core and biocompatible coating, in the ideal case, a functionalized nanoparticle should have four components to meet different tasks [89]:

1. Antitumor effects
   This effect is achieved by the association of substances that act directly against the tumor, such as chemotherapeutic agents, nucleic acids, radionuclides, etc. This heading also includes the induction of hyperthermia using an alternating magnetic field.
2. Overcoming cancer drug resistance
   Substances aimed to provide an effective therapy by blocking drug resistance of the tumor are coupled to the nanoparticles. Here the ABC transporter inhibitors or antibodies come into consideration.
3. Diagnostic investigations and imaging
   Functionalized nanoparticles should include a substance used for diagnostic purposes. This would allow therapy and diagnostic investigation to be combined into "theranostics". Magnetic nanoparticles are already in use as contrast media in magnetic resonance imaging.
4. Enhancement at the target site
   In order to concentrate the nanoparticles in the desired area and treat the tumor in a targeted manner, it is possible to combine them with antibodies that bind specifically to the tumor. The accumulation of magnetic nanoparticles using a magnetic field is another option.

6 Metastasized cancer – limitations and possibilities

The therapy of metastasized cancer will remain a great challenge, even when using nanotechnology. At the time of diagnosis, nearly 50% of the tumors did already spread. For this reason, only palliative care can be offered to most of these patients. Nevertheless, the therapy of the primary focus also results in therapeutic effects on the metastases [90]. Of course, not every satellite tumor can be targeted

by MDT as pursued by the Section for Experimental Oncology and Nanomedicine (SEON), but one can focus on life-threatening or massively quality-of-life-limiting metastases. However, there are already approaches to treat the metastasized cancer in a curative intention. Yang et al. introduced a new magnetic lymphatic-targeting drug delivery system, based on functionalized carbon nanotubes. They achieved successful inhibition of lymph node metastasis by the subcutaneous administration of gemcitabine-loaded magnetic multiwalled carbon nanotubes as well as with loaded magnetic-activated carbon particles under a magnetic field [91].

7 Conclusions

The treatment of cancer has already made considerable advances with the use of magnetic nanoparticles. There are numerous possibilities for their use. Drug delivery allows a wide variety of substances (chemotherapeutic agents, radionuclides, antibodies, nucleic acids, etc.) to be transported in a targeted manner to the site where they are needed and intended to act. It is possible to combine drug delivery with hyperthermia as adjuvant therapy, in order to improve the desired anticancer effects. But magnetic nanoparticles can also be used to enable local hyperthermia to be used alone. Thanks to nanotechnology, there are also many innovations in diagnostic imaging. The diagnostic and therapeutic goals can often be combined in "theranostics", which is certainly an important aspect in the use of magnetic nanoparticles. The number of publications and the scope of research projects on the subject of magnetic nanoparticles in cancer therapy indicate that further significant improvements are to be expected in this field in the future. Given the demographic trends in the industrialized nations and the associated increasing relevance of cancer, the outlook seems promising.

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Department of Otorhinolaryngology, Head and Neck Surgery
Section for Experimental Oncology and Nanomedicine (SEON)
The SEON emerged from Professor Alexiou's working group after his receiving of the first chair for Nanomedicine in Germany, which was endowed by the Else Kröner-Fresenius-Stiftung in 2009. The group can look back to more than 15 years of experience in the application of iron oxide nanoparticles in cancer treatment. The favored therapy approach is "Magnetic Drug Targeting." The main goal of SEON is to enhance cancer treatment and simultaneously to reduce the side effects of chemotherapy, by accumulating the nanoparticle-bound drug with strong external magnetic forces. In the nearer past, SEON has broadened its activities to the use of iron oxide particles in the treatment of arteriosclerosis and also in regenerative medicine.

Stephan Dürr earned a Medical Degree from the Friedrich-Alexander-University Erlangen-Nuremberg and received his MD at the Institute of Pathology at the University Hospital Erlangen. Since 2004, he has been working at the Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Erlangen, where he specialized as an otorhinolaryngologist/head and neck surgeon in 2009. Within the ENT Department, he joined the Section for Experimental Oncology and Nanomedicine in 2010. There, he works as a research fellow on Magnetic Drug Targeting.

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Marc Schwarz studied Biology at the Friedrich-Alexander-University Erlangen-Nuremberg. After finishing his PhD theses at the Department of Neurosurgery of the University Hospital Erlangen, he stayed as a postdoctoral research fellow at the Department of Neuroradiology and focused on glioma imaging and treatment. Since the Section for Experimental Oncology and Nanomedicine and the Department of Neuroradiology started cooperating, he expanded his field of research on magnetic nanoparticles in cancer therapy and imaging.

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