

Magnetic Nanoparticles for Hepatocellular Carcinoma Diagnosis and Therapy

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver, ranking as the second most common cause of death from cancer worldwide. Magnetic nanoparticles (MNPs) have been used so far in tumor diagnosis and treatment, demonstrating great potential and promising results. In principle, three different approaches can be used in the treatment of tumors with superparamagnetic iron oxide nanoparticles: magnetically induced hyperthermia, drug targeting and selective suppression of tumor growth. This review focuses on the use of iron oxide nanoparticles for the diagnosis and treatment of liver cancer and offers a walkthrough from the MNPs imaging applicability to further therapeutic options, including their potential flaws. The MNP unique physical and biochemical properties will be mentioned in close relationship to their subsequent effects on the human body, and, also, their toxic potential will be noted. A presentation of what barriers the MNPs should overcome to be more successful will conclude this review.

Key words: magnetic nanoparticles – hepatocellular carcinoma – diagnosis – therapy.

Abbreviations: AMF: Alternating magnetic field; DOX: Doxorubicin; GD: Gadolinium; HCC: hepatocellular carcinoma; I31I: Iodine 131; MDT: Magnetic drug targeting; ML: Magnetoliposomes; MNP: magnetic nanoparticles; MRI: Magnetic Resonance Imaging; PNIPA: Poly-N-isopropylacrylamide; SPIONS: Superparamagnetic iron oxide nanoparticles; VEGF: Vascular endothelial growth factor.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver, ranking as the second most common cause of death from cancer worldwide. The underlying condition for developing HCC is cirrhosis, known to be associated with chronic viral hepatitis B or C in 80% of the cases [1], with a mortality rate of 54% [2] to 70% [3] in patients with compensated cirrhosis. Grim prognosis as well as the fact that the only substantial treatment remains hepatic resection, positions HCC as an important health problem worldwide, especially in newly industrialized countries.

Given that HCC is a highly vascularized tumor, the angiogenesis process [4] allows the tumor to develop, invade and metastasize [5], and restrains the therapy to limited options. Thus, sorafenib is the only available molecular targeted agent with positive results for angiogenesis inhibition [6, 7]. Research into new diagnostic and therapeutic fields for HCC offer a wide range of possibilities by trying to adapt to the tremendous potential and variability of the nanotechnology field.

By far, the most commonly used magnetic nanoparticles (MNP) are ferrite nanoparticles or iron oxide nanoparticles, which due to their superparamagnetic properties, offer numerous possibilities in drug and gene delivery, diagnostics and therapeutics. A large portion of their potential is oriented towards cancer diagnosis and targeted tumor therapy. That is why, in the last few years, many advances in the cancer field have consisted of the intensive study of theranostic nanomedicine.

In principle, three different approaches can be used in the treatment of tumors with superparamagnetic iron oxide nanoparticles (SPIONS): magnetically induced hyperthermia, drug targeting and selective suppression of tumor growth

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[8]. Also, tumor diagnosis can be greatly improved because of the MNPs capability to offer a better contrast in Magnetic Resonance Imaging (MRI), considerably increasing its sensitivity [9]. Moreover, another promising technique, enhanced by SPIONs properties, is Magnetic Particle Imaging which promises a very high temporal resolution, with high acquisition rates, offering an even greater sensitivity than MRI [10]. All of these create a need for developing new types of MNPs and for further studying their properties.

This review focuses on the use of MNPs in the HCC diagnosis and treatment options and provides a walkthrough from the imaging applicability to further therapeutic options, including their potential flaws. Their unique physical and biochemical properties will be mentioned in close relation to their consequent effects on the human body, and, also, their toxicity potential will be mentioned. A presentation of what barriers MNP should overcome to be more successful will conclude this review.

DISTRIBUTION AND BIOLOGICAL EFFECTS

Over the years, the continuous development of biomedical applications has emphasized the great potential of MNPs, due to their flexibility in the developing process with a general or individualized response from the targeted area. When discussing therapy, the general purpose is to concentrate the largest possible amount of MNPs within the tumor, so the biological response takes place. However, this process has been discussed so far only after local or intravenous injection and absorption after gavage [11]. These ways have proven to be rather difficult to control, as the biological performance may be influenced by various factors. For instance, most of the MNPs have been reported to be selectively taken up by the Kupffer cells (Fig. 1), whereas these cells are not present in a large number within HCC [12]. Intravenous injection has

been developed as a feasible and more reliable setting starting up from small size [13] to larger animals [12] and even human use [14].

The MNPs biological behavior has been discussed in terms of toxicity, biodegradation and elimination, characteristics that vary according to their design properties [15, 16]. Alongside the positive results in nanomedicine and with the continuous interest in MNPs, there is an increased need for the investigation of their toxicological properties and the long term effects on human health. Efforts have been made, in the last decade, to obtain a clearer picture regarding the safety issues associated with MNPs. The same nanoproperties that make them suitable for innovative achievements can also cause cytotoxic effects, affecting major cell components, namely mitochondria and nucleus [17].

Generally, MNPs are considered safe with a toxicological effect known to be dose dependent [18-21]. In a recent study, toxicity has been established for a dose of 200 $\mu\text{g}/\text{mL}$ or higher [22]. Another study, which compared metal oxide nanoparticles and carbon nanotubes, demonstrated *in vitro* the safety and the absence of cytotoxicity below 100 $\mu\text{g}/\text{mL}$, offering additional support for the suggested dose-dependent toxicity [23]. Besides dosage, other characteristics of the MNPs, such as size and morphology, might be responsible for additional side effects [24]. Another important factor that determines toxicity is the coating material and the resulting breakdown products [25]. The effects of different coatings on cell behavior and morphology are also important, the results showing that dextran-magnetite nanoparticles Fe_3O_4 result in cell death and reduced proliferation similar to that caused by uncoated MNPs [26]. Another study showed that uncoated particles induce greater toxicity compared to the biocompatible polyvinyl alcohol-coated particles [27].

Toxicological response varies also according to the administration route and with the cell/tissue type. For example, an *in vivo* study on wistar rats showed that SPIONs can induce

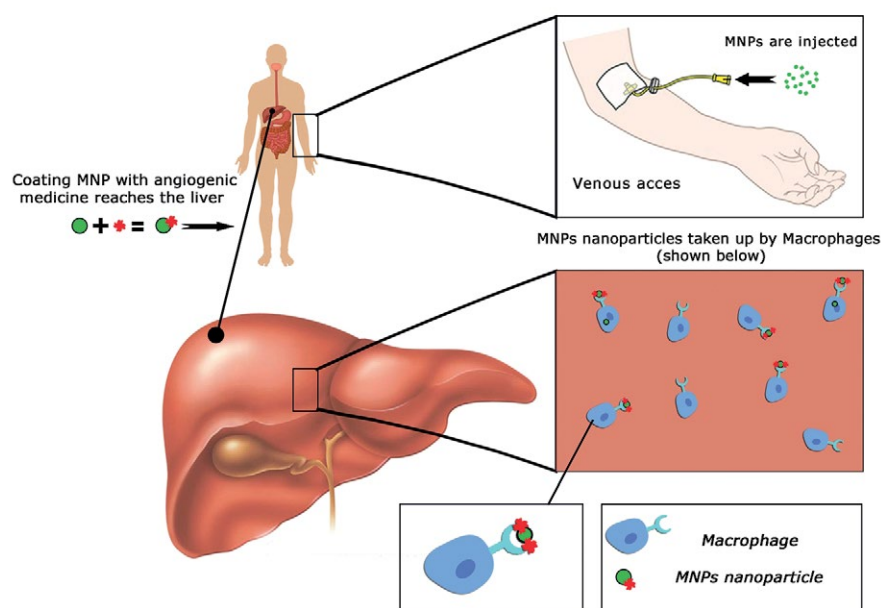


Fig. 1. Intravenous delivery and capture of the magnetic nanoparticles by the Kupffer cells.

cellular damage in the liver, kidneys, and lungs, with no effect on the brain and heart [28]. However, no change was observed in the animals' general health, while 75% of the nanoparticles were cleared from the bloodstream after 72 hours. Intravenous approach determines the accumulation of the nanoparticles in organs such as liver, kidneys, spleen, lungs and brain [29, 30]. However, irreversible organ toxicity was excluded up to 21 days [30]. Intraperitoneal injection in mice also determines the passage of the particles through the blood brain barrier, but with no functional disturbance or any apparent toxicity [31].

In humans, there are a limited number of studies which have investigated the toxicity of MNPs. One of these found that Ferumoxtran-10, which is a dextran-coated SPIO, caused mild side effects (in 6% of the patients) such as hives, headache, back pain, vasodilatation, all of which being short in duration [14].

IRON OXIDE NANOPARTICLES AND IMAGING

Imaging modalities vary in aspects such as sensitivity, spatial and temporal resolution, and quantitative capabilities, meaning that each one of these can be further improved. That is why continuous efforts are being made in order to maximize all of the above and to create a close to ideal imaging technique [32-34].

Magnetic nanoparticles are used as contrast agents for MRI because of their superparamagnetic properties, which allow them to be magnetized only under the influence of an externally applied magnetic field, and to lose this magnetization once the field is deactivated [35, 36]. This property allows SPIONs to be used in MRI as negative contrast agents [37]. After local tissue accumulation, they shorten the spin-spin relaxation time producing hypointense signals in T2/T2*-weighted images, creating darker regions, thus increasing the contrast [38]. Depending on the core diameter, they can also affect T1 relaxation time, giving hyperintense signals in T1-weighted images, but with a less pronounced contrast [39].

SPIONs pharmacokinetic properties allow them to accumulate, in a non-specific way, into the mononuclear phagocyte system, which facilitates their use in MRI of organs such as liver and spleen [40], lymph nodes [41] and bone marrow [42]. With a mean hydrodynamic diameter between 100 and 150 nm, SPIONs are non-specifically absorbed by Kupffer cells in the normal liver tissue. This causes, in a consequent MRI analysis, a drop of signal in the liver in T2*-weighted images. An alteration of the normal hepatic tissue, such as in the case of HCC, cholangiocellular carcinoma or liver metastases, provides a signal drop due to the non-retained SPIONs [43]. As a consequence, an increased lesion-to-liver contrast will be achieved, increasing the sensitivity for tumor detection [44, 45].

There were two SPIO compounds available for clinical use in liver imaging: ferumoxide (Endorem®, Guerbet) [46] and ferucarbotran (Resovist®, Bayer Healthcare Pharmaceuticals) [47]. Both of them were solely approved for liver MRI, even though they had different characteristics. On one hand, Resovist® can be used with both dynamic and delayed imaging given the possibility of rapid bolus administration, whereas Endorem® is used just with delayed phase imaging,

because of the slow bolus administration. Also, Resovist® has a smaller hydrodynamic diameter (45-60 nm), which will shorten both T1 and T2 relaxation times. Both compounds were discontinued due to the small sales market and because of the introduction of the hepatobiliary Gadolinium (GD)-based contrast agent, GD-EOB (Primovist®, Bayer Healthcare Pharmaceuticals), which has a better ability to detect liver lesions [48].

A better accuracy of SPIO-enhanced MRI compared to non-enhanced MRI has been shown to be more effective in detecting focal liver lesions [49]. A multicenter trial found a 27% increase in sensitivity for the detection of hepatic lesions using ferumoxide-enhanced T2-weighted images, compared to non-enhanced images, and a 40% increase compared to non-spiral computed tomography [50].

The differentiation of dysplastic nodules from HCC is imperative for early and precise treatment. Several studies focused on the potential of SPIO-enhanced MRI to observe different patterns of contrast between these lesions. Kupffer cells are either absent, or found in different proportions, depending on the nature of each lesion. Since SPIONs are taken-up by these cells, different patterns will be achieved in each type of lesion, with the possibility to differentiate them. MNP-MRI may be useful in differentiating HCC from hyperplastic nodules; however, the difficulty encountered in some cases indicates that there are other factors that determine the accumulation of MNPs, besides the Kupffer cells ratio [43]. A study [51] found a case where a well-differentiated HCC appeared hypointense in T2-weighted images using SPIO-enhanced MRI, indicating an accumulation of the particles within the tumor. This was confirmed in a subsequent study, which observed that Kupffer cell-count ratio decreased as the degree of differentiation of HCCs declined, meaning that well-differentiated HCCs have a similar number of Kupffer cells as the normal surrounding parenchyma, explaining the hypointense signals in some HCC lesions [52]. The same results were later confirmed, indicating that SPIO intensity ratio correlates well with the Kupffer cell-count ratio of the tumoral lesion in HCC and dysplastic nodules [53]. Subsequently, SPIONs intensity ratios and histological grading of HCC were found to be inversely correlated, so that the SPIONs intensity ratio increased with the decline in HCC differentiation.

Moreover, ION-based contrast agents are considered to be the only ones capable of distinguishing between HCC and dysplastic nodules, limited only by possible similarities in Kupffer cells number [54-59]. A recent meta-analysis using data extracted from 15 eligible studies revealed the clear benefit of using SPIO-enhanced MRI in differentiating HCC from other focal hepatic lesions, and the potential for distinguishing dysplastic nodules from advanced HCC in cirrhotic livers [60]. A 98% sensitivity was relevant for detecting advanced HCC, using the level of hyperintensity as the main criteria in SPIO-enhanced T2*-weighted images.

Validating MNPs for diagnosis also implies a comparison with other available imaging techniques. A proven benefit of SPIO-enhanced MRI was demonstrated when compared to dual-phase spiral CT, obtaining a significantly higher sensitivity (70.6% vs. 58.1%, $p < 0.05$) [61]. Moreover, combining the results from non-enhanced and SPIO-enhanced T2-weighted

MRI offered a significantly higher sensitivity and also a greater accuracy in differentiating benign from malignant lesions, as compared to each method alone and to images obtained with spiral CT [49]. Three imaging modalities were compared in 72 HCC tumors in a study which found detection rates of 69% for triple-phase dynamic CT (single helical), 89% for triple-phase dynamic MR imaging, and 86% for SPIO-enhanced MRI [45]. A small difference was noted between dynamic MRI and SPIO-MRI detection rates, but with significantly higher differences between both of them and dynamic CT.

To overcome the limitations implied by Kupffer cells encapsulation, extracellular fluid contrast agents such as GD chelates, which produce positive contrasting in T1-weighted MRI were introduced. In contrast to SPION dependence on Kupffer cells, GD-enhanced MRI relies on the blood flow to the hepatic lesions. Given the increased arterial supply of most HCCs, extracellular fluid contrast agents are highly valuable as tools in diagnostics. So far, a clear superiority of either one of the two was not demonstrated. The majority of the comparative studies found a greater diagnostic performance for GD in detecting HCC [48, 62-66]. However, other authors obtained either a superior accuracy of SPIO [67], or equal sensitivity between the two contrast agents [68]. Therefore, no clear consensus exists regarding which of the two methods should be used. The downside of SPIO-enhanced MRI lies in the false negative results offered by small and well-differentiated HCCs, where the large number of Kupffer cells explains the drop of the signal inside the tumor. A small lesion size, with or without hypovascular features, can justify the possible absence of contrast enhancement during GD-based MRI, creating false negative results. Thus, when GD images are not diagnostic, SPIO-enhance MRI may be used for a further characterization of the lesion. Other authors concluded that the diagnostic accuracy of HCC can be improved by using double-contrast MRI, with both SPIO and GD, achieving a higher accuracy compared with SPIO-enhanced MRI alone (0.86 vs. 0.76) [66]. Until now, SPIO-enhanced MRI has been proven to be an effective method for detection, evaluation and follow-up investigations in HCC patients.

IRON OXIDE NANOPARTICLES AND HYPERTHERMIA

Over the years, thermotherapy has been widely used for cancer research with several clinical approaches such as radiofrequency, microwaves or lasers [69]. These techniques, however, may cause additional damage to the healthy tissue when exposing it to heat, therefore inducing harmful side effects. This new challenge has led to the research into a new methodology of heating up and destroying cancer cells. Magnetic fluid hyperthermia, considered as one of the main directions of nanotechnology, stands out as a new alternative. SPIONs may induce local heat under an oscillating magnetic field, causing the tumor tissue temperature to increase to a certain value and provide the desirable effect. Mostly similar to radiofrequency, magnetic hyperthermia easily obtains a temperature over 42°C, causing a rapid apoptotic process of the tumor cells with little effect on the normal tissue [70]. However, the use of MNPs for hyperthermia depends not only

on their paramagnetic properties, but also requires additional attention on some features such as size, coatings or toxicity, as well as the concentration of MNPs in the tumor tissue [71].

So far, available preclinical data reveals that hyperthermia might be feasible to treat HCC tumors. Dispersing MNPs within a tumor allows them to enter the cancer cells in a passive way according to their characteristics. Furthermore, exposing them to a magnetic field causes a heat reaction by the Neel relaxation method and produces apoptosis.

The effects of magnetic fluid hyperthermia which contains various concentrations of Fe₂O₃ nanoparticles on SMMC-7721 liver cancer cells, was evaluated [72]. After each sample of cells and MNPs were exposed to 1 h irradiation and incubated, a large amount of MNPs were captured by the tumor cells and the exposure to a high frequency magnetic field showed not only a high rate of apoptosis, but also the inhibition of the proliferation rate. Consequently, after exposing the SMMC-7721 cells to 300 A, the temperature rose to 39-54°C, a level where it remained constant for 40 minutes suggesting that this type of magnetic fluid might be a successful constant-method of hyperthermia. The immunocytochemical staining also showed that the ferrofluid concentrations influenced Bax and Bcl-2 expression.

Moreover, tumor heating of cancer cells, in synergy with other cancer related therapies, has received a great deal of attention. Attaching other substances with chemotherapeutic effects may enhance the tumor response to treatment. The use of As₂O₃/Fe₂O₃ combined with magnetic fluid hyperthermia, on mice liver tumor xenografts indicated that their association had a higher therapeutic effect than Fe₂O₃ alone [73]. Subsequently, another study, which used As₂O₃/Mn_{0.5}Zn_{0.5}Fe₂O₄ MNP complex on a HepG2 cell line, suggested a possible complementary role with heat enhancing the cytotoxic effects of the chemotherapeutic drug [74]. Doxorubicin (DOX) bounding on a thermosensitive polymer coating MNPs has been tested as a dual therapy of HCC [75]. This complex might foster the death of cancer cells due to the double effect of the magnetic field application and the release of DOX.

Nevertheless, hyperthermia has its boundaries. Even though results might be promising, more *in vitro* and *in vivo* studies should be performed on toxicity, targeted distribution and adequate tumor control.

TARGETED THERAPY

The HCC surgical treatment or ablative therapies are rarely an option because of the advanced stage in which the patients present [76], therefore promoting systemic chemotherapy as the only way to prolong the overall survival rate. However, the need for high doses and the non-selective properties of chemotherapeutic agents determine numerous off-target side effects. Localized targeted chemotherapy allows a proper concentration of the therapeutic agent to reach the tumor, while, also, minimizing the effect on healthy tissue.

Magnetic drug targeting (MDT) represents a new delivery system for therapeutic agents which has been employed in loco-regional cancer treatment [77, 78]. The MNPs involved are coated with a polymer to which a cytotoxic agent is bound allowing the drug to reach the targeted tissue when an external

magnetic field is applied. Magnetic drug targeting was assessed in many different types of cancers, making it an attractive idea, even though its clinical efficacy is yet to be proven [77-79].

A major area of interest is represented by the use of magnetoliposomes (ML) due to their ability to change structure and permeability under low frequency magnetic fields, making them suitable as controlled-release drug delivery agents [80, 81]. A study assessed the possibility of intracellular RF-triggered DOX release from the dMLs (polyethylene glycol-stabilized bilayer-decorated ML) using Huh-7 HCC cell line [79, 82]. The foundation for this study was laid down by previous work, which showed that dMLs can retain their cargo, including DOX, until triggered to release [83-85]. The hypothesis was to make use of this ability in order to create a suitable approach for HCC chemotherapy. The results of the study showed cell viability reduced to 40% after 8h and complete cell death observed after 24h. The therapeutic mechanism was intracellular RF-triggered DOX release from the dMLs, and not intracellular hyperthermia due to nanoparticle heating via magnetic losses [82].

Another study [86] focused on MDT and the use of sorafenib. Because of the serious side effects [87], one strategy is to develop magnetic nanovectors loaded with sorafenib in order to enhance their delivery. The results showed that it is possible to obtain stable complexes, which are able to inhibit cancer cell proliferation through the sorafenib cytotoxic action, and to localize this effect in the desired area due to the magnetically-induced drug accumulation.

Simultaneous dual modality therapies are plausible and even more attractive, as demonstrated in several studies on different cancer types [72, 88]. One of the studies indicated the possibility of intra-arterial delivery of MNP-PNIPA (Poly-N-isopropylacrylamide)-DOX complex solution and their delivery when an alternating magnetic field (AMF) is applied in a HCC rat model. A subsequent study proved the feasibility of a dual-modality therapy concept, with MDT and magnetic hyperthermia for HCC, using MNP technology, emphasizing that after AMF exposure, DOX was successfully released within the targeted tissue [89].

A novel therapeutic approach in HCC treatment is gene therapy. It entails the functional replacement of a defective gene and the consequent expression of the therapeutic gene. Genes can be integrated into SPIONs, which offer protection for the nucleic acids against enzymatic degradation and aid cellular internalization. An integrative approach has been developed performing simultaneous real-time tumor monitoring, gene therapy and internal radiotherapy [90]. This was achieved using a type of SPIONs (SilenceMag) carrying small interfering RNA (siRNA) with radiolabeled Iodine 131 (¹³¹I) against the human vascular endothelial growth (VEGF) factor in nude mice. The results revealed that electromagnetic field-guided ¹³¹I-hVEGF siRNA/SilenceMag exhibited an antitumor effect and concluded that it might be a promising future treatment option against HCC.

MNP DESIGN PROPERTIES

The incentive research and wealth of expertise of MNP theranostics need to be improved so that treatment may

progress from *in vitro* and *in vivo* studies through trials and into a clinical status. With the vast potential of therapeutic options, from hyperthermia to gene therapy and the use of different compounds or drugs attached to their surface, MNP may be useful in countering the global challenge represented by HCC.

One of the drawbacks of MNP therapeutics is their delivery to the HCC tumor. Systemic delivery, distribution [91] and detection of tumors is a complex process which requires MNPs to pass through three phases: blood stream delivery, extravasation and attacking the cancer cells after reaching the interstitial space [92, 93]. Therefore, the key feature for distribution might be their size. Studies have shown that these three phases may require different MNP sizes to achieve a positive effect. At first, MNPs should have an optimal diameter in order to increase plasma half-life, and, after passing through the vascular wall, a smaller size would be required in order to achieve a better distribution [94]. On the other hand, the therapeutic agent should reach its highest amount within the cancer cells and avoid side effects on normal tissue. This will come in handy when compared to conventional chemotherapy, since most of the MNPs are developed as carriers and side effects of the cytotoxic agents could be avoided.

Magnetic nanoparticles biological performance is also influenced by the core-shell preparation. Their shape and charge density are also important parameters when designing specific nanoparticles. Thus, a high charge of their surface will account for a higher clearance from the mononuclear phagocyte system [95]. Among different shapes, it seems that the design is a key feature when discussing circulation and renal clearance. With the need for a longer circulation, it seems that elongated nanoparticles take more time to be cleared from the vascular network than the ones with a spherical shape [96].

Hepatocellular carcinoma is one of the most vascularized solid tumors [97], characterized by sinusoidal capillarization and arterialization of its blood supply. While tumor blood vessels may be divided according to their perfusion and permeability, HCC has been evaluated as a solid tumor with good perfusion and functional blood vessels, which will require specifically designed nanoparticles to improve the condition of the patients having this disease.

CONCLUSIONS

The rising tendency of providing new methods to intervene in HCC diagnosis and treatment promotes the use of MNPs as a step forward due to their various characteristics and potential. Taking into account that a prolonged time between diagnosis and treatment in HCC tumors represents a great disadvantage for the patient, the continuous research in nanomedicine may lead to new methods of synthesis, targeting and destroying cancer cells by developing highly new complex MNPs. Hence, the continuous manufacturing and testing of various methods of theranostics for MNP-based methods at a preclinical stage are mandatory before clinical implementation.

Conflicts of interest: No conflicts to declare.

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wrote the manuscript. C.M.T. contributed to the design of the study, selection of studies and revision of the manuscript. A.S. performed overall study design and final revision of the manuscript. All authors approved the final draft submitted.

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Nanoparticulele magnetice pentru diagnosticul și tratamentul cancerului hepatocelular

ABSTRACT / REZUMAT

Carcinomul hepatocelular este tumora hepatică primitivă cel mai frecvent întâlnită, și reprezintă a doua cauză de deces prin cancer la nivel mondial. Până în prezent, nanoparticulele magnetice (NM) au fost utilizate cu rezultate promițătoare atât în diagnosticul, cât și în tratamentul tumorilor. În principiu, pentru abordarea tumorilor, NM pot fi orientate în trei direcții: hipertermia indusă magnetic, terapia țintită și supresia creșterii tumorale. Acest referat se concentrează pe utilizarea NM pentru diagnosticul și tratamentul cancerului hepatic, oferind informații privind imagistica prin NM, dar și privind opțiunile terapeutice disponibile. Mai mult, sunt descrise și punctele lor slabe precum și modul de a le mări potențialul. Proprietățile lor fizice și biochimice unice sunt menționate în relație strânsă cu efectele asupra corpului uman, fiind prezentate și efectele toxice. Referatul prezintă de asemenea barierele pe care NM trebuie să le depășească pentru a deveni mai performante.