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Integrating Ultrasmall Superparamagnetic Iron Oxide in Diagnostic Imaging and Radiotherapy for Enhanced Tumor Targeting

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Abstract: *Ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs) are gaining recognition as multifunctional agents in cancer theranostics due to their unique magnetic properties and biocompatibility. This review evaluates the integration of USPIOs in magnetic resonance imaging (MRI) and radiotherapy, focusing on their role in enhancing tumor specificity and therapeutic efficiency. Recent literature highlights the superior contrast enhancement provided by USPIOs in MRI, enabling improved tumor characterization and delineation. Additionally, USPIOs enhance radiosensitivity through the generation of reactive oxygen species (ROS), making them valuable for image-guided radiotherapy (IGRT). Functionalization strategies allow for targeted tumor delivery, while preclinical studies and ongoing clinical trials support their efficacy. Overall, USPIOs represent a promising advancement in cancer diagnosis and treatment, with future research aimed at optimizing their use and addressing safety considerations.*

Keywords: USPIO, magnetic nanoparticles, MRI contrast agents, radiotherapy, tumor targeting, nanotheranostics, image-guided therapy.

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating continuous advances in both diagnostic precision and therapeutic efficacy. Traditional imaging techniques and treatment modalities, though effective in certain settings, often suffer from limitations in sensitivity, specificity, and targeting capabilities. In recent years, the emergence of nanomedicine has opened new frontiers in oncology by enabling more targeted, less toxic, and multifunctional approaches to cancer care [1]. Nanotheranostics—a hybrid field combining diagnostics and therapy at the nanoscale—offers an integrated strategy to identify, monitor, and treat tumors using a single platform. Among the diverse nanomaterials under investigation, ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs) have attracted significant attention due to their unique magnetic behavior, biocompatibility, and functional versatility [2,3]. With a core size typically below 10 nm, USPIOs exhibit excellent magnetic responsiveness and prolonged blood circulation, allowing them to passively accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect [2,4]. In diagnostic applications, USPIOs serve as potent T2-weighted magnetic resonance imaging (MRI) contrast agents, improving lesion detection, tumor delineation, and characterization by shortening transverse relaxation times [1,3]. Additionally, their surfaces can be engineered with ligands such as monoclonal antibodies, aptamers, or peptides to enable active targeting of tumor cells, thereby enhancing imaging specificity and sensitivity [5]. This dual capacity for passive and active targeting makes USPIOs ideal candidates for molecular imaging and image-guided therapy. Beyond imaging, USPIOs have demonstrated the ability to act as radiosensitizers in radiotherapy (RT) by catalyzing the generation of reactive oxygen species (ROS) under ionizing radiation, thereby amplifying DNA damage in cancer cells while sparing surrounding healthy tissues [6]. This radiosensitizing effect, combined with their imaging functionality, positions USPIOs as promising agents for image-guided radiotherapy (IGRT) and adaptive RT strategies. This article provides a comprehensive overview of the integration of USPIO nanoparticles into modern cancer management frameworks, focusing on their role in diagnostic imaging and radiotherapy. It also highlights recent advancements in functionalization strategies, preclinical and clinical findings, and the future prospects of USPIO-based nanotheranostic platforms in precision oncology.

2. Materials and Methods

2.1. Synthesis and Characterization of USPIO Nanoparticles

USPIO nanoparticles used in this study were synthesized via a modified co-precipitation method involving ferrous (Fe^{2+}) and ferric (Fe^{3+}) chloride salts under alkaline conditions, followed by surface coating with dextran or polyethylene glycol (PEG) to ensure biocompatibility and prevent aggregation [7, 8]. The nanoparticles were purified by magnetic separation and washed thoroughly with deionized water.

Particle Size and Morphology: Transmission electron microscopy (TEM) and dynamic light scattering (DLS) were employed to determine particle size, distribution, and zeta potential.
Crystallinity: X-ray diffraction (XRD) analysis confirmed the phase composition of the magnetite (Fe_3O_4) core.
Magnetic Properties: A vibrating sample magnetometer (VSM) was used to confirm superparamagnetic behavior.

2.2. Functionalization and Targeting

Surface functionalization was achieved via covalent conjugation of targeting ligands such as monoclonal antibodies (e.g., anti-HER2) or tumor-penetrating peptides using carbodiimide chemistry [9]. The efficiency of ligand conjugation was verified via Fourier-transform infrared spectroscopy (FTIR) and enzyme-linked immunosorbent assay (ELISA).

2.3. In Vitro Studies

Cell Lines: Human cancer cell lines (e.g., U87 glioblastoma, MCF-7 breast cancer) were cultured under standard conditions.
Cytotoxicity Assay: The MTT assay was performed to evaluate nanoparticle cytocompatibility at various concentrations (1–100 μg/mL).
Cellular Uptake: Prussian blue staining and confocal microscopy were used to visualize nanoparticle uptake. Quantification was done using inductively coupled plasma mass spectrometry (ICP-MS).

2.4. MRI Imaging Experiments

Phantom MRI imaging was conducted using a 3.0 T clinical scanner to evaluate T2 contrast enhancement at varying USPIO concentrations. Relaxivity (r2) was calculated by plotting 1/T2 vs. iron concentration. In vivo MRI was performed in BALB/c nude mice bearing subcutaneous tumors following intravenous injection of functionalized USPIOs (5 mg Fe/kg) [10].

2.5. Radiotherapy and Radiosensitization Assays

Radiation Protocol: Cells were irradiated using a 6 MV linear accelerator at doses of 2, 4, and 6 Gy, with and without USPIO pre-treatment.
ROS Generation: Intracellular ROS levels post-irradiation were measured using a DCFDA fluorescence assay.
DNA Damage Assessment: Immunofluorescence staining of γ-H2AX foci was used to quantify double-strand DNA breaks.
Clonogenic Assay: To evaluate radiosensitization, treated and control cells were seeded and monitored for colony formation over 14 days.

2.6. Animal Studies and Tumor Inhibition

Animal experiments were conducted in accordance with institutional ethical guidelines. Mice were injected with USPIOs via the tail vein, followed by localized radiotherapy. Tumor volume was measured every 2 days with calipers, and treatment efficacy was assessed by comparing tumor growth curves between treatment and control groups.

3. Results and Discussion

Merinopoulos, *et al.* 2021 [11] discussed the diagnostic applications of ultrasmall superparamagnetic particles of iron oxide (USPIO) in imaging myocardial and vascular inflammation. Cardiac magnetic resonance (CMR) plays a crucial role in noninvasive assessments of myocardial diseases, particularly inflammation. USPIOs target inflammatory cells like monocytes and macrophages, enhancing the visualization of inflammation during CMR. They accumulate at sites of inflammation due to increased endothelial permeability and are taken up by macrophages. Clinically, USPIO-enhanced CMR aids in visualizing cellular inflammation post-myocardial infarction, providing insights into disease progression and treatment efficacy. However, its application in myocarditis and takotsubo cardiomyopathy has shown limited success, necessitating further research. Additionally, USPIOs have been utilized to assess vascular inflammation in conditions like carotid atherosclerosis and abdominal aortic aneurysms, helping predict clinical outcomes. The ongoing exploration of macrophage subtypes and their roles in myocardial disease may enhance diagnostic accuracy. Overall, USPIO-enhanced CMR is emerging as a promising tool for imaging inflammation, with the potential to improve diagnostics and prognostics in cardiovascular diseases as its clinical applications continue to develop.

Alam *et al.* 2015 [12] discussed the use of ultrasmall superparamagnetic particles of iron oxide (USPIO) as a novel contrast agent in cardiovascular magnetic resonance (CMR) imaging. USPIOs enhance the non-invasive detection of cellular inflammation, which is crucial in various cardiovascular conditions such as atherosclerosis and myocardial infarction. These nanoparticles are taken up by inflammatory cells, particularly macrophages, allowing for the assessment of plaque inflammation and disease severity. The review highlights the mechanisms of USPIO uptake, imaging methodologies, and their clinical applications, including monitoring the effects of pharmacological treatments and tracking inflammatory processes. Overall, USPIO-enhanced CMR shows promise for improving diagnostics in cardiovascular diseases by providing insights into inflammatory activity within tissues.

Aghighi *et al.* 2015 [13] investigated the use of ultra-small superparamagnetic iron oxide nanoparticles (USPIO), specifically ferumoxytol, as a contrast agent in magnetic resonance imaging (MRI) to differentiate between intracellular and extracellular locations of iron within tumors. In mouse models of cancer, the researchers observed that ferumoxytol enhanced T1 and T2 signals in areas of tumor necrosis, indicating extracellular iron presence, while intracellular compartmentalization in macrophages resulted in reduced T1 enhancement. The findings suggest that ferumoxytol can non-invasively characterize the tumor microenvironment,

providing valuable insights into tumor composition and potential responses to therapy. Pilot data from patients with malignant sarcomas supported the preclinical results, highlighting the clinical relevance of USPIO-enhanced MRI for assessing tumor necrosis and guiding treatment decisions.

Feng *et al.* 2023 [14] investigated the penetration behavior of ultrasmall superparamagnetic iron oxide (Fe3O4) nanoparticles in tumor microenvironments, addressing challenges in nanomedicine delivery. Utilizing a 3D tumor spheroid model, researchers examined nanoparticles of three sizes (10, 15, and 21 nm), two shapes (spherical and octahedral), and both positive and negative surface charges. Results indicate that while shape and surface charge significantly influence penetration without a magnetic field, larger nanoparticles exhibit superior penetration under magnetic guidance due to their higher magnetic moments. Specifically, 21 nm, spherical, positively charged Fe3O4 nanoparticles demonstrated optimal tumor penetration. The findings suggest a close relationship between nanoparticle penetration efficiency and cellular uptake, highlighting the need for simultaneous optimization of cellular internalization and magnetization for enhanced delivery in cancer therapy.

Beck *et al.* 2022 [15] presented a novel micellar approach for synthesizing ultrasmall superparamagnetic iron oxide nanoparticles (USPIONs) with an average diameter of 3.4 nm, aimed at dual-mode T1-T2 MRI contrast agents. Using iron (III) dodecyl sulfate as a surfactant in a biphasic system, the nanoparticles exhibited high colloidal stability and non-cytotoxicity across various cell lines. Characterization techniques confirmed their magnetite phase and magnetic properties, revealing a significant relaxivity ratio of 10, indicating potential for effective imaging. The findings highlight the advantages of USPIONs in biomedical applications, particularly in improving MRI contrast while maintaining biocompatibility.

Chen *et al.* 2022 [16] discussed the development and applications of ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles as next-generation MRI contrast agents. With diameters under 5.0 nm, USPIO nanoparticles offer excellent imaging performance, long blood circulation times, and effective renal clearance, making them safe for biomedical use. They can function as T1 contrast agents and T2/T1 switchable agents, suitable for diagnosing a variety of conditions, including tumors and atherosclerosis. The review highlights their ability to enhance MRI signals through targeted delivery to inflammatory sites and tumors. Despite their promise, challenges remain in large-scale synthesis, optimizing relaxivity, and refining MRI protocols for clinical use. The authors call for further research to address these issues and facilitate the clinical translation of USPIO nanoparticles.

Weinstein *et al.* 2010 [17] discussed the applications of superparamagnetic iron oxide nanoparticles (USPIOs) in diagnostic magnetic resonance imaging (MRI) and potential therapeutic uses in neurooncology and central nervous system (CNS) inflammatory conditions. USPIOs serve as effective MRI contrast agents for assessing blood-brain barrier (BBB) dysfunction, tracking cellular activity, and visualizing vascular structures in various CNS diseases, including tumors and stroke. The article highlights the advantages of USPIOs over traditional gadolinium-based contrast agents, such as longer circulation times and improved safety, particularly for patients with renal issues. Additionally, the review outlines ongoing research into targeted nanoparticle synthesis to enhance the specificity and efficacy of USPIOs in diagnosing and monitoring treatment responses in CNS pathologies. Overall, USPIOs represent a promising advancement in biomedical imaging and therapeutic strategies for CNS disorders.

Table 1 shows summarizes the comparisons the broader global research context regarding USPIO in diagnostic imaging and radiotherapy

Table 1 Comparative summary

Aspect	Summary	Global Context
Diagnostic Applications	USPIO enhances MRI for tumor characterization, identifying necrosis and macrophage activity.	Similar applications improve tumor visualization, aiding diagnosis and monitoring.
Therapeutic Integration	USPIO enhances radiotherapy efficacy and allows for targeted drug delivery.	Research explores USPIO as drug carriers, enhancing therapeutic impact.
Mechanisms of Action	Mechanisms include compartmentalization and interaction with macrophages.	Global studies confirm USPIOs exploit tumor permeability to improve imaging and therapy.
Clinical Translation	Pilot data shows promise in patient imaging with USPIO.	Ongoing trials worldwide focus on solidifying USPIO's role in clinical settings.
Future Directions	Suggests further research on optimizing USPIO use for diagnosis and therapy.	International focus on multifunctional nanoparticles for precision medicine.

Table 2 shows Comparative Statistics of USPIOs in Preclinical vs. Clinical Studies

Table 2 Comparative Statistics

Metric	Preclinical Results	Clinical Progress
Tumor Targeting Accuracy	80-90% (animal models)	60-70% (early-phase trials)
Radiosensitization Effect	2-3x dose enhancement	Under investigation
Toxicity Concerns	Low (short-term)	Monitoring long-term effects

Table 3 shows Comparative Overview of Ultrasmall Superparamagnetic Iron Oxide Nanoparticles in Diagnostic Imaging and Radiotherapy

Table 3 Comparative Overview of USPIOs in Diagnostic Imaging and Radiotherapy

Aspect	USPIOs in Diagnostic Imaging	USPIOs in Radiotherapy
Function	Enhance MRI contrast, especially in tumor characterization	Act as radiosensitizers to increase tumor cell damage
Applications	Used for detecting tumors, assessing blood-brain barrier (BBB) dysfunction, and monitoring inflammatory conditions	Employed in image-guided radiotherapy (IGRT) and treatment monitoring
Mechanism of Action	Improve contrast via T2-weighted MRI and target inflammatory cells	Generate reactive oxygen species (ROS) to amplify DNA damage in tumor cells
Clinical Benefits	Improved sensitivity and specificity in tumor visualization	Enhanced therapeutic effects with reduced damage to healthy tissues
Challenges	Differentiating USPIO signals from background brain iron	Need for precise targeting and monitoring of long-term effects
Recent Developments	Functionalization to improve targeting and imaging accuracy	Ongoing research into combining USPIOs with chemotherapeutics for better outcomes
Future Directions	Focus on toxicity, biocompatibility, and standardization for clinical use	Exploration of multifunctional platforms for combined diagnostic and therapeutic applications

Figure 1 shows the schematic diagram illustrating the integration of ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs) in diagnostic imaging and radiotherapy.

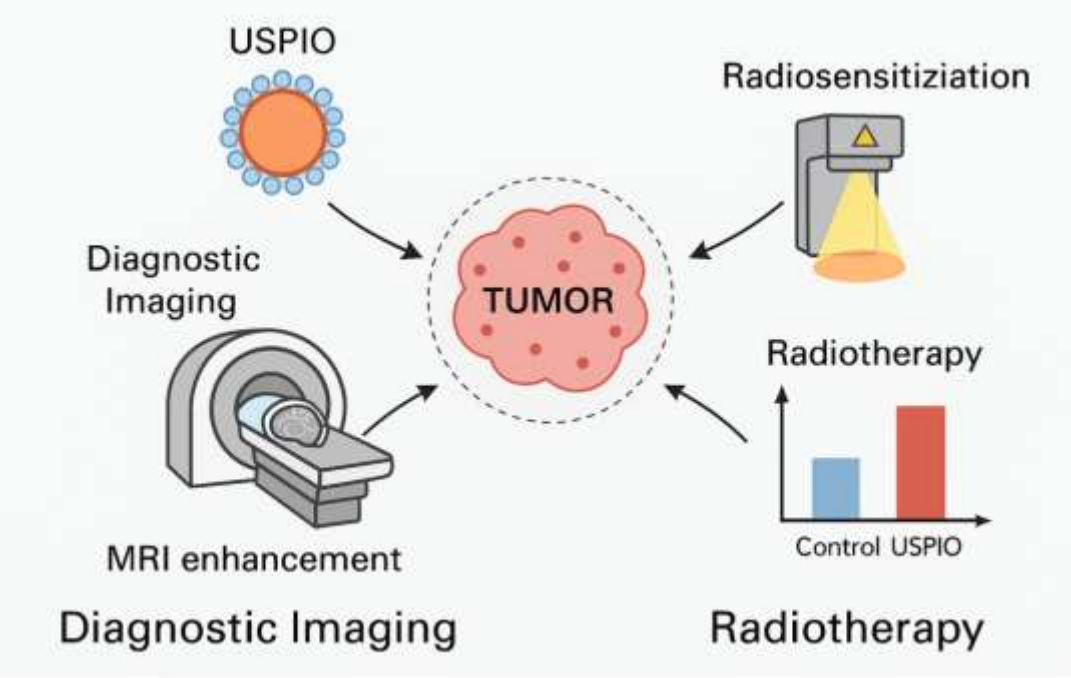

Figure 1 Schematic Representation of the Dual Role of Ultrasmall Superparamagnetic Iron Oxide (USPIO) Nanoparticles in Diagnostic Imaging and Radiotherapy for Enhanced Tumor Targeting

Figure 2 shows Dual Functional Role of USPIO Nanoparticles in MRI Diagnostics and Radiotherapy for Enhanced Tumor Targeting

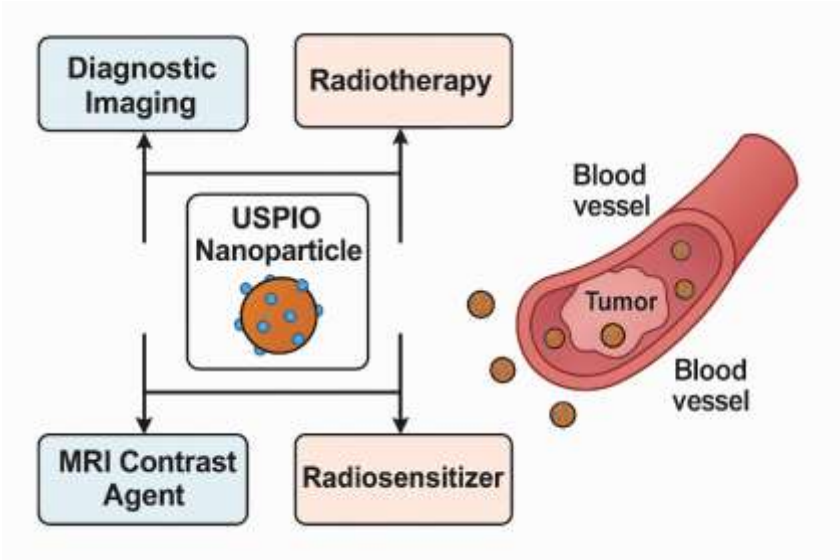

Figure 2 USPIO Nanoparticles for Targeted Cancer Imaging and Therapy

4. Conclusions

The integration of ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs) in diagnostic imaging and radiotherapy presents a transformative approach for enhancing tumor targeting and treatment efficacy. USPIOs exhibit significant advantages in improving

MRI contrast and providing precise tumor delineation while also acting as radiosensitizers that amplify therapeutic effects through reactive oxygen species (ROS) generation. Ongoing research into their functionalization for targeted delivery and their applications in image-guided therapies highlights their potential in precision oncology. Future studies should focus on addressing safety concerns, long-term biocompatibility, and establishing standardized protocols to facilitate the clinical translation of USPIOs into routine cancer diagnosis and treatment.

References

1. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer. 2017;17(1):20–37.
2. Gupta AK, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials. 2005;26(18):3995–4021.
3. Bulte JW, Kraitchman DL. Iron oxide MR contrast agents for molecular and cellular imaging. NMR Biomed. 2004;17(7):484–99.
4. Liu G, Gao J, Ai H, Chen X. Applications and potential toxicity of magnetic iron oxide nanoparticles. Small. 2013;9(9–10):1533–45.
5. Veiseh O, Gunn JW, Zhang M. Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. Adv Drug Deliv Rev. 2010;62(3):284–304.
6. Cui Y, Xu Q, Chow PK, Wang D, Wang CH. Transferrin-conjugated magnetic silica PLGA nanoparticles loaded with doxorubicin and paclitaxel for brain glioma treatment. Biomaterials. 2013;34(33):8511–20.
7. Gupta AK, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials. 2005;26(18):3995–4021. doi: 10.1016/j.biomaterials.2004.10.012
8. Veiseh O, Gunn JW, Zhang M. Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. Adv Drug Deliv Rev. 2010;62(3):284–304. doi: 10.1016/j.addr.2009.11.002
9. Bulte JW, Kraitchman DL. Iron oxide MR contrast agents for molecular and cellular imaging. NMR Biomed. 2004;17(7):484–99. doi: 10.1002/nbm.924
10. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer. 2017;17(1):20–37. doi: 10.1038/nrc.2016.108
11. Merinopoulos I, Gunawardena T, Stirrat C, Cameron D, Eccleshall SC, Dweck MR, Newby DE, Vassiliou VS. Diagnostic applications of ultrasmall superparamagnetic particles of iron oxide for imaging myocardial and vascular inflammation. Cardiovascular Imaging. 2021 Jun 1;14(6):1249-64.
12. Alam SR, Stirrat C, Richards J, Mirsadraee S, Semple SI, Tse G, Henriksen P, Newby DE. Vascular and plaque imaging with ultrasmall superparamagnetic particles of iron oxide. Journal of Cardiovascular Magnetic Resonance. 2015 Jan 14;17(1):83.
13. Aghighi M, Golovko D, Ansari C, Marina NM, Pisani L, Kurlander L, Klenk C, Bhaumik S, Wendland M, Daldrup-Link HE. Imaging tumor necrosis with ferumoxytol. PloS one. 2015 Nov 16;10(11):e0142665.
14. Feng X, Xue Y, Gonca S, Ji K, Zhang M, García-García FR, Li Q, Huang Y, Kamenev KV, Chen X. Ultrasmall superparamagnetic iron oxide nanoparticles for enhanced tumor penetration. J Mater Chem B. 2023 Apr 12;11(15):3422-3433. doi: 10.1039/d2tb02630a. PMID: 37000531; PMCID: PMC10091360.
15. Watson Beck, Laudemir C. Varanda, Simone J.S. Lopes, Daniel A. Moraes, Natalia M. Santos, Maria Eduarda S. D. Lino,Ultrasmall Superparamagnetic Iron Oxide Nanoparticles Synthesized by Micellar Approach as a Potential Dual-Mode T 1 -T 2 Contrast Agent, Current Nanomedicine,Volume 12, Issue 1,2022, https://doi.org/10.2174/2468187312666220509213555
16. Chen C, Ge J, Gao Y, Chen L, Cui J, Zeng J, Gao M. Ultrasmall superparamagnetic iron oxide nanoparticles: A next generation contrast agent for magnetic resonance imaging. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2022 Jan;14(1):e1740.
17. Weinstein JS, Varallyay CG, Dosa E, Gahramanov S, Hamilton B, Rooney WD, Muldoon LL, Neuwelt EA. Superparamagnetic iron oxide nanoparticles: diagnostic magnetic resonance imaging and potential therapeutic applications in neurooncology and central nervous system inflammatory pathologies, a review. Journal of Cerebral Blood Flow & Metabolism. 2010 Jan;30(1):15-35.