

Radiology-Guided Drug Delivery Systems: Toxicological Safety and Clinical Applications in Modern Medicine

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Abstract

Targeted deposition, controlled activation, and real-time treatment response monitoring are made possible by radiology-guided drug delivery systems, which combine medical imaging with engineered carriers to increase the spatial and temporal accuracy of therapy. The main imaging modalities like X-ray/fluoroscopy, computed tomography, magnetic resonance imaging, and ultrasound are summarized in this review along with their respective contributions to navigation, anatomical localization, functional or molecular guidance, and, on some platforms, triggerable release. Major delivery platforms, including nanoparticles, liposomes/micelles, ultrasound-responsive microbubbles, catheter-based systems, and stimuli-responsive formulations, are discussed, with emphasis on design features that support image visibility and selective activation. Particular attention is given to radiology-triggered strategies such as ultrasound- and radiofrequency-mediated effects and radiotherapy-triggered release, where imaging enables verification and adaptive control. Toxicological safety is addressed through biodistribution, clearance, acute versus chronic risk, modality-specific hazards (e.g., radiation exposure, thermal effects, cavitation), and the added complexity of combination-product regulation. Preclinical evaluation frameworks incorporating imaging-based pharmacokinetics and pharmacodynamics are examined, along with translational barriers including standardization, manufacturing scalability, infrastructure demands, ethics and consent, and evolving regulatory oversight, especially as intelligent radiology systems emerge. Overall, evidence indicates the strongest clinical momentum in oncology, with expanding opportunities in vascular, neurologic, and inflammatory indications. Standardized workflows, rigorous safety science, and clear regulatory pathways are essential to translate radiology-guided delivery into broadly accessible precision medicine.

Keywords: radiology-guided drug delivery; theranostics; stimuli-responsive nanocarriers; imaging-triggered therapy; toxicological safety

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1. Introduction

The use of imaging technology in therapeutic decision-making is one of the greatest developments in contemporary medicine. Radiology has now advanced to a field whose main aim was merely to diagnose up until it has become an active field that facilitates and leads to treatment. This has been facilitated by the improvements in imaging resolution, real-time acquisition, and multimodal visualization that has collectively broadened the use of image-guided interventions in minimally invasive and targeted therapies. Oncology, e.g.,

magnetic resonance imaging (MRI)-guided methods have made it possible to localize tumors precisely, plan

treatments, and monitor therapy, illustrating the use of imaging as a direct endpoint of therapeutic activity, as opposed to merely being a diagnostic endpoint¹. Based on these advancements, there has been the integration of radiology with targeted drug delivery systems, which has become one of the promising approaches to enhance the precision and efficacy of therapy. Radiology-guided drug delivery uses imaging modalities to overcome the

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spatial and temporal distribution of therapeutic agents, as well as to identify pathological locations. Recent developments in intelligent delivery systems have seen the emergence of externally modulated systems which respond to near-infrared light, and this suggests image-guided activation could be used to maximize drug release in target areas and minimize exposure to normal tissues². The trends of such approaches have to do with the more general change of the therapies in terms of imageability and dynamical control. Other inventions in medical image processing, visualization and intraoperative guidance have further helped in the growth of image-guided interventions. Advanced computer technology can today be used to create three-dimensional reconstructions, real-time navigation, and better visualization of anatomical and functional data, enhancing the accuracy of a procedure and patient outcome³. These technological transformations have helped to strengthen the view that imaging-guided therapies are not a minor enhancement of current practices but a paradigm shift in the design and implementation of interventions in clinical practice⁴.

A defining reason behind the fusion of radiology and drug delivery is the need to curb the inherent limitations of conventional systems of administration. There is, in general, poor specificity of systemically administered drugs, low concentration at disease sites and high off-target toxicity. Image-guided delivery systems attempt to surmount these issues by allowing the selective targeting, real-time monitoring, and targeted release of therapeutic agents. Multifunctional nanoparticles combining imaging and therapeutic functions have especially proved to be promising in nuclear medicine, enabling clinicians to track biodistribution and provide treatment at the same time⁵. Image-guided and localized delivery approaches also have benefits when used in combination therapy models where both the location and the release of the drug are important toward maximizing the synergistic effect and reducing cumulative toxicity. Localized delivery platforms are able to reach higher intratumoral drug concentrations using less systemic burden compared to systemic combination regimens, which facilitate more effective and safer cancer treatment systems⁶. These advantages are very in line with the recommendations of precision medicine that focus on customized therapeutic interventions that are based on molecular and spatial disease properties⁷. The connection of imaging and drug delivery has been further enhanced by nanotechnology, which has allowed the creation of platforms that respond to biological stimuli and are also imageable. The example of Redox-sensitive and stimulus-activated nanomachines capable of supporting imaging-guided combinational therapies illustrates the ability of diagnostic and therapeutic functions to be incorporated into a single system, taking advantage of the flexibility to tailor treatments and monitoring⁸. The impact of such innovations is the increased complexity of the radiology-guided drug delivery systems.

Although these developments have been made, there are still major challenges in the transformation of image-guided drug delivery technologies into standard clinical practice. Long-term safety, imaging sensitivity and

biodistribution remain a problem, and regulatory approval remains an impediment to a large-scale adoption. The existing studies in the areas of cancer imaging and nanomedicine report on the opportunities and challenges of translation of these technologies into clinical practice, both in revealing the promising future of these technologies and also in terms of safety and efficacy⁹. However, clinical experience with interventional radiology guided interventions, such as use with solid tumours in children, has shown that the image-guided treatment methods can be used to reduce morbidity resulting from treatment and still achieve therapeutic outcomes¹⁰.

This review will be aimed at a critical evaluation of radiology-guided drug delivery systems with a specific focus on toxicology, safety and clinical use. The review has been organized such that it initially defines the principles and imaging modalities on which these systems are based, and then a discussion is made regarding platforms of delivery and activation mechanisms. Later paragraphs deal with toxicology issues, preclinical and translational issues, and the recent clinical examples, and the final paragraph will discuss future outlooks on the role of radiology-guided drug delivery in contemporary medicine.

2. Principles of Radiology-Guided Drug Delivery

Radiology-guided drug delivery is based on the combination of therapeutic systems and medical imaging in order to obtain the specific spatial and temporal control over drug localization, activation, and monitoring. In contrast to traditional delivery methods, which are based mostly on passive biodistribution, radiology-guided methods employ active utilization of the imaging feedback to guide therapeutic agents to particular anatomical or pathological locations. The key to this idea is the creation of image-visible or image-responding carriers that can be monitored and, in certain instances, activated by external or endogenous stimuli so that therapy can be dynamically altered in response to imaging results¹¹.

One of the fundamental rules of radiology-guided drug delivery is the localization of anatomical and functional anatomy and functionality. High-resolution has been found to be important in the provision of critical information on the morphology of tissues, the vascularity, and the dynamic physiological behaviour, which has a direct impact on delivery efficiency. Higher-order imaging technologies that allow thorough structural and functional imaging, e.g. of intricate cardiac chambers, exemplify the importance of achieving high precision in anatomical delineation and motion measurement in order to render targeted intervention and prevent unwanted side effects¹². The focus of proper localization guarantees that therapeutic agents are actually focused on the target site with less extent of dispersion to normal tissues.

Besides the accuracy of the anatomy, functional imaging is also important in shaping the drug delivery process by giving a clear understanding of tissue perfusion, viability and mechanical properties. The assessment of dynamics and tissue functions in the chamber by imaging indicates that it is possible to capture and quantify changes with

time to inform the timing and placement of therapeutic interventions¹³. Such functional information can be used in drug delivery, where adaptive strategies are used where drug release or activation is correlated with physiological events, which increases therapeutic efficacy.

The other key concept in radiology-guided drug delivery is the ability to control the activation of therapeutic systems. With the increase in the use of modern delivery systems, there are stimuli-responsive systems that are introduced to this system to enable drugs to be liberated in reaction to particular stimuli, including temperature, pH, mechanical power, or the presence of an external source of energy. Another example of the use of imaging-guided stimuli to activate tumour-targeted nanoparticle systems is innovative stimuli activation methods to induce targeted delivery of therapeutic nanoparticles to disease foci and avoid systemic toxicity, while ensuring high local concentration of drugs¹⁴. Close relationships are also established between physicochemical and biological processes that control localization and retention of therapeutic agents and

radiological guidance. In nm, the conceptual framework used in the derivation of radiopharmaceutical localization principles, i.e., passive diffusion, receptor-mediated localization, and metabolic trap, can be applied to image-guided drug delivery systems to determine the accumulation patterns of the system in target locations and release a signal that is detectable¹⁵. These systems are also finding their way out of their usual applications in radiopharmaceuticals into multifunctional drug carriers in which imaging, targeting and therapeutic capabilities are built into a single platform.

Altogether, the principles of radiology-guided drug delivery focus on accurate localization, functional assessment, controlled activation, and real-time monitoring. These systems allow moving away from fixed treatment paradigms and adopting dynamic and image-guided approaches to treatment by combining imaging science with novel methods of drug delivery. This integration is a basis of further developments in carrier design, safety analysis, and clinical use of it, which is discussed later. Figure 1 represents the overall workflow of the radiology-guided drug delivery.

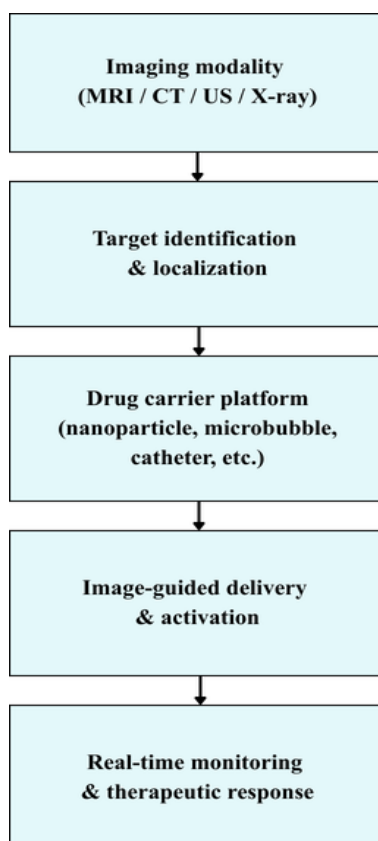


Figure 1. Conceptual workflow of radiology-guided drug delivery systems.

3. Imaging Modalities Used for Drug Guidance

The use of imaging modalities is a fundamental component of radiology-guided systems of drug delivery, allowing the visualization, guidance, and monitoring of therapeutics *in vivo*. Imaging methodology has a direct effect on delivery accuracy, depth of penetration, temporal resolution and safety profile. There is growing dependency on multimodal imaging potentials to balance these parameters in the modern drug guidance strategies and to assist in delivering accurate and flexible therapeutic interventions. The development of stimuli-responsive and image-functional nanocarriers has also added to the rationale of matching the design of drug delivery with the strengths and weaknesses of particular imaging modalities¹⁶. Table 1 presents the main imaging modalities applied to drug guidance, their main strengths and weaknesses.

Table 1. Imaging modalities for radiology-guided drug delivery

Modality	Primary strength	Key limitation
X-ray /Fluoroscopy	Real-time navigation, high spatial resolution	Ionizing radiation, poor soft-tissue contrast
CT	Precise 3D anatomical localization	Radiation exposure, limited functional data
MRI	Superior soft-tissue & functional imaging	Cost, longer acquisition time
Ultrasound / Hybrid	Real-time imaging, trigger capability	Operator dependence, penetration limits

3.1 X-Ray and Fluoroscopy-Based Guidance

X-ray and fluoroscopy-based guidance is also commonly used in interventional procedures because it has a high spatial resolution, is fast to obtain images and has a wide clinical implementation. These modalities will also be useful in the real-time navigation of catheters, needles, and implantable delivery systems. Open-source and more sophisticated navigation systems have shown the potential of fluoroscopy-guided interventions to improve accuracy and reproducibility of the procedure, particularly in the process of minimally invasive interventions that need ongoing visualization¹⁷. Nevertheless, their visualization of the soft tissue is not as good, and exposure to ionizing radiation limits their application to long-term drug distribution, requiring other methods of imaging.

3.2 Computed Tomography (CT)

The spatial resolution and anatomy of the computed tomography (CT) are superior and are therefore fit to achieve more specificity when it comes to localization of drug delivery devices and the evaluation of deep-seated targets. The use of CT-based imaging has been used successfully in drug distribution monitoring within complex anatomic regions, such as intracranial and intranasal routes of delivery, where correct anatomic definition is essential¹⁸. In spite of these benefits, CT has ionizing radiation, and it only gives limited functional information, which can limit its application in longitudinal monitoring or repeated therapeutic direction.

3.3 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) has become one of the most popular modalities of radiology-guided drug delivery since it has the highest quality of soft-tissue contrast, nonexistent ionizing radiation, and functional and molecular imaging. State-of-the-art MRI can be used to identify tissue microstructure, perfusion and physiological alterations in fine detail to aid in targeted therapy as well as real-time evaluation of treatment response. MRI-compatible and image-visible nanocarriers have increased the applications of MRI

beyond passive imaging in nanomedical applications to active guidance and monitoring of drug delivery systems¹⁹. However, operational expenses, time taken to acquire, are all viable challenges.

3.4 Ultrasound and Hybrid Imaging Systems

Drug guidance has special benefits with ultrasound and hybrid imaging systems, such as real-time images, portability, and active control of drug release. One of the most appealing image-guided delivery systems is ultrasound, since it may be used as the imaging modality, and as the external stimulus to cause the drug to be released from responsive carriers. An example of multifunctional nanostructured systems used in ultrasound-induced drug release demonstrates how therapeutic activation and imaging could be incorporated in a single system, usually coupled with other imaging/monitoring modalities to improve localization and tracking²⁰. Nonetheless, ultrasound imaging is dependent on the operator and its penetration in specific tissues is limited, which can influence reproducibility and depth targeting.

A relative analysis of these modalities underscores the fact that any drug delivery application cannot be universally found in using any single imaging modality. X-ray and CT are both very accurate in spatial resolution, and both are associated with the radiation exposure; MRI is more accurate at a higher cost and complexity in both the soft-tissue and functional imaging, whereas ultrasound is real-time guided, activated, and variable in penetration and operator-dependent. There is therefore a reduction in the use of hybrid and multimodal imaging approaches, as an attempt to take advantage of the strengths of their counterparts and reduce the weaknesses of each one. This type of integrative strategy is the focus of the future of radiology-guided drug delivery to safer, medically accurate and clinically flexible therapeutic agents. A comparative analysis of these modalities reveals that not one type of imaging is generally best in every application of drug delivery. The main operational functions of various imaging modalities in drug guidance are schematically presented in Figure 2.

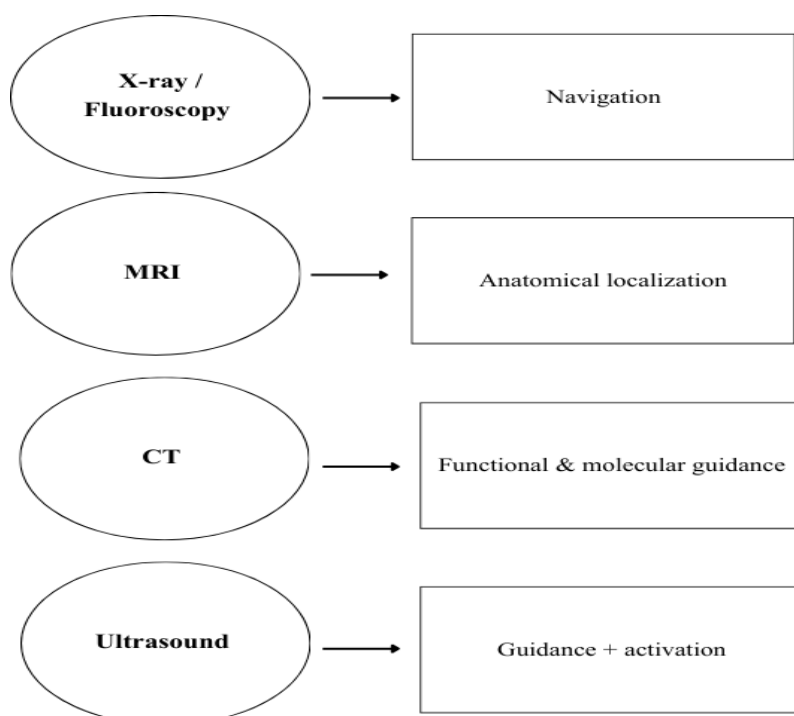


Figure 2. Imaging modalities and their primary roles in drug guidance.

4. Drug Delivery Platforms and Carrier Systems

The principle of radiology-guided drug delivery is not only based on the imaging modality, but also on the design of the delivery platform, which should be balanced in drug loading capacity, stability of circulation, accumulation at the target site, and biocompatibility. Carrier systems are also becoming dual purpose: delivering a therapeutic entity (in addition to delivering an image) in a responsive case, or through device-based deployment. Nanocarrier therapeutics and theranostic systems have also been formulated in cancer treatment, especially in anatomically complex organs

like the liver, to increase intratumoral delivery and the capability of visualizing and monitoring treatment distribution and response²¹. The four carrier classes that prevail in the modern development include nanoscale carriers (nanoparticles, liposomes, and micelles), ultrasound-responsive systems (such as microbubbles), device-enabled delivery systems, and stimuli-responsive or image-activable formulations. Table 2 gives a summary of primary carrier platforms employed in radiology-guided drug delivery and how they are commonly applied in tracking, targeting and controlled release.

Table 2. Major drug delivery platforms used in radiology-guided systems

Platform type	Core advantage	Typical application
Nanoparticles	Tunable size and surface, image integration	Targeted tumor delivery
Liposomes / Micelles	Drug solubilization and stability	Systemic and localized chemotherapy
Microbubbles	On-demand ultrasound-triggered release	Localized therapy with temporal control
Catheter-based systems	Direct site-specific delivery	Interventional radiology procedures
Stimuli-responsive carriers	Conditional, image-confirmed activation	Radiotherapy-enhanced drug delivery

4.1 Nanoparticles, Liposomes, and Micelles

The most studied carriers have been nanoparticles, liposomes, and micelles, because of their size that can be controlled, as well as their surface chemistry and ability to be functionalized. Nanoparticles may be designed to help increase circulation time, tumor accumulation and imaging elements to allow tracking or theranostic delivery and can address the need to deliver therapies specifically to the area of tumours in cancers that demand spatial control of therapy²¹. Liposomes provide a clinically mature, largely translational preclinical history, a platform upon which it is possible to encapsulate both hydrophilic and lipophilic drugs, as well as allow flexible surface modification to facilitate targeting. Amphiphilic block copolymers form micelles, which are specifically appropriate in solubilizing

hydrophobic agents and can be modified to be disassembled at the target tissue. Hybrid approaches involving using micelles and liposomes are actively explored in order to combine the stability and payload flexibility of liposomes with the penetration and solubilization benefits of micellar systems and enhance the delivery efficiency in heterogeneous tumor microenvironments²².

4.2 Microbubbles and Ultrasound-Responsive Carriers

Microbubbles and ultrasound-responsive carriers can go beyond passive targeting of drug delivery, providing an externally controlled, on-demand delivery method. The ultrasound-based delivery systems take advantage of acoustic cavitation, microstreaming, and temporary

membrane permeabilization to increase local drug delivery and cellular absorption. As contrast agents or therapies Microbubbles can serve as contrast agents and delivery vehicles or can be used together with nanoparticle preparations to enhance tissue penetration and delivery depths. The carrier composition, ultrasound parameters and tissue characteristics can be adjusted to the modulation of delivery efficiency, enabling an extremely localized release and restricting systemic exposure²³. Such controllability has given ultrasound-responsive platforms special appeal to the applications that need dynamic control of release timing and dose.

4.3 Implantable and Catheter-Based Delivery Systems

A further spatial level of control can be found in implantable and catheter-based delivery systems, which allow the precise placement of direct administration of a drug into or close to diseased tissue. These methods are part of the interventional radiology practice in which imaging guidance would be essential to make sure that they are correctly placed and deposited. The introduction of smart catheter technologies is also a significant move, and future generations of systems should include sensing, monitoring, and therapeutic functions that can facilitate a closed-loop control of drug delivery depending on real-time physiological signals²⁴. These platforms decrease systemic dependency on biodistribution and are particularly beneficial in lesions in which high local concentrations are necessary or where localized regional dosing is needed repeatedly.

4.4 Stimuli-Responsive and Image-Activatable Formulations

Image-activatable and stimuli-responsive formulations are a very fast-growing category of carriers that are supposed to deliver drugs on a demand basis. Such systems can be triggered by endogenous tumor properties, e.g. redox conditions or pH, or external stimuli such as heat, light, magnetic fields, or radiation. Image-activatable approaches are especially attractive within the context of radiology guidance, where image confirmation of target site delivery of the trigger or

imaging itself serves as the stimulus. An example of this method in oncology is stimuli-responsive nanoradiosensitizers, in which preparations are designed to specifically enhance radiotherapy effects in tumors and reduce those in normal tissue²⁵.

Selection of platforms in radiology-guided drug delivery is a systems-level choice that depends on the anatomy of the target, biology of the disease, imaging workflow, and safety limitations. Engineering work with nanoparticles, liposomes, and micelles allows flexible molecular-scale engineering; noninvasive, controllable release using ultrasound-responsive carriers; direct spatial control using catheter-based systems; and temporal control and selectivity with stimuli-responsive formulations. The combination of these carrier systems creates the technological backbone on which the activation approaches, toxicological assessment and clinical translation are established in other sections.

5. Radiology-Triggered and Image-Responsive Therapies

Image electroreactive and radiology-triggered therapies are a new technology which builds on radiology-guided drug delivery, where the imaging system is involved in the active execution of the therapy as opposed to localization or verification. In such strategies, radiological capability delivers physical energy that triggers or increases drug release or provides visualization that can result in adaptive medication during treatment. Equipment capability, calibration, maintenance and workflow integration are closely related to the feasibility and safety of such systems, when observed in regular clinical practice. Fluctuation of medical equipments in health care facilities has been found to directly affect the effectiveness and dependability of more intricate image-guided therapies, and this explains the significance of sound technological infrastructure to support radiology-initiated therapies²⁶. Table 3 is a summary of radiology-driven activation pathways and the imaging functions that can be used to verify and adaptively monitor. The imaging guidance, energy delivery, drug activation and real-time feedback interaction is a closed-loop as shown in Figure 3.

Table 3. Radiology-triggered activation mechanisms

Activation mechanism	Trigger source	Imaging role
Thermal	RF / focused ultrasound	Target localization, verification
Mechanical	Ultrasound cavitation	Guidance and release confirmation
Electromagnetic	RF energy	Spatial control of activation
Radiation-activated	Ionizing radiation	Dose-aligned drug release
Real-time imaging	MRI / CT / hybrid	Adaptive monitoring and control

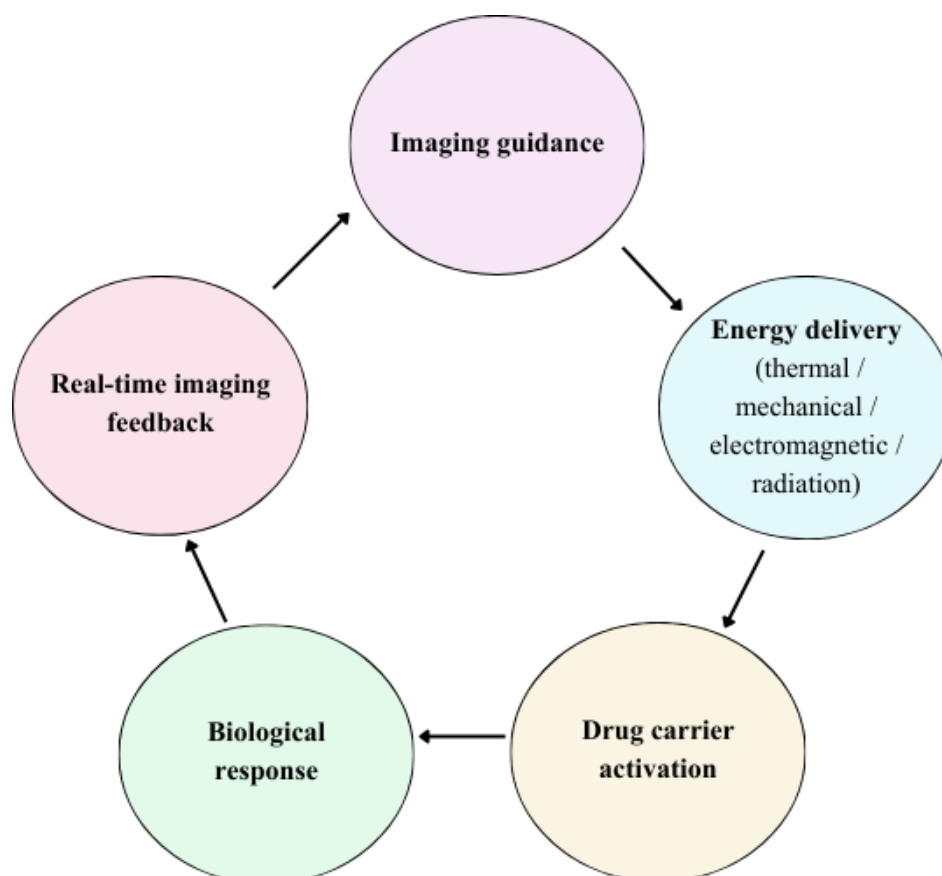


Figure 3. Closed-loop concept of radiology-triggered and image-responsive therapy

5.1 Imaging-Triggered Verification and Adaptive Control

Imaging-guided verification is at the forefront of therapies in which the intensity of treatment is paramount or where the localization of the therapy is imperative. Radiotherapy High-dose radiotherapy requires imaging confirmation of the positioning and treatment conditions of the targeted area to guarantee that the distribution of energy is consistent with the intended dose distributions. Clinical applications of triggered imaging techniques have been shown to be useful in radiotherapy of prostate cancer treatment, in which geometrical deviations can generate significant changes in tumour control and toxicity²⁷. The same principles can be directly applied to the radiology-generated drug delivery because, in many cases, therapeutic activation requires precise localization and confirmation of energy delivery in specified target volumes.

5.2 Thermal, Mechanical, and Electromagnetic Activation Mechanisms

The activation mechanisms of radiology could be categorized based on the leading physical process of drug release or increasing tissue permeability. Some thermal processes are based on the local heating to cause carrier phase transitions, enhance the fluidity of membranes, or speed up diffusion. Most frequently, mechanical mechanisms are used in ultrasound-related acoustic cavitation and microstreaming, where transient disruption of biological barriers and increased drug penetration are achieved. Radiofrequency (RF) fields

and ionizing radiation are examples of electromagnetic mechanisms that can be used to produce resistive heating, change chemical bonds, or cause responsive materials. Radiofrequency ablation is a good clinical example of electromagnetic energy-tissue interaction. The ionic agitation and resistive heating caused by the effect of alternating electrical current lead to predictable fields of coagulative necrosis. Such physical principles are becoming more applicable in the pharmaceutical delivery process since RF energy could be added to locally delivered or RF-responsive formulations to extend the therapeutic impact of ablation²⁸.

5.3 Radiation-Activated Drug Release

Radiation-activated drug delivery takes advantage of the spatial conformity of therapeutic irradiation to activate drug release selectively in irradiated regions. The recent improvements in the radiosensitive nanomaterials have allowed the creation of carriers with radiation-cleavable linkers, a responsive polymer matrix, or catalytic subunits responsive to radiation-induced chemical reactions. These types of systems enable pharmacologic release patterns to reflect radiation dose distributions, and drug action to be essentially synchronized with radiotherapy geometry, with minimal off-target exposures²⁹. Such a plan is truly a model of how imaging, energy delivery and pharmacology could be combined with a single therapeutic approach, in which radiation can be used both as a cytotoxic agent and as a spatially local agent to activate drugs.

5.4 Real-Time Imaging for Dose Control and Therapeutic Monitoring

Adaptive control in radiology-triggered treatment is based on real-time imaging that allows comparing the intended and delivered therapy continuously and building on the concept of adaptive control. Where therapeutic activation is dictated by imaging per se, even small differences in the energy deposition or position may become significant in efficacy and safety. Recent examples of real-time and volumetric imaging of radiation dose delivery deep in the liver exemplify how intra-treatment imaging can determine dose delivered to the anatomically complicated and moving organs, and go beyond past treatment planning in a dynamic way towards therapeutic control³⁰. In radiology-controlled drug delivery, these functions are needed to control a correspondence of fields of activation to target tissues. Image-responsive and radiology-activated therapies are characterized by the purposeful integration of imaging validation, energy delivery and adaptive monitoring in order to attain localized and controllable pharmacologic effects. Spatial accuracy is guaranteed by imaging-based verification, thermal and electromagnetic mechanisms can be used to control activation, and radiation-responsive platforms can adjust dose geometry to drug release. With the maturity of these systems, their clinical contribution will not only be determined by the carrier design but also the integrity and incorporation of imaging technologies into therapeutic processes²⁶.

6. Toxicological Considerations and Safety Profiles

An integrated toxicological framework that takes into account the multifunctionality of radiology-guided drug delivery systems is necessary for their safety evaluation. These platforms often create exposure scenarios that go beyond traditional pharmacology by combining therapeutic agents, engineered carriers, imaging contrast materials, and externally applied physical energy. Therefore, material behavior, imaging-related risks, and adherence to regulatory safety thresholds governing combined drug-device technologies must all be considered in toxicological assessment in addition to drug-related effects³¹.

6.1 Biodistribution, Accumulation, and Clearance Pathways

The biodistribution and clearance profile of the carrier and related imaging components are key factors that determine safety in radiology-guided delivery systems. Engineered platforms may distribute to non-target organs like the liver, spleen, kidneys, and lungs after administration, but they may also show prolonged circulation and increased accumulation at disease sites. Anticipating both therapeutic benefit and off-target toxicity requires a quantitative understanding of these processes. A potent tool for characterizing *in vivo* pharmacokinetics, radiolabeled tracing techniques allow for noninvasive, whole-body evaluation of blood circulation time, tissue uptake, and elimination pathways over long periods of time³². These methods are especially useful for long-term safety assessment in radiology-guided systems because they offer dynamic

information that is challenging to obtain through traditional sampling-based toxicology.

Surface chemistry and material composition have a significant impact on accumulation and clearance behavior. Functionalization techniques for metal- and carbon-based nanomaterials can improve targeting efficiency and imaging performance, but they may also change biodegradability and prolong tissue retention, raising the risk of cumulative or delayed toxicity. Large-animal models, like pig cancer systems, are being used more frequently to increase translational relevance because they more closely resemble human-scale anatomy, vascular transport, and organ-level clearance patterns than small-animal models³³.

6.2 Acute Versus Chronic Toxicity of Carriers and Contrast Agents

Toxicological effects associated with radiology-guided drug delivery can manifest on both acute and chronic timescales. Acute toxicity is typically observed shortly after administration and may include cytotoxic effects, inflammatory responses, hemocompatibility disturbances, or hypersensitivity reactions. Imaging contrast agents used for guidance or monitoring can contribute to such effects, particularly in patients with compromised renal function or when repeated administrations are required³³.

A more complicated safety issue is chronic toxicity, particularly for systems intended for long-term therapeutic use, extended circulation, or repeated imaging. Long-term exposure to slow-clearing carrier materials or contrast agents can cause oxidative stress, cumulative organ burden, or mild functional impairment that is difficult to identify in short-term studies. Therefore, extended-duration toxicological evaluation is crucial for multifunctional platforms, especially those that include non-biodegradable or inorganic components³⁴. Correlating long-term material retention with physiological or functional changes is made possible by imaging-based follow-up, which supports a more thorough safety assessment.

6.3 Imaging-Related Risks: Radiation Exposure, Heating, and Cavitation

In addition to material-related toxicity, radiology-guided systems introduce risks inherent to imaging and activation modalities. Ionizing radiation from computed tomography, fluoroscopy, or radiotherapy-based activation contributes to cumulative dose exposure, particularly in protocols involving frequent imaging or adaptive treatment strategies. Careful justification and optimization of imaging frequency are therefore critical to minimize long-term stochastic risk. Thermal and electromagnetic effects represent further safety considerations. Radiofrequency-based imaging and activation techniques can induce localized tissue heating, especially when conductive or energy-responsive carriers are present. Established radiofrequency exposure limits are designed to prevent harmful thermal effects and are directly applicable to radiology-guided therapeutic systems incorporating RF energy delivery^{31, 35}. Ultrasound-mediated approaches also pose mechanical risks related to cavitation and

microstreaming, which may cause vascular or tissue injury if energy parameters are not precisely controlled.

6.4 Regulatory Toxicology Requirements and Safety Thresholds

From a regulatory perspective, radiology-guided drug delivery platforms are typically classified as combination products, integrating pharmaceutical agents, medical devices, and imaging components. This classification imposes stringent toxicological requirements spanning systemic toxicity, material biocompatibility, long-term safety, and modality-specific exposure limits. Regulatory frameworks increasingly emphasize the need for toxicology data that explicitly address interactions between carriers, imaging agents, and physical activation mechanisms, rather than evaluating each component in isolation. To reduce uncertainty in human risk prediction, regulatory toxicology packages are progressively incorporating imaging-based pharmacokinetic data and anatomically realistic preclinical models. Large-animal studies, combined with quantitative imaging endpoints, are viewed as valuable tools for bridging the gap between experimental safety assessment and clinical translation^{32,35}. Adherence to defined safety thresholds and harmonized regulatory standards is therefore essential for the responsible and sustainable clinical adoption of radiology-guided drug delivery systems.

7. Preclinical Evaluation and Translational Challenges

The key to the successful transfer of radiology-guided drug delivery systems experimental systems to the clinical settings relies on an integrated approach of toxicology, imaging and therapeutic efficacy as part of extensive preclinical evaluation measures. In contrast to the traditional systems of drug delivery, these ones can be characterized by the combination of pharmacological drugs and imaging reporters, and in certain instances, activation mechanisms of devices. In turn, preclinical study needs to consider the effects and toxicity of drugs only, and not the effects and interactions of imaging and between carriers, energy delivery, and biological tissues. Theranostic approaches to MRI guidance models of colorectal cancer show that imaging can be integrated into preclinical practice to simultaneously assess the accuracy of targeting, treatment effect, and safety. During the initial stages of development, *in vitro* models are very important since it allows a quick screening of cytotoxicity, hemocompatibility, oxidative stress, and inflammatory reactions with respect to the candidate formulations. These tests are also critical in the determination of material-related toxicity and the reduction of formulation options before animal testing. Nevertheless, the *in vitro* systems do not reproduce the complexity of the entire body physiology, especially the factors of immune clearance, vascular transport, and organ-specific distribution. This is why *in vivo* studies cannot be ignored to evaluate acute and subchronic toxicity, biodistribution, and clearance on physiologically relevant conditions. Longitudinal imaging of carriers and their persistence in animal

studies enables imaging studies to have an advantage over classic endpoint-based toxicology by demonstrating the dynamic patterns of exposure with time³⁶.

Radiology-guided drug delivery platforms have a characteristic benefit in imaging-based pharmacokinetics and pharmacodynamics analysis. Based on noninvasive imaging, real-time imaging of drug distribution, target engagements, as well as biological response has been achieved, eliminating the use of repeated invasive samples. In the changing radiotheranostic environment, these data obtained through imaging have been reported to enhance the knowledge of dose response relationships and even aid in optimization of dose schedules and activation factors. This is especially essential in the case of imaging-responsive systems, where therapeutic activity is contingent on accurate spatial-temporal correspondence between imaging-responsive activation and drug delivery³⁷.

Irrespective of these benefits, it is hard to extrapolate animal experiment results to human research. Carrier behaviour and activation dynamics can be significantly affected by differences in anatomy, tissue composition, immunological responses and resolution of imaging. Small-animal models are invaluable in mechanistic studies but have a tendency to be inadequate to represent the spatial scale and procedural limitations to imaging-guided interventions in clinical settings. There is a greater focus thus given to preclinical workflows that match up imaging protocols and treatment geometries to clinical practice, enhancing translatability and minimizing uncertainty in the initial phases of clinical trials³⁷. Other obstacles to translation encompass inconsistency in imaging procedures, absence of standardized toxicological models in multifunctional carriers, and regulatory hurdles of combination products. In order to solve these problems, harmonized evaluation plans, quantitative imaging standards, and enhanced linkage between the preclinical and clinical development pipelines will be necessary to facilitate safe and effective clinical utilization of radiology-guided drug delivery systems.

8. Clinical Applications in Modern Medicine

Radiology-guided drug delivery is no longer an experimental concept but a reality with clinical applications in diverse medical fields, with oncology being the oldest and most in-depth studied field. Targeted therapy, coupled with imaging and ablative therapies have been added to cancer therapy to allow localization of the tumour at high precision, preferential placement of drugs and the ability to evaluate treatment response in real time. Such clinical uses of nuclear medicine with chemotherapy demonstrate the improvement in accuracy of delivery of the therapeutic system and minimization of systemic toxicity by use of imaging-guided delivery in personalized and experimental oncologic therapy³⁸. These methods have changed the way treatment is planned, as they have enabled the delivery of drugs, activation or monitoring of drugs into the tumor and not via systemic exposure.

Another example of the clinical effect of radiology-guided delivery in oncology is magnetic resonance imaging (MRI)-guided theranostic strategies. MRI-targeted platforms have shown that they can be used to localise therapeutic agents, track intratumoral distribution, and assess response time in the colorectal cancer environment to support adaptive treatment³⁹. Likewise, image-guided tumour ablation approaches (which can be used together with localized drug delivery) enjoy the benefit of a precise imaging response to define ablation boundaries, minimize tissue damage, and can be used to improve outcomes due to synergistic chemo-ablative effects.

Outside the oncology field, radiology-guided intervention has become especially popular in cardiovascular and neurovascular medicine, where anatomic complexity and procedural accuracy are of the utmost importance. Image-guided delivery systems assist in the delivery of therapeutics in an interventional procedure to minimize off-target exposure and enhance the safety of the procedure. The growing role of more sophisticated imaging in diseases involving the vascular and central nervous system highlights the possibilities of radiology-based methods to deal with difficult disease manifestations and anatomical differences⁴⁰. Such uses can assist in showing that imaging-guided delivery can be customized to a variety of clinical settings beyond solid tumours.

Drug delivery is of special concern to neurological conditions, especially because of the limiting effect of the blood-brain barrier (BBB). The solutions are provided by radiology-guided strategies, which allow local delivery, transient modulation of the BBB, or targeting under imaging guidance in the central nervous system. New clinical findings that are interconnecting disease processes in the body with the central nervous system further highlight the importance of treatment

modalities in neurological care, which must be fine and image-directed⁴⁰.

Radiology-guided delivery is also promising in the fields of inflammatory, infectious and musculoskeletal diseases, in which the pathology has to be properly localized to be treated. The use of imaging-guided detection of an infectious or inflammatory focus will allow treating the cause with a specific intervention, reducing the number of unnecessary exposures to antimicrobials or anti-inflammatory agents. Musculoskeletal Infection: The musculoskeletal process has been shown to provide better diagnostic and treatment stratification on biomarkers that are localized using imaging, which supports the importance of accurate localization in musculoskeletal infection treatment 41.

9. Current Limitations, Ethical, and Regulatory Issues, and Future Perspectives

In spite of the shown great potential of radiology-guided drug delivery solutions in clinical trials, the lack of their wide use is yet to be controlled by technical, ethical, regulatory, and economic issues. In technical terms, these strategies are based on high-quality imaging infrastructure, delivery platforms, and well-coordinated working processes. Reproducibility and clinical scalability can be constrained by variability in the quality of imaging, interoperability between systems and procedural standardization. Moreover, with the introduction of nanotechnology in imaging-guided therapy, material consistency, large-scale production, and long-term stability become issues that make it difficult to be implemented in the routine⁴². Table 4 is a synthesis of the translational barriers and implementation issues, in terms of the preclinical validation requirements against the ethical, regulatory, and access limitations.

Table 4. Key translational and regulatory challenges

Challenge area	Primary issue	Impact on translation
Preclinical modeling	Limited clinical realism	Uncertain human predictability
Safety & ethics	Cumulative exposure risks	Need for long-term monitoring
Regulatory pathways	Combination product complexity	Delayed approvals
Cost & access	Infrastructure and training burden	Limited clinical adoption

Patient safety is also very much associated with ethical considerations because, in most cases, radiology-guided delivery entails the cumulative exposure to drugs, contrast agents, and physical energy, including radiation or ultrasound. Informed consent is a complicated issue to ensure, especially when there is limited long-term safety data or in cases where cumulative exposure is potentially harmful. To provide ethical clinical use, there must be open communication with risks, meticulous selection of patients, and long-term follow-up to determine the possible negative effect of repeating imaging or carrying material persistence⁴².

The regulatory approval routes are an extra hurdle since most of the radiology-guided platforms are considered as combination products combining drugs, devices, and imaging agents. There is often a lack of clarity regarding what is required in such multifunctional systems,

depending on the existing regulatory frameworks, leading to uncertainty over such systems. The further integration of intelligent and adaptive systems into radiology makes regulation more complex as it brings the issue of data privacy, accountability, and sustainability in automated or semi-autonomous clinical workflows⁴³.

Moving forward, the future will be based on better standardization, more transparent regulation, and manufacturability. The development of imaging technology, nanomedicine, and intelligent systems provides the possibilities to improve precision and safety, but their effective implementation into practice will have to be linked to ethical practice, regulatory, and fair access to make radiology-guided drug delivery become an inseparable part of contemporary precision medicine.

10. Conclusion

Radiology-directed drug delivery is changing the definition of targeted therapy by linking the place where therapy is given with when and how that treatment is released through the use of imaging as a positioning and (in certain systems) an activation interface. Image guidance, in modalities, allows localization of the target site in real time, verification of the target site, and real-time adjustment of the treatment, and advanced carriers, such as the multifunctional nanoparticles, hybrid liposome-micelle systems, ultrasound-responsive platforms, smart catheters, and stimuli-activable formulations, enhance the therapeutic index by promoting exposure of the target site and reducing toxicity of the system. Meanwhile, effective clinical translation depends on demanding safety science: quantitative mapping of biodistribution/clearance, distinguishing between an acute and chronic risk, and direct consideration of modality-specific hazards (radiation dose, thermal exposure, cavitation) and product interactions. Preclinical pipelines where imaging-based PK/PD are combined with workflows that are clinically realistic can eliminate uncertainties in human scaling and enhance adoption evidence. Oncology clinical research has been most successfully propelled, but increased applicability in vascular, neurologic, and inflammatory disease conditions is indicative of increased breadth. Eventually, standardization, scalable production, open ethics, and clear regulatory avenues will be required to move forward, making radiology-guided delivery a viable component of precision medicine.

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