

Radiology-Guided Drug Delivery Systems: Current Status and Future Directions

Dr Karunakaram Sriram^{1*}, Dr Karthik Krishna Ramakrishnan², Dr Amogh Diwakara³, Dr Paarthisaan Natarajan⁴

¹ MBBS, Postgraduate, Department of Radiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu – 602105, India.

Email: drsriram.1797@gmail.com

ORCID: 0009-0001-1669-3062

² MD, Associate Professor, Department of Radio-Diagnosis, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu – 602105, India.

Email: kkdrkr@gmail.com

ORCID: 0000-0002-1690-769X

³ Postgraduate Resident, Department of Radiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu – 602105, India.

Email: amoghdiwakar3@gmail.com

⁴ Professor and Head of the Department, Department of Radiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu – 602105, India.

Email: drpaarthipan@gmail.com

ORCID: 0000-0002-8972-5969

Corresponding Author: Dr Karunakaram Sriram, drsriram.1797@gmail.com

ABSTRACT

Purpose: To define radiology-guided drug delivery systems as therapeutic control systems and critically evaluate their current clinical status, evidence base and translational requirements. **Methods:** A targeted narrative search of PubMed/MEDLINE, ClinicalTrials.gov, regulatory communications and professional-society sources was updated through 15 July 2026. Pivotal randomized trials, prospective human studies, first-in-human investigations and mechanistic studies that directly measured tissue exposure, spatial distribution, target coverage or absorbed dose were prioritized. Technical execution, direct delivery validation, clinical efficacy and generalizability were appraised separately. **Results:** Clinically established examples include transarterial drug-eluting embolics and receptor-targeted radioligand therapy. Focused ultrasound with microbubbles has advanced to multicentre early-phase evaluation for transient blood-brain barrier opening, with direct human pharmacokinetic evidence that imaging-confirmed permeability can increase tissue drug exposure. MRI-guided focused-ultrasound hyperthermia can trigger thermosensitive carriers, and real-time MRI-guided convection-enhanced delivery can reveal reflux, leakage and inadequate target coverage while treatment is still modifiable. Radiopaque embolics and CT or cone-beam CT permit three-dimensional mapping of carrier deposition, whereas PET and SPECT provide whole-body target selection, biodistribution and absorbed-dose estimation. Across platforms, the main limitations are surrogate-drug mismatch, heterogeneous tissue transport, small single-arm studies, inconsistent quantitative standards, combination-product regulation, manufacturing complexity and substantial procedural burden. A visually successful delivery field should not be interpreted as proof of clinical efficacy. **Conclusion:** The field should move from image-guided placement to closed-loop image-guided pharmacology. Future trials should prespecify spatial delivery adequacy, validate imaging surrogates against drug exposure or absorbed dose, report uncertainty and test whether acting on quantitative feedback improves safety, exposure or patient outcome.

Keywords: image-guided drug delivery, interventional radiology, focused ultrasound, magnetic resonance imaging, convection-enhanced delivery, drug-eluting beads, radiotheranostics, dosimetry, nanomedicine, precision medicine

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1. INTRODUCTION

Traditionally, drug development has focused on optimizing molecular potency, systemic pharmacokinetics and dose in the average population. However, many treatment failures are due to the fact that the active agent is not delivered to the targeted cells at the appropriate concentration for the appropriate duration and/or at an appropriate normal tissue exposure. This issue is particularly evident in poorly perfused tumors, organs shielded by biological barriers, and complex vascular territories and tissues where diffusion is constrained by pressure, fibrosis, necrosis or heterogeneous receptor expression. Radiology can overcome these limitations, since it is able to give spatial

information at the same scale at which delivery is successful or unsuccessful.

The term “image-guided drug delivery” is used in a very general sense, and includes routine needle placement, image able nanocarriers, energy-triggered release and radiopharmaceutical therapy. This kind of breadth can lead to the confusion of simple access and therapeutic control. For this review, a system is considered radiology-guided if it uses imaging to: (1) select a patient or lesion based on anatomy or a molecular biomarker; (2) plan a trajectory, vascular territory, energy field or activity prescription; (3) navigate a delivery device; (4) trigger release or transient tissue permeabilization; (5) verify spatial distribution, leakage or target coverage; (6) quantify a delivery-relevant dose;

or (7) change the ongoing or subsequent treatment. This definition includes catheter navigation, acoustic cavitation control, MRI thermometry, radiopaque carrier mapping and radionuclide dosimetry within a single definition, and excludes procedures in which MRI is used only to verify that an injection was made.

The key central clinical claim is not that imaging renders all local therapies effective. Instead, imaging can make measurable quantities of otherwise hidden delivery variables. The stakes are seen in the history of convection enhanced delivery (CED) in neuro-oncology. An interleukin-13 (IL-13) targeted toxin was not found to be superior to Gliadel wafers in a phase III trial, but post hoc analysis revealed that the placement of the catheters and distribution of the drug were often suboptimal and the biological activity of the drug was difficult to interpret [1–2]. In contrast, modern real-time MRI-guided CED studies are able to visualize a co-infused contrast agent, move cannula position, and estimate volume of distribution and detect reflux or leakage [3–5]. This is also the case for transarterial therapy, where radiopaque microspheres can be used for mapping deposition, and for radio theranostics, where molecular imaging can be used to select receptor-positive disease and post-therapy imaging can be used to estimate absorbed dose.

This review will thus be limited to the interface between imaging and delivery physics and pharmacology. It evaluates the existing platforms per modality and clinical indication, differentiates between proven benefit and technical feasibility, outlines common translational failure modes and suggests a research agenda for closed-loop image-guided pharmacology. The evidence base is dominated by oncology and this is reflected in emphasis; where the same design principles apply, non-oncologic opportunities are discussed.

2. REVIEW METHODS AND EVIDENCE APPRAISAL

A targeted narrative search of PubMed/MEDLINE and ClinicalTrials.gov was performed and complemented by official regulatory communications and practice standards and reference-list screening. The search was carried out up to 15 July 2026. The concepts covered radiology-guided or image-guided drug delivery, focused ultrasound, microbubbles, sonoporation and blood-brain barrier opening, MRI thermometry and thermosensitive carriers, MRI-guided convection-enhanced delivery, transarterial drug-eluting and radiopaque embolics, PET/SPECT guided theranostics, radioligand therapy and dosimetry, and imageable nanomedicine. Seminal earlier studies were kept if they provided a mechanism or an explanation for a later clinical result. Randomized trials, prospective human studies, first-in-human studies, multicentre trials and primary studies with a direct measurement of drug concentration, distribution, coverage or absorbed dose were given priority. Indications and requirements for implementation were verified with regulatory and professional-society sources [6–11].

This review was designed to be narrative, as no protocol was registered, no formal risk of bias instrument was used and no meta-analysis was attempted. Evidence was interpreted based on study design, sample size, developmental phase, directness of the delivery endpoint and clinical maturity. Established" means that

the technology is available in clinical practice or is adopted in the regulations in at least one major clinical setting, not necessarily best. Advanced clinical" refers to replicated or multicentre human feasibility studies with continued efficacy assessment; "early clinical" refers to small prospective or first-in-human studies; and "translational" refers to mostly preclinical development or human biodistribution studies without established thresholds for treatment selection.

2.1 Interpretive framework

The unit of appraisal was the delivery claim and not the novelty of the device. Four domains were considered separately: technical execution, direct delivery validation, clinical efficacy and generalizability. A procedure can be technically successful but not be able to provide the desired tissue exposure, and a delivery signal can be quantitatively accurate but not proven to be predictive of patient benefit. This separation was used throughout the narrative and evidence tables.

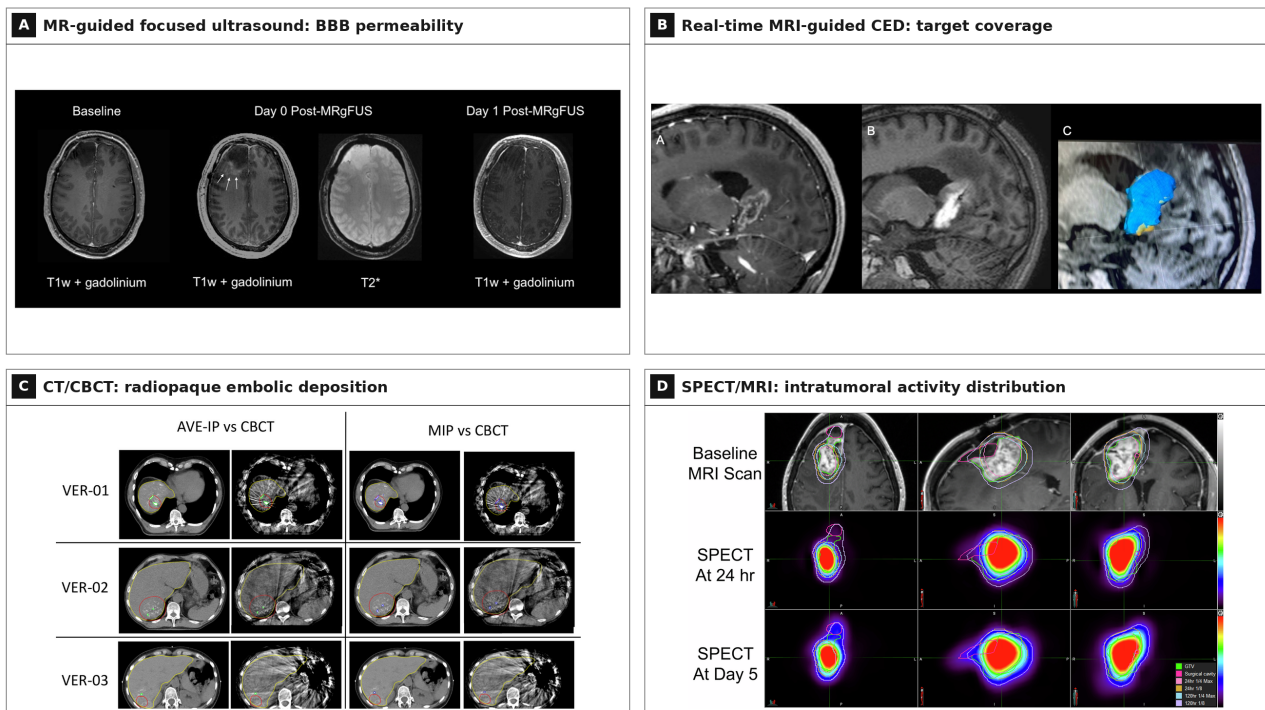
Imaging readouts were classified as device or energy localization, carrier/co-infusate distribution, pharmacokinetic exposure, or absorbed dose. The level of evidence for each class is dependent on the clinical decision to be made. For adaptive dosing, the relationship between the signal and the drug or radiation dose delivered to the device must be calibrated, an uncertainty estimate must be provided, and a prespecified action threshold must be set, in addition to the device position.

3. CONCEPTUAL FRAMEWORK: FROM GUIDANCE TO PHARMACOLOGIC CONTROL

3.1 The seven functions of imaging

There are seven interdependent functions of radiology that help to contribute to delivery. Selection is the identification of anatomical accessibility, vascular supply, receptor expression or permeability. Planning translates those data to a trajectory, arterial territory, sonication field, infusion volume or administered activity. Navigation is the process of determining the position of the device or focal energy. Triggering is the release of drug or change in tissue permeability by mechanical or thermal energy. Verification is a question of the destination of the carrier or co-infusate. The result is quantified as coverage, perfusion change, attenuation, activity concentration or absorbed dose. Adaptation is a change in treatment in response. Mature systems usually have multiple functions and tie them together with a decision rule; immature systems may only have navigation.

The distinction matters because procedural accuracy is not equivalent to pharmacologic accuracy. A catheter tip may be geometrically correct while the infusate refluxes along the tract. A bead may be visible in a tumor-feeding artery while drug penetration remains shallow. Gadolinium distribution may approximate a liposomal formulation during CED but diverge as molecular size, binding and clearance differ. PET uptake may show target expression without guaranteeing radiosensitivity. Therefore, every system requires a validated chain linking imaging signal → delivery state → tissue exposure → biological effect. Representative clinical imaging readouts are shown in Figure 1.



Representative clinical imaging readouts in radiology-guided drug delivery. (A) T1-weighted MRI before and after MR-guided focused ultrasound shows localized contrast enhancement consistent with transient blood-brain barrier opening, with no new T2*-weighted abnormality. (B) Real-time MRI during convection-enhanced delivery (CED) of liposomal irinotecan with a gadolinium co-infusate shows growth of the infusate volume and volumetric target coverage. (C) Registered average-intensity projection, maximum-intensity projection and cone-beam CT images demonstrate radiopaque drug-eluting bead deposits across liver cases. (D) MRI and serial SPECT demonstrate intratumoral distribution and retention of convection-delivered ^{186}Re -obisbameda. Panels adapted from Mainprize et al. [19], Narsinh et al. [3], Beaton et al. [55] and Brenner et al. [36], respectively, under Creative Commons Attribution 4.0 licences. Images were cropped, resized and assembled; panel headings were added. No source-image data were altered.

3.2 Modality, platform and route are separate design variables

Modality is not a delivery mechanism. Ultrasound can be used for guiding a needle, hyperthermia, stable microbubble cavitation or for monitoring flow. MRI can navigate devices, measure temperature, track a co-infusate and characterize perfusion. Fluoroscopy and CT can visualize arterial morphology, visualize radiopaque carriers and quantify 3D deposition. PET and SPECT can identify molecular targets and measure whole body biodistribution and estimate absorbed dose. The carrier or therapeutic can be free drug, liposome, microsphere, microbubble, hydrogel, implant, viral vector, antibody or radioligand. The route can be intravenous, intra-arterial, intratumoral, intraparenchymal, intracavitary or depot. All three

need to fit into the biological barrier and the clinical workflow for translational success.

3.3 Delivery endpoints should be spatial

In a typical drug trial, a dose of drug is given and its effect on the response of an organ is related. Radiology-guided delivery enables a more informative chain: prescribed dose $\rightarrow$ delivered spatial field $\rightarrow$ local exposure $\rightarrow$ voxel- or subregion-level response $\rightarrow$ patient outcome. Examples include the fraction of tumor covered by gadolinium during CED, the volume of contrast enhancement after focused-ultrasound BBB opening, bead attenuation within viable HCC, lesion-level PET uptake of an imageable liposome and tumor absorbed dose after radioligand therapy. These endpoints reveal intrapatient heterogeneity, which cannot be captured by a single blood concentration or whole-lesion response category [3–5,12–16].

Operational taxonomy of radiology-guided drug delivery systems.

Category	Operational definition	Representative systems	Primary imaging readout	Key caveat
Navigation-guided	Imaging positions the device or route; the drug itself is not visualized.	US/CT-guided intratumoral injection; fluoroscopic catheterization.	Needle/catheter location, vascular territory.	Correct position does not prove adequate distribution.
Trigger-guided	Imaging-compatible energy changes carrier release or tissue permeability.	Microbubble FUS; MR-HIFU with thermosensitive liposomes.	Acoustic emissions, temperature, BBB enhancement.	Energy field and biological response may be nonlinear.
Carrier-visible	The carrier or embolic is intrinsically or indirectly imageable.	Radiopaque DEBs; labeled liposomes; imageable hydrogels.	Attenuation, MR signal, PET activity.	Carrier location may not equal free-drug concentration.
Co-infusate-visible	A contrast surrogate is infused with the therapeutic.	Gadolinium-tracked CED.	Volume of distribution, reflux, leakage, coverage.	Surrogate–drug mismatch requires calibration.
Molecularly selected	Imaging confirms target expression before systemic targeted delivery.	Somatostatin-receptor and PSMA radioligand therapy.	Target-to-background uptake, lesion eligibility.	Uptake threshold does not capture all resistance mechanisms.
Dosimetry-guided	Post-therapy imaging estimates tissue or organ absorbed dose.	¹⁷⁷ Lu-based PRRT/RLT; ¹²⁴ I-omburtamab CED.	Time–activity curves, absorbed dose.	Methods and sampling schedules remain heterogeneous.
Adaptive closed loop	A quantitative imaging signal modifies delivery during or between cycles.	Acoustic feedback FUS; real-time MRI CED; adaptive radiopharmaceutical dosing.	Cavitation metric, coverage, thermal or absorbed dose.	Requires validated thresholds, automation and auditability.

4. CURRENT STATUS BY IMAGING MODALITY

4.1 Ultrasound: real-time guidance, cavitation and thermal release

4.1.1 Microbubble-mediated permeabilization and sonoporation

The only major imaging modality that can be used in real-time at the bedside and also as a mechanical and/or thermal effector is ultrasound. Microbubble-mediated delivery involves the use of intravenously injected gas-filled contrast agents that oscillate in the acoustic field. Stable cavitation may transiently increase the permeability of the vascular and cell-membranes, while uncontrolled inertial cavitation may increase the risk of endothelial injury, hemorrhage and tissue damage. Passive acoustic detection and feedback control are thus key enabling technologies and not optional monitoring capabilities. Experimental testing has shown that acoustic-emission controllers can be used to titrate pressure to a cavitation response, and to minimize variability [17].

The most clinically advanced application is transient BBB opening. Early human studies have been performed with either implantable or MR-guided transcranial systems to show that localized, reversible permeability change can be achieved in patients with primary or recurrent brain tumors [18–21]. A small safety study by Mainprize and colleagues demonstrated BBB opening by non-invasive MRgFUS immediately prior to chemotherapy [19]. Idhah et al. showed repeated pulsed-ultrasound opening in recurrent glioblastoma [20]. A phase 0 study using acoustic-emission control indicated that opening could be localized and monitored via the intact skull [21]. These studies were conducted to demonstrate feasibility, not survival benefit.

The most compelling direct human pharmacokinetic data were from a phase I trial of an implantable ultrasound device in recurrent glioblastoma. Sixty-eight cycles of treatment were given to 17 patients, and MRI revealed transient opening; paired tissue analysis demonstrated 3.7-fold greater paclitaxel and 5.9-fold greater carboplatin levels in sonicated brain compared to non-sonicated brain [12]. This is significant as it links permeability determined by imaging to the actual concentration of drug in the tissue. It doesn't, alone, prove clinical efficacy, and the platform is still procedure-heavy.

Multicentre translation progress was made with the BT008NA phase I/II study, which combined microbubble-enhanced transcranial FUS with adjuvant temozolomide (TMZ) in 34 patients at five sites [22]. The study demonstrated safety and feasibility in a distributed workflow, with exploratory efficacy analyses, given the open-label, single-arm nature of the trial. A technical report in 2026 reported workflow enhancements such as

a larger sonication grid and procedural efficiency, highlighting that human factors, skull geometry, imaging quality and treatment time are all part of the delivery system [23].

FUS has also provided macromolecules. MRgFUS also enhanced the delivery of radiolabeled trastuzumab to target lesions in a first-in-human study of patients with HER2-positive brain metastases [24]. Preclinical research with carmustine and other drugs indicates that the extent of benefit is related to drug characteristics, vascular architecture, and acoustic parameters and timing [25]. Therefore, BBB opening should not be considered as a generic multiplier, but should be characterized on a case-by-case basis for each drug–device combination.

4.1.2 Thermal triggering of drug release

Focused ultrasound hyperthermia can be used to induce hyperthermal response in thermosensitive liposomes within a target temperature range, and MRI thermometry can be used to map the heated area. The TARDOX phase I study showed that hyperthermia by focused ultrasound was able to release doxorubicin from lyso-thermosensitive liposomes in liver tumors and was feasible in a small group of humans [26]. The HEAT trial was a phase III trial that assessed the combination of lyso-thermosensitive liposomal doxorubicin and radiofrequency ablation in unresectable HCC, and failed to achieve its primary endpoint, but exploratory analyses indicated that heating time was a factor in the outcome [27]. The message of the lesson is not that thermal release is not effective, but that carrier kinetics, thermal dose, spatial overlap and timing need to be co-optimized and controlled in advance.

MRI-guided HIFU offers excellent thermometry and anatomical targeting, but is long, requires compatible equipment and robust motion compensation. New formulations are designed to enhance release rates, stability and extend the therapeutic window. The clinical translation is exemplified by a phase I protocol and large-animal work, and definitive therapeutic benefit is yet to be demonstrated [28–29]. To get clinically adopted, it will be necessary to demonstrate that spatially verified release is beneficial compared to simpler systemic or locoregional alternatives.

4.1.3 Non-thermal ultrasound enhancement outside the brain

In pancreatic cancer, a small clinical study used diagnostic-range ultrasound, microbubbles and gemcitabine in ten patients with inoperable disease and showed feasibility with no additional major toxicity [30]. Sample size and historical comparison are limiting factors for interpretation. There are similar strategies for the delivery of genes, RNA and immune-modulating agents, although the majority of these are still at the preclinical stage. In these applications, standardized cavitation metrics, agent-specific

dose–response studies and trials that distinguish between a true delivery effect and vascular or immune effects of ultrasound alone are needed.

4.2 MRI: soft-tissue targeting, thermometry and distribution mapping

MRI is the most information-rich modality for image guided delivery. It offers high soft-tissue contrast, multiplanar planning, diffusion and perfusion biomarkers, temperature mapping and real-time visualization of infusate (if a suitable agent is co-delivered). Some disadvantages are cost, accessibility, procedure time, motion sensitivity, and compatibility with the device and the behavior of the contrast surrogate compared to the therapeutic.

4.2.1 Real-time MRI-guided convection-enhanced delivery

CED is based on the principle of a pressure gradient to drive molecules across the interstitial space, circumventing the BBB and minimizing reliance on diffusion [31]. Initial investigations revealed that distribution could be seen with co-infused MRI tracers in large animals [32–33]. Clinical experience has since shown that reflux, leakage into cerebrospinal-fluid spaces, heterogeneous tissue resistance and poor catheter placement can be the determining factors of outcome. The PRECISE experience is a cautionary tale: a drug that is seemingly biologically unsuccessful can be made to work if the delivery field is not.

Modern platforms feature better cannula design, multiport delivery, implantation and real-time correction. Topotecan CED was shown to be feasible in recurrent high-grade glioma in a first-in-human multiport catheter study [34]. In a phase Ib study, chronic, pulsatile topotecan delivery via an implanted catheter–pump system was demonstrated, providing a pathway toward repeated local delivery, as opposed to a single infusion [35].

Narsinh et al. presented a phase I trial of liposomal irinotecan co-infused with gadolinium and real-time MRI in 18 adult patients with recurrent high-grade glioma [3]. Personalized dose and volume varied between 20–680 mg and 2–17 mL, respectively;

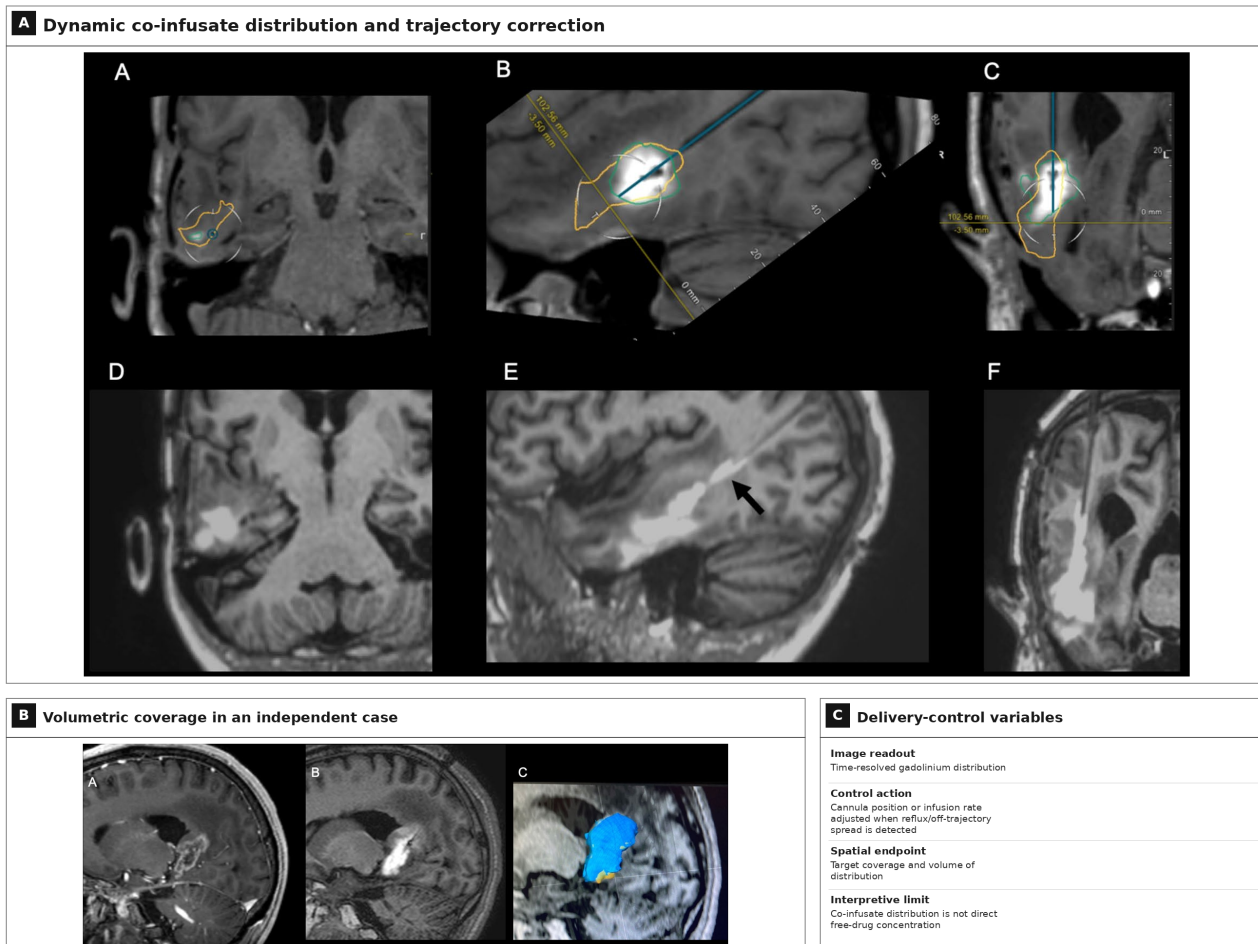
MRI helped in the correction of technical issues, in cannula positioning and in assessment of tumor coverage. The DLT was one grade 3 stroke. The study illustrates the impact of image guidance on delivery in a trial setting, but is a single-dose early-phase experience.

In pediatric diffuse intrinsic pontine glioma, PNOC009 provided nanoliposomal irinotecan with real-time imaging in six patients in 13 treatments [4]. Mean target coverage was only about one-third, and there was significant variation; neurologic adverse events occurred, and the study was terminated early due to drug-supply constraints. This is scientifically useful because it does not obscure the distribution problem. It also demonstrates why coverage should be a co-primary technical endpoint for early delivery trials.

Radiotheranostic CED completes the circuit. A phase I dose escalation study was conducted in 50 children after radiotherapy with MR-guided CED of 124I-omburtamab [5]. The maximum tolerated activity was 6 mCi; distribution, clearance and dosimetry were quantified by serial PET/MRI, and the mean lesion-to-whole-body absorbed-dose ratio was high. The single arm survival estimate is hypothesis generating and not comparative evidence. In a similar fashion, a nanoliposomal construct of rhenium-186, 186Re-obisbemada, was tested in a multicentre phase I trial with serial SPECT-based distribution assessment and dosimetry [36].

4.2.2 What MRI can and cannot quantify

Gadolinium co-infusate is appealing because it offers immediate visual feedback, but distribution cannot be taken for granted to be the same as a liposome, antibody, viral vector or free drug. Molecular size and surface charge, tissue binding and clearance varies. Thus, a solid program should include co-distribution calibration in the preclinical setting, sensitivity analysis and, if possible, paired tissue or PET validation. Report the acquisition parameters, the volume of distribution, the target coverage, leakage fraction and reflux length derived from MRI with the segmentation uncertainty. Some representative real-time control examples are illustrated in Figure 2.



Real-time MRI reveals CED as a spatially controllable process. (A) Serial T1-weighted MPRAGE images show initial and final gadolinium co-infusate distribution, the tumor outline, final target coverage and reflux along the catheter tract, which informed trajectory correction. (B) A second case shows baseline tumor, intraoperative distribution and three-dimensional segmentation.

(C) Clinically actionable variables include time-resolved distribution, cannula-position or infusion-rate adjustment, target coverage and explicit recognition of surrogate-drug mismatch. Adapted from Narsinh et al. [3] under a Creative Commons Attribution 4.0 licence; source images were cropped and resized, and panel headings and summary text were added.

4.3 Fluoroscopy, CT and cone-beam CT: vascular delivery and radiopaque carriers

4.3.1 Drug-eluting bead transarterial chemoembolization

The most advanced radiology-based drug delivery field is transarterial therapy. DruGeluting BeAdS (DEB) are beads that can be loaded with chemotherapy by means of ionic interactions and then released following selective arterial embolization, providing both vascular occlusion and prolonged local chemotherapy. Early pharmacokinetic studies in HCC revealed high intratumoral exposure to doxorubicin and lower systemic exposure [37]. Randomized PRECISION V trial compared doxorubicin-eluting beads to conventional TACE in 212 patients; the primary superiority endpoint was not clearly achieved in the overall population, but the bead platform did show superior toxicity and selected subgroup outcomes [38]. Randomized trials since then have yielded mixed results, and a Japanese trial found context-dependent results and failed to prove DEB-TACE to be superior to conventional TACE in all cases [39–40].

The accurate interpretation is that DEB-TACE is a delivery technology, and not a pharmacologic guarantee, that is reproducible and mature. Patient selection, tumor vascularity, selectivity, bead size, embolization endpoint, retreatment strategy and liver reserve are all important factors for outcome. Current HCC recommendations consider TACE as a class of locoregional therapy and suggest a multidisciplinary approach to selecting the formulation [6–7].

The use of drug eluting embolics has also been tested in colorectal liver metastases. A small randomized phase III trial of irinotecan-coated beads showed improved survival compared to FOLFIRI, although the study was small and the findings have not superseded systemic standards [41]. The take home message is that the locoregional delivery should not be judged alone, but should be compared to modern systemic therapy and combined with it.

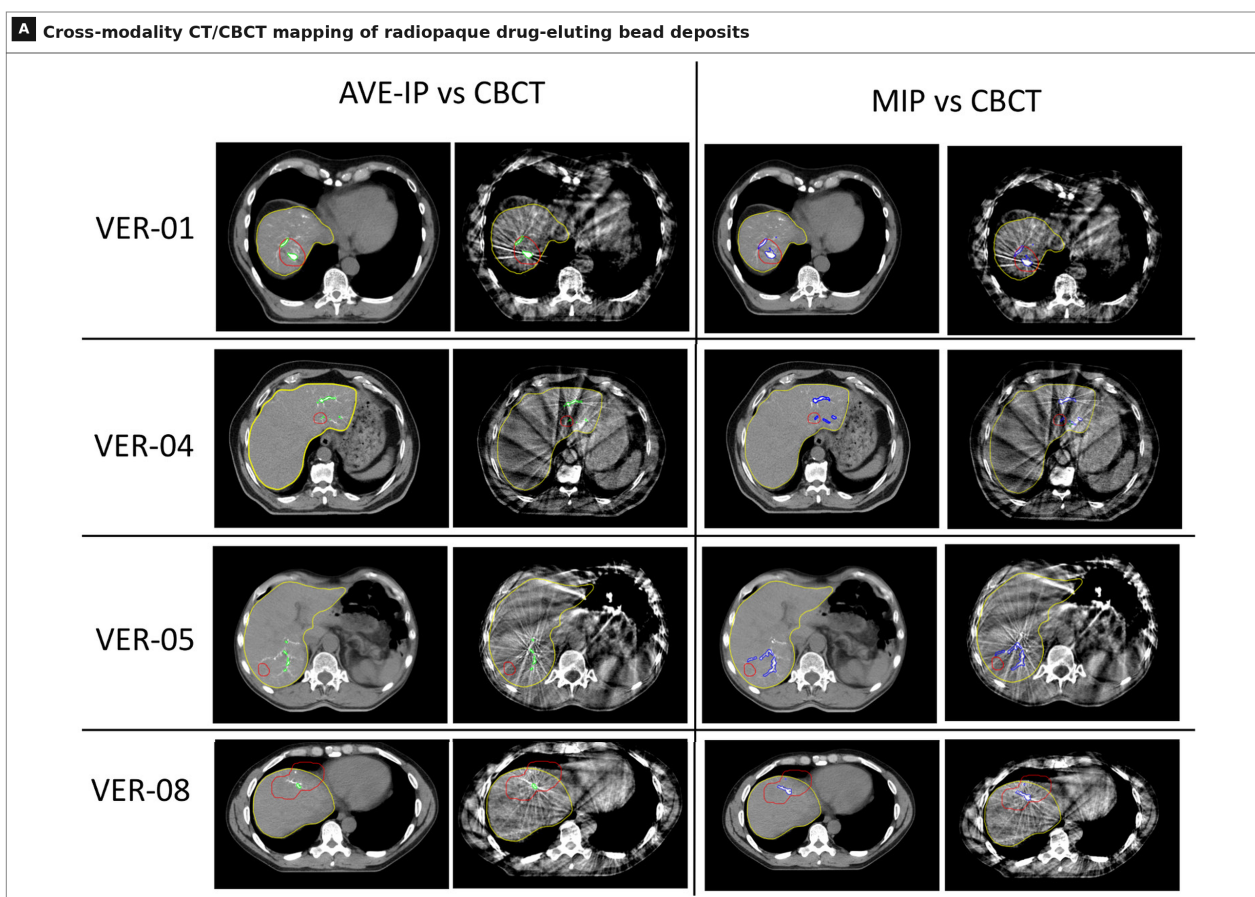
4.3.2 Radiopaque drug-eluting beads and quantitative deposition mapping

Conventional microspheres are indirectly inferred from contrast stasis and post embolization imaging. Radiopaque beads contain iodine or another x-ray visible material which can be directly seen on fluoroscopy, CT and CBCT [13,42]. This shifts the intraprocedural question from "Was the artery treated?" to "Where did the carrier accumulate? In preclinical studies, 3-D bead distribution has been correlated with local penetration of doxorubicin and tissue coverage [42]. In woodchucks with HCC, spatial prediction of drug dose from radiopaque bead deposition has been explored using CBCT-based models [43]. First-in-human studies also have demonstrated that beads can be segmented and registered between CBCT and radiotherapy-planning CT and thus can be used as spatial fiducials without necessarily being equivalent to attenuation and free-drug concentration [55].

In 50 patients with early or intermediate HCC, doxorubicin-loaded radiopaque beads were found to be safe for prospective human use with an objective response rate of 80% at 6 months, and higher rates of necrosis were found with increased bead

density [14]. The study was single arm and attenuation remains a surrogate for carrier deposition. Partial-volume effects, tissue perfusion and drug elution, imaging protocol, and bead concentration are all factors that need to be calibrated in quantitative translation. However, radiopaque embolics are one

of the most direct routes to spatial dosimetry in interventional oncology in real time using images. Direct CT/CBCT visibility and cross-modality registration of radiopaque deposits is shown in figure 3.



Quantitative CT/CBCT visualization of radiopaque drug-eluting bead deposits. Cross-modality registration of radiopaque bead deposits on average-intensity projection, maximum-intensity projection and cone-beam CT is shown in selected patients; contours distinguish target, liver and bead distributions. These images establish visibility and cross-modality registration, not a validated conversion from x-ray attenuation to free-drug concentration. Adapted from Beaton et al. [55] under a Creative Commons Attribution 4.0 licence; selected rows were cropped and assembled, and a panel heading was added.

4.3.3 Imaging burden and procedural trade-offs

Fluoroscopy and CBCT expose to both ionizing radiation and iodinated-contrast. The repetitive CBCT acquisitions can increase feedback, but can also increase procedure time. Beam hardening, motion, residual contrast and segmentation also have an impact on quantification. In the future, low dose protocols, automated vessel and tumor segmentation, standardized attenuation calibration and predeclared stopping rules that balance coverage with non-target embolization and hepatic injury should be adopted.

4.4 PET and SPECT: molecular selection, biodistribution and absorbed dose

4.4.1 Radiotheranostics as image-selected molecular delivery

PET and SPECT offer the most conceptually complete approach to image-guided drug delivery: a diagnostic ligand is used to localize target-positive disease, a therapeutic radionuclide is delivered via the same or a similar molecular vector, and post-therapy imaging is used to assess the biodistribution and absorbed dose. This is the practice now for certain neuroendocrine and prostate cancers.

NETTER-1 demonstrated that ^{177}Lu -DOTATATE plus octreotide is effective in progressive somatostatin-receptor-positive midgut NETs with a significant improvement in progression-free survival over high-dose octreotide [44]. Final

overall survival was numerically longer, but not statistically significant, in part because of crossover and subsequent treatment [45]. NETTER-2 then showed a progression-free survival advantage in the first-line treatment of higher grade, well-differentiated gastroenteropancreatic neuroendocrine tumors [46]. These trials demonstrate the feasibility of using molecular imaging as an eligibility test for systemic targeted delivery.

In metastatic castration-resistant prostate cancer, VISION demonstrated that ^{177}Lu -PSMA-617 in combination with standard of care (SOC) resulted in better imaging-based progression-free and overall survival in PSMA-positive disease [47]. TheraP showed a greater prostate-specific antigen response and favourable toxicity profile than cabazitaxel in a selected population [48] and subsequent analyses clarified the interpretation of survival [49]. PSMAfore was then extended to evidence in taxane naïve disease following androgen-receptor pathway inhibition [50–51]. Regulatory indications have been growing in line with this [8]. Alpha emitting methods like ^{225}Ac -PSMA are promising but are less standardized, and have been supported primarily by non-randomized data [52].

4.4.2 From fixed activity to individualized dosimetry

Even with the theranostic concept, many radioligand regimens have been based on fixed or body-surface adjusted activity. Patient level dosimetry studies exhibit great variation in the tumor, kidney, marrow and salivary-gland absorbed dose [16]. Optimization of dose for therapeutic radiopharmaceuticals is becoming more important in current regulatory guidance [10]. To

achieve individualized dosing, harmonized time-point sampling, reconstruction, segmentation, partial-volume correction and uncertainty propagation are needed. Personalized dosimetry is starting to be incorporated into prospective development programs from first in human dose escalation onward [53]. It also needs to show that dose adaptation results in a clinically relevant outcome, not just a number that is calculated.

The future might be a fusion of pretreatment imaging, limited post-therapy sampling and pharmacokinetic modeling to predict subsequent cycles. Digital-twin and machine-learning technologies are beginning to be used, but they should be used as models that have uncertainty, rather than as independent prescribers. Prospective validation of calibration across scanners, centers, patient populations and changing tumor biology is required.

4.4.3 Imageable nanomedicine as a companion diagnostic

The heterogeneous vascular permeability and retention is a factor that is frequently used in nanomedicine. PET labelling can be used to determine if a carrier arrives at individual lesions before or during treatment. In a first in human study, liposomal deposition in patients with metastatic HER2-positive breast cancer was seen to vary by about 35-fold between lesions and patients using ^{64}Cu -MM-302 PET [15]. Exploratory analyses indicated that higher deposition may be beneficial, but no threshold was found to be validated and the therapeutic MM-302 program was not adopted as a standard [54]. The study is still groundbreaking, as it has directly revealed delivery heterogeneity and has demonstrated how a companion-imaging agent could save or redirect nanomedicine development.

Comparison of imaging modalities for drug delivery.

Modality	Delivery roles	Quantitative readouts	Principal strengths	Principal limitations	Current maturity
Ultrasound	Real-time navigation; microbubble cavitation; hyperthermia; release or permeability triggering.	Acoustic-emission spectrum, temperature estimate, contrast perfusion, BBB enhancement.	Portable, real time, non-ionizing, can be therapeutic.	Operator/device dependence; skull and gas interfaces; cavitation and thermal safety; quantification standards.	Advanced clinical for BBB opening; early clinical for triggered release/sonoporation.
MRI	Planning; thermometry; real-time CED; perfusion/permeability; implant guidance.	Temperature, volume of distribution, coverage, reflux/leakage, perfusion and diffusion metrics.	High soft-tissue contrast; multiplanar; multiparametric; no ionizing radiation.	Cost, access, motion, device compatibility, long procedures, surrogate mismatch.	Advanced for navigation; early clinical for closed-loop CED and triggered release.
Fluoroscopy/CT/CBCT	Arterial navigation; depot placement; radiopaque carrier mapping; 3D confirmation.	Vessel territory, attenuation, carrier volume and coverage.	Fast, high spatial resolution, mature interventional workflow.	Radiation, iodinated contrast, artifacts; attenuation is not direct drug concentration.	Established for transarterial delivery; emerging quantitative deposition mapping.
PET/SPECT	Target selection; whole-body biodistribution; post-therapy imaging; dosimetry.	Standardized uptake, activity concentration, time-activity curves, absorbed dose.	Whole-body molecular specificity; strongest bridge between selection and therapy.	Radiation, multi-time-point burden, resolution, tracer availability, reconstruction variability.	Established radiotheranostics; evolving individualized dosimetry and nanocarrier imaging.

5. PLATFORM- AND INDICATION-SPECIFIC SYNTHESIS

5.1 Hepatic malignancy: the most mature interventional pharmacology

Hepatic tumors are ideal for locoregional delivery due to dual blood supply, selective arterial access and established cross sectional response imaging. TACE has evolved from conventional arterial chemotherapy to calibrated microspheres, small-bead formulations, radiopaque carriers and combinations. However, there is also a consistent pattern in the evidence: the improved delivery pharmacokinetics do not always lead to universal survival advantage. Although DEB-TACE can decrease systemic exposure to doxorubicin and standardize the release, conventional TACE may be equally or more effective in certain situations [37–40]. Thus, future studies should be compared on a whole strategy basis (patient selection, selectivity, imaging endpoints, retreatment and systemic combinations) and not on a bead chemistry alone basis.

The radiopaque beads offer a chance for intraprocedural adaptive embolization. A workflow could divide the viable tumour on pre-treatment MRI, plan the arterial territories, map the bead deposition on CBCT, and identify the under-covered viable regions and determine if the microcatheter should be redirected or if the procedure should be terminated due to the risk of non-target. The missing piece is a validated conversion of attenuation to local active-drug exposure. Paired explant studies, standardized phantoms, spectral CT and pharmacokinetic modeling are priorities.

5.2 Neuro-oncology: distribution is the therapeutic bottleneck

Neuro-oncology is the most compelling indication for delivery engineering due to the limitations of systemic and local treatment imposed by the BBB, infiltrative growth and eloquent anatomy. It

also has the most obvious instances of delivery failure. CED can circumvent the BBB, but is sensitive to the placement of the catheter, infusion pressure, tissue anisotropy, and leakage. FUS must open the BBB in a non-invasive fashion and allow for skull attenuation, as well as the heterogeneous microbubble behavior and the pharmacology of each systemic agent.

The two platforms could eventually be complementary. FUS is repeatable, non-invasive, can be used for widespread infiltrative regions or repeated systemic therapy, and CED can be used to deliver very high local concentrations or large biologics to a defined volume, but requires neurosurgical access. Imaging-defined permeability and perfusion could be used to select between hybrid strategies, or FUS could be used to enhance the margins of a core treated with CED. Survival should not be the first measure of comparative studies. First, they should set up reproducible spatial exposure, target coverage, normal-brain dose and patient burden.

There are quantitative lessons to be learned from human trials. Sonabend et al. have directly measured the concentration of the chemotherapy after the implantable ultrasound [12]. Narsinh et al. demonstrated the use of MRI to correct delivery of CED in real time [3]. Low and variable tumour coverage was found in PNOC009 [4]. 124I-omburtamab was able to combine CED with PET/MRI dosimetry [5]. All these studies point towards a common end point: technical success, distribution volume, target coverage, off-target exposure, tissue or imaging pharmacokinetics, acute neurological toxicity, patient reported burden and then efficacy.

5.3 Pancreatic and other solid tumors

Pancreatic cancer is an attractive yet challenging target for ultrasound enhanced delivery due to the presence of desmin rich stroma, hypoperfusion and high interstitial pressure. The ten-patient gemcitabine-micro bubble study showed that the procedure is feasible [30] but there is no strong evidence of

efficacy. Externally triggered liposomes might be more appropriate for accessible liver, breast, soft-tissue or bone lesions where the thermal field can be monitored and motion controlled. Although most clinical procedures use imaging for placement, hydrogels for intratumoral or peritumoral delivery could be used to enhance retention of immunotherapies, chemotherapies or gene vectors.

These tumors should be approached for platform selection beginning with the dominant barrier. A perfusion-limited tumor might be a target for vascular modulation; a pressure-limited tumor might be a target for slow infusion or matrix modification; a mobile organ might be a target for gating; a heterogeneous receptor landscape might be a target for molecular imaging and lesion-level selection. “One carrier for all solid tumors” will not work.

5.4 Neuroendocrine and prostate cancers: systemic delivery with molecular image selection

Radioligand therapy demonstrates that radiology-guided delivery need not be local or device-based. Target imaging identifies a whole-body phenotype, while post-therapy imaging reveals inter-lesional and organ-level dose. The next clinical step is to replace binary eligibility with quantitative treatment selection and adaptation. Potential strategies include minimum lesion uptake

thresholds, exclusion of discordant disease with complementary imaging, organ-risk modeling, cycle-to-cycle activity adjustment and early response biomarkers. Randomized data will be needed to show that individualized dosimetry improves survival, quality of life or toxicity relative to standardized regimens.

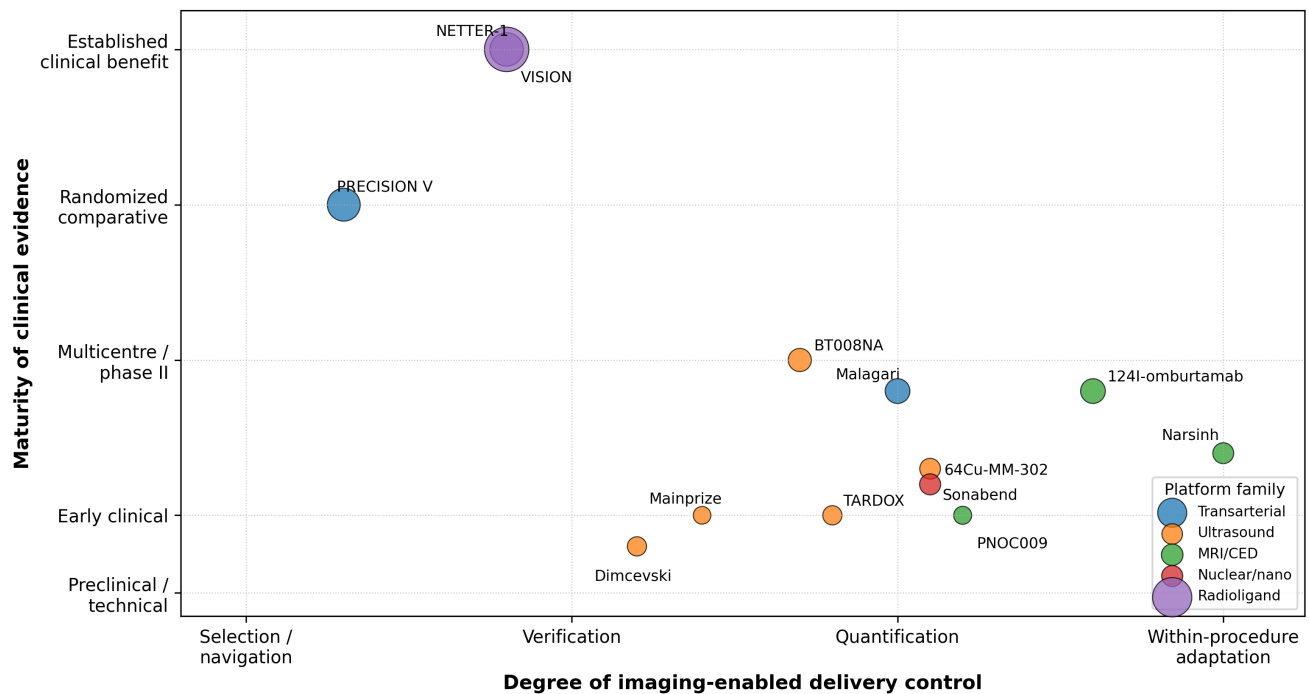
5.5 Non-oncologic frontiers

The same rules hold outside of oncology. FUS-mediated BBB opening is being studied as a method of delivery for biologics or gene therapy and for neurodegenerative disease. Ultrasound can be used in conjunction with thrombolysis, antimicrobial penetration and nucleic-acid delivery. Imageable depots can be used for the localization of anti-inflammatory or regenerative agents in joints, myocardium or ischemic tissue. But these regions are still heterogeneous and many studies show a biophysical effect, but not clinically meaningful drug delivery. Disease specific endpoints will need to be established and a clear demonstration of imaging changing treatment, not just documenting it, will be required. The evidence maturity has been separated from the level of imaging control in figure 4 to prevent the technical sophistication from being confused with clinical benefit.

Representative clinical evidence across radiology-guided delivery platforms.

Platform / study	Population and design	Imaging-control function	Key finding	Critical interpretation
PRECISION V [38]	HCC; randomized; n=212.	Fluoroscopic transarterial delivery of doxorubicin-eluting beads.	Primary superiority not established overall; toxicity and selected subgroups favored DEB.	Mature PK platform, but not universally superior to conventional TACE.
Gray et al., TARDOX [26]	Liver tumors; phase I; n=10.	Focused-ultrasound hyperthermia with image-monitored release.	Feasible targeted release of liposomal doxorubicin.	Proof of mechanism; too small for efficacy conclusions.
Dimcevski et al. [30]	Inoperable pancreatic cancer; n=10.	US + microbubbles during gemcitabine.	Feasible without major added toxicity.	Historical comparison and small sample limit efficacy inference.
Mainprize et al. [19]	Primary brain tumors; early phase.	MRgFUS BBBO before chemotherapy.	Localized reversible opening feasible.	Safety/feasibility, not outcome proof.
Sonabend et al. [12]	Recurrent GBM; phase I; n=17, 68 cycles.	Implantable US; MRI-confirmed BBBO.	3.7× paclitaxel and 5.9× carboplatin in sonicated brain.	Direct PK validation; clinical benefit unproven.
Woodworth et al., BT008NA [22]	High-grade glioma; multicentre phase I/II; n=34.	Microbubble transcranial FUS + TMZ.	Multisite safety and feasibility supported.	Single-arm; survival comparisons exploratory.
Narsinh et al. [3]	Recurrent high-grade glioma; phase I; n=18.	Real-time MRI-guided CED of liposomal irinotecan + gadolinium.	20–680 mg in 2–17 mL; one grade 3 stroke DLT; MRI improved placement/coverage.	Demonstrates adaptive technical value; single-dose early phase.
PNOC009 [4]	Newly diagnosed DIPG; n=6, 13 treatments.	Real-time imaging of CED co-infusate.	Mean target coverage about 35%; one DLT; trial stopped early.	Quantifies distribution failure; efficacy indeterminate.
124I-omburtamab CED [5]	DIPG; phase I; n=50.	MR-guided CED + serial PET/MRI dosimetry.	MTD 6 mCi; high lesion-to-whole-body dose ratio.	Theranostic CED; survival is single-arm and hypothesis-generating.
Malagari et al. [14]	Early/intermediate HCC; prospective single arm; n=50.	CT-visible doxorubicin-loaded radiopaque beads.	80% objective response at 6 months; dense deposition correlated with necrosis.	Promising spatial surrogate; no randomized comparator.
64Cu-MM-302 PET [15]	Metastatic HER2+ breast cancer; n=19.	PET of radiolabeled liposomal carrier.	Approximately 35-fold lesion-level uptake variability.	Companion diagnostic concept; no validated treatment threshold.
NETTER-1 [44]	Progressive midgut NET; phase III.	SSTR imaging-selected 177Lu-DOTATATE.	Large PFS benefit versus high-dose octreotide.	Established image-selected systemic delivery.
VISION [47]	PSMA-positive mCRPC; phase III; n=831.	PSMA PET selection; 177Lu-PSMA-617.	Improved imaging-based PFS and OS.	Established RLT; fixed activity leaves room for adaptive dosimetry.

Evidence maturity and degree of imaging control are not equivalent



Bubble area is proportional to the square root of reported study size; positions are an explicit qualitative synthesis, not effect estimates.

Evidence maturity and degree of imaging-enabled delivery control. The x-axis ranges from selection or navigation to within-procedure adaptation; the y-axis ranges from technical or early clinical evidence to established clinical benefit. Bubble area is proportional to the square root of reported study size. Positions are an explicit qualitative synthesis of representative studies in Table 3 and do not represent effect size, regulatory status in every jurisdiction or a formal evidence-grade score. Original figure created for this review.

6. SAFETY, MANUFACTURING AND IMPLEMENTATION

6.1 Platform-specific hazards

Safety assessment must treat the system as a combination of drug, carrier, device, imaging agent, energy source and workflow. FUS risks include cavitation-related hemorrhage, edema, off-target permeability, thermal injury and treatment variability caused by skull or tissue properties. CED risks include hemorrhage, infarction, infection, reflux, leakage, catheter injury and neurologic deficit. Transarterial systems add post-embolization syndrome, hepatic decompensation, ischemic biliary injury and non-target embolization. Radioligand therapy can injure marrow, kidneys, salivary glands and other receptor-expressing tissues and requires radiation-protection infrastructure. CT- and fluoroscopy-intensive workflows add radiation and iodinated contrast; MRI workflows add implant safety, heating and contrast considerations.

Early trials should prespecify both pharmacologic and delivery-system adverse events. A neurological event after CED, for example, may arise from catheter trajectory, pressure, off-target distribution or the drug itself. Attribution should be supported by spatial imaging whenever possible. Likewise, FUS studies should report acoustic emissions, microbubble dose, target volume, contrast leakage and hemorrhage-sensitive MRI rather than only clinical symptoms.

6.2 Combination-product regulation and manufacturing

Many platforms are combination products in practice even when regulatory pathways are divided. A thermosensitive liposome depends on a compatible energy device and thermometry sequence. A CED drug depends on cannula geometry, pump control, co-infusate, planning software and MRI compatibility. A radioligand depends on diagnostic imaging, radiochemistry, dosimetry and isotope supply. Changing one component can alter the benefit–risk profile of the whole system.

Manufacturing challenges include particle size and drug-loading uniformity, release kinetics, radiochemical purity, sterility, shelf life, stability after labeling, microbubble consistency and device tolerances. Multicentre trials require release criteria that are linked to delivery performance, not only conventional pharmaceutical quality. For software-guided systems, version control, cybersecurity and audit trails should be part of quality assurance.

6.3 Workflow and human factors

Procedural success depends on staffing, room availability, training and the cognitive burden of interpreting feedback under time pressure. A technically elegant system may fail if it requires prolonged MRI time, multiple transfers, specialist-only reconstruction or a complex chain of handoffs. The 2026 MRgFUS technical report illustrates how grid design and workflow refinement can materially affect treatment efficiency [23]. Human-factors engineering should therefore begin before pivotal trials and include simulation, failure-mode analysis, competency metrics and usability across high- and lower-volume centers.

Recurrent translational failure modes and mitigation strategies.

Failure mode	Mechanism	How it biases interpretation	Mitigation / recommended metric
Correct device, wrong distribution	Reflux, leakage, anisotropic tissue flow, vascular shunting.	Apparent drug failure despite inadequate exposure.	Real-time distribution imaging; coverage %, leakage volume, reflux length.
Surrogate–drug mismatch	Contrast agent, carrier and free drug have different transport/binding.	Over- or underestimation of delivered dose.	Preclinical co-distribution calibration; paired PET/tissue PK; uncertainty bounds.
Uncontrolled trigger	Variable cavitation or thermal field.	Heterogeneous release and safety events.	Acoustic feedback, MR thermometry, thermal/cavitation dose reporting.
Anatomical motion or registration error	Respiration, deformation, interval change.	Geographic miss or erroneous coverage map.	Gating, deformable registration, intraprocedural re-imaging.
Carrier visible, drug not quantified	Attenuation reflects bead concentration but not elution/penetration.	False equivalence between deposition and tissue exposure.	Calibration phantoms, pharmacokinetic models, explant validation.
Binary molecular eligibility	Single uptake threshold ignores heterogeneity and discordant disease.	Target-positive label masks resistant lesions.	Lesion-level uptake, complementary imaging, heterogeneity metrics.
Fixed activity despite variable PK	Organ/tumor absorbed doses vary widely.	Under-treatment or avoidable toxicity.	Harmonized dosimetry and prospective adaptive-dose trials.
Single-centre technical success	Expert workflow not portable.	Overestimates real-world reproducibility.	Multicentre run-in, credentialing, central QA and automation.
Efficacy-first trial design	No delivery endpoint or early stopping rule.	Negative trial is mechanistically uninterpretable.	Co-primary technical endpoint; prespecified minimum delivery adequacy.

7. CRITICAL APPRAISAL OF THE EVIDENCE

7.1 Technical success is not clinical benefit

Evidence is not consistent. Randomized phase III outcome data for radioligand therapy are available. There are many published clinical trials and randomized comparisons of transarterial embolics, with varying results. Small, single arm or phase I/2 studies are the primary support for FUS BBB opening, MRI-guided CED, radiopaque deposition mapping and imageable nanomedicine. A good review should therefore avoid a rhetorical trajectory that goes from feasibility to efficacy to standard of care.

Technical endpoints are still clinically relevant. Assuming that the tissue concentration measured directly after FUS is accurate, and that the catheter was placed correctly during CED, and that the uptake of nanoparticles was measured at the level of the lesion, can be incorrect, and lead to an expensive phase III program. What matters is whether the endpoint is well-enough validated for the decision that is being made. A surrogate can be useful for procedural adaptation even prior to validation as a survival predictor.

7.2 Distribution failure should be an analyzable endpoint

In early delivery trials, often technically unsuccessful procedures are not included in the pharmacologic interpretation or only reported as completed or not completed. This way, the mechanism is lost. The adequacy of distribution should be determined prior to the study and used as an exposure variable. A trial may have a minimum fraction of viable target covered, a maximum leakage fraction, an acceptable normal-tissue absorbed dose or a specified BBB-opening volume. Patients who fall below the threshold may be categorized in a technical-failure group, instead of being lumped in with biologically resistant disease.

7.3 Spatial heterogeneity is both problem and biomarker

Inpatient heterogeneity is typically considered as noise but can be used as a biomarker with image guided delivery. Low uptake of nanocarriers, low receptor expression, high interstitial pressure or poor arterial access might necessitate the use of a different platform. In a lesion, under covered viable rims may be a predictor of recurrence. Spatially registered biopsies, circulating biomarkers and

longitudinal imaging may be useful to differentiate inadequate exposure from intrinsic resistance.

7.4 External validity and equity

Special centers are dedicated to MRI-integrated suites, focused-ultrasound arrays, radiopharmaceutical production and dosimetry teams. Trials should assess procedure time, anesthesia, travel burden, number of visits, availability and failure rates of isotopes and drugs in routine use. Simplified imaging schedules, remote dosimetry review, standardized software and modular devices could enhance access, but should not compromise safety. Avoided ineffective cycles and reduced systemic toxicity should be considered in economic evaluation, in addition to capital cost.

7.5 Limitations of this review

This is a broad and narrative rather than systematic review. Qualitative cross-platform comparisons are due to differences in indication, therapeutic payload, imaging endpoint, development stage and comparator. Emerging 2025-2026 studies are mostly early phase and regulatory status could change from country to country. The radiological figures have been adapted and are illustrative examples of delivery readouts, but are not intended to be evidence of comparative efficacy. These restrictions further highlight the need for consistent delivery endpoints and future planned comparative studies.

8. FUTURE DIRECTIONS

8.1 Closed-loop control

The future direction is a closed loop, that is, imaging is performed, interpreted and turned into a treatment action with a documented rule. Examples of such are increasing or decreasing the acoustic pressure depending on the cavitation emissions, redirecting a catheter when a sector of the tumor is not treated in CBCT, changing the CED rate when reflux is seen, extending hyperthermia when the release volume is insufficient or changing the activity of the next radioligand after dosimetry of the tumor and organs. Closed-loop control should involve validated thresholds, real-time computation, fail-safe states and clear clinician authority.

8.2 Artificial intelligence and robotics

Automation of segmentation, vessel mapping, trajectory design, temperature forecasting, reconstruction and dose prediction can be achieved with the help of artificial intelligence. Robotics can fix needles or catheters, correct for movement and perform complex sonication patterns. The most important thing will be to

minimize variability, not to eliminate judgment. Models should express uncertainty, identify OOD samples and a full audit trail. Technical failures and diversity of anatomy should be part of training data otherwise automation will repeat the biases of expert-center data.

8.3 Patient-specific pharmacokinetic and digital-twin models

Patient-specific models can be used to incorporate anatomy, perfusion, receptor density, diffusion, carrier release and prior-cycle imaging to predict spatial exposure. Reduced-time-point imaging with physiologically based pharmacokinetic models might be used to help support adaptive activity in radiopharmaceutical therapy. Models could predict reflux and volume of distribution from tissue properties in CED. Arterial flow and bead transport models would be able to predict deposition in TACE. A credible digital twin should be calibrated in a prospective manner, be uncertainty-aware and be updated if observed imaging deviates from what is predicted.

8.4 Multimodal and hybrid systems

No single modality measures every relevant variable. Hybrid PET/MRI can link molecular target expression with soft-tissue distribution and dosimetry. CBCT plus MRI can align carrier deposition with viable tumor. Ultrasound can provide real-time triggering while MRI confirms permeability or temperature. Hybrid systems should be designed around a clinical decision, not technological maximalism; every additional modality adds cost, registration error and workflow burden.

8.5 Spatial pharmacology and response-adaptive trials

Future trials should treat the image as a pharmacologic dataset. Voxel- or subregion-level exposure maps can be registered to early diffusion, perfusion or metabolic response, later recurrence and image-localized biopsy. This enables exposure–response modeling within patients and may reduce sample size for mechanism-focused studies. Pivotal trials can then test a strategy: standard delivery versus quantitative image-guided adaptation, with clinical outcomes and toxicity as endpoints.

Recommended endpoint and reporting framework for clinical trials.

Domain	Minimum reporting set	Preferred advanced metric	Why it matters
Target definition	Segmentation method; viable vs necrotic target; registration method.	Probabilistic target map with uncertainty.	Prevents false precision in coverage calculations.
Device / energy delivery	Position, trajectory, infusion rate, pressure, acoustic or thermal parameters.	Time-resolved device–tissue state.	Separates procedural from pharmacologic failure.
Spatial distribution	Volume of distribution, target coverage, reflux/leakage, non-target deposition.	Voxel-level carrier or activity map.	Makes exposure heterogeneity analyzable.
Quantification	Calibration method, reconstruction, segmentation and partial-volume correction.	Uncertainty-propagated spatial dose.	Enables comparison across centers and cycles.
Pharmacokinetics	Systemic samples and timing; tissue concentration when feasible.	Paired image–tissue PK model.	Validates the imaging surrogate.
Safety	Drug- and device-specific adverse events with spatial attribution.	Dose–toxicity surface for organs at risk.	Improves causality and dose optimization.
Clinical outcome	Response, PFS/OS, quality of life, procedure burden.	Response conditional on delivered spatial dose.	Connects mechanism to patient benefit.
Reproducibility	Scanner/device/software version, QA, operator experience.	Multicentre credentialing performance.	Determines external validity.

9. PRIORITY RESEARCH AGENDA

A rigorous translational research program should be organized around questions that are falsifiable and decision-relevant. The

priorities below are ordered by their ability to make negative and positive trials mechanistically interpretable.

Priority research agenda for radiology-guided drug delivery.

Priority	Research question	Recommended design	Decision enabled
1. Validate the imaging surrogate	How closely does the imaging signal track carrier, free drug or absorbed dose?	Paired preclinical/human imaging, tissue sampling or orthogonal tracer studies with uncertainty analysis.	Whether the signal can guide treatment or only document it.
2. Define delivery adequacy	What minimum coverage or dose is needed for biological effect without unacceptable toxicity?	Dose-escalation or adaptive designs with prespecified spatial thresholds.	Technical success criteria and early stopping rules.
3. Demonstrate adaptability	Does acting on the signal improve delivery?	Randomize or sequentially compare feedback-enabled versus fixed delivery.	Value of closed-loop control.
4. Link spatial dose to response	Do under-dosed regions recur, and do adequately dosed regions respond?	Voxel-level longitudinal registration and spatial survival models.	Mechanistic endpoint for pivotal trials.
5. Standardize multicentre implementation	Can the workflow reproduce performance outside expert centers?	Credentialed multicentre run-in, phantom QA, central review and failure audits.	External validity and scale-up.
6. Compare complete strategies	Does the image-guided delivery strategy improve patient outcomes over contemporary care?	Randomized strategy trial including device, imaging, drug and adaptation rule.	Clinical effectiveness and cost-effectiveness.
7. Optimize equity and burden	Who cannot access or tolerate the workflow?	Prospective collection of travel, time, anesthesia, cost and demographic data.	Implementation redesign and equitable adoption.

10. CONCLUSIONS

Radiology-guided drug delivery has moved beyond image-guided access toward spatially measured treatment. Its most mature forms - drug-eluting transarterial therapy and radioligand therapy

- show that imaging can shape pharmacokinetics, patient selection and dosimetry, while also demonstrating that technical sophistication does not guarantee comparative superiority or individualized dosing. Focused ultrasound, MRI-guided CED,

radiopaque embolics and imageable nanomedicine are valuable because they expose delivery variables that were previously hidden. The decisive question is now whether acting on those measurements improves exposure, safety, quality of life or patient outcome.

Closed-loop image-guided pharmacology should be the organizing goal. Trials should define delivery adequacy before enrolment, validate imaging surrogates against carrier, free-drug or absorbed-dose measurements, report spatial exposure with uncertainty, and classify technical failure separately from biological resistance. Comparative evaluation should test the adaptive strategy - not only the device - against contemporary standards. With scalable manufacturing, quantitative quality assurance, human-factors engineering and equitable access, radiology can become not merely the route to the target but an auditable controller of therapy.

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