Published in final edited form as:

Magn Reson Imaging Clin N Am. 2015 November ; 23(4): 643–655. doi:10.1016/j.mric.2015.05.012.

Magnetic Resonance-Guided Drug Delivery

Andrew S. Mikhail, PhD^a, Ari Partanen, PhD^{a,b}, Pavel Yarmolenko, PhD^c, Aradhana M. Venkatesan, MD^d, and Bradford J. Wood, MD^{a,*}

^aCenter for Interventional Oncology, Department of Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892, USA

^bPhilips Healthcare, 3000 Minuteman Road, Andover, MA 01810, USA

^cThe Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Medical Center, 111 Michigan Avenue, Washington, DC 20010, USA

^dSection of Abdominal Imaging, Department of Diagnostic Radiology, M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030-4009, USA

Keywords

MR imaging; Drug delivery; Tumor targeting; Nanomedicine; Cancer; Thermosensitive liposome; High-intensity focused ultrasound; Imaging guidance

ADVANCED DRUG DELIVERY SYSTEMS

Targeted drug delivery, whereby therapeutic agents are transported from the site of administration specifically to diseased tissues, remains a “holy grail” of pharmaceutical research. This concept has significant potential in oncology, since side effects from chemotherapeutic drugs with narrow therapeutic windows (the range between effective and toxic doses) can limit the dose and compromise the efficacy of treatment. Recent progress in pharmaceutical nanotechnology has led to the development of a variety of advanced drug delivery systems (DDS) with the capacity to transport small-molecule drugs to tumors, resulting in reduced systemic toxicity and improved treatment outcomes.

In general, DDS-based drug formulations possess several advantages over their conventional counterparts, including (1) enhanced tumor targeting, (2) extended systemic circulation, and (3) controlled drug release. Careful design of DDS can exploit these characteristics to dramatically increase the safety margin of cytotoxic drugs with traditionally narrow therapeutic windows. Examples of DDS used for this purpose include polymeric micelles,¹ liposomes,² polymer-drug conjugates,³ and antibody-targeted therapies (Fig. 1).⁴ To date, liposomes have achieved significant success, with several formulations receiving clinical approval and many others, including temperature-sensitive liposomes (TSLs), are in clinical trials.²

*Corresponding author. bwood@nih.gov.

DDS may be “passively” targeted by exploiting features of the tumor microenvironment to enhance drug accumulation, and/or “actively” targeted by binding of DDS to cancer cells or endothelium via specific chemical affinity. Tumor accumulation via passive targeting is achieved because of the characteristically hyperporous blood vessels of neoplasms (resulting in increased extravasation of macromolecules and nanoparticles) and dysfunctional lymphatic drainage, a phenomenon referred to as the enhanced permeability and retention (EPR) effect.⁵ Active tumor targeting exploits the specific molecular affinity of bioactive ligands, such as peptides and antibodies, for cellular receptors preferentially expressed in malignant tissues to enhance tumor localization, retention, and cellular uptake.⁶

Barriers to Effective Drug Delivery

Following successful tumor targeting, stable DDS tend to be confined to perivascular tissues because of their limited penetration into the tumor interstitium.^{7–9} If the drug remains bound to or encapsulated by the carrier, concentrations deep within the interstitium and in regions of low vascular density or high interstitial pressure will be limited. Recent efforts to improve drug delivery have focused on increasing both the amount and bioavailability of drugs delivered to a tumor by incorporating external release stimuli into the drug delivery paradigm. Drug release may be triggered by endogenous stimuli such as tissue pH¹⁰ and redox reactions¹¹ associated with the micro-environment of tumors, or by application of exogenous triggers such as alternating magnetic fields,¹² heat,¹³ and light.¹⁴ Unlike endogenous stimuli, the spatiotemporal application of exogenous triggers can be controlled, providing a means for modulating drug release.

Insufficient dosing of tumors during chemotherapy resulting from poor intratumoral drug distribution and penetration is regarded as a major limitation of intravenous drug delivery. Many factors present barriers to drug delivery at the intratumoral level, including inefficient angiogenic vessels, the spatial heterogeneity of the tumor vasculature network, high cellular and stromal density, and elevated interstitial fluid pressure, among others.^{1,15–17} Indeed, numerous studies have demonstrated the limited penetration of both conventional and DDS-based chemotherapy from tumor blood vessels into the interstitium.^{8,9,18} These regions, deep within the interstitial space, are prone to transport-mediated and hypoxia-mediated drug resistance, and are a cause of tumor recurrence.¹⁷ Identifying and mitigating transport barriers by means of chemical,¹⁵ thermal, or mechanical alteration¹⁹ of the tumor micro-environment, and by enhanced guidance of drug delivery, are active areas of research.

Image-Guided Drug Delivery

In the emerging era of personalized medicine, the ability to provide optimal treatment to the “right patient at the right dose at the right time” is a central tenet. However, new tools are required to facilitate better customization of therapy based on the specific needs of individual patients. Recently, image-guided drug delivery, which leverages clinical imaging modalities for guidance of DDS, has emerged as a viable strategy for enhancement of targeted, personalized drug therapies. In this drug delivery paradigm, imaging may be used to identify target and nontarget anatomy or for screening, planning, monitoring, and postprocedural assessment of treatment outcome (Fig. 2).

MR imaging is particularly well suited for the purpose of image-guided drug delivery because of its ability to acquire images and quantitative measurements with high spatiotemporal resolution during therapy. MR imaging-guided drug delivery may facilitate or augment existing minimally invasive image-guided therapies, with the eventual goals of improving efficacy or expanding the indications beyond existing local and regional paradigms. The remainder of this article reviews the current state of MR imaging-guided drug delivery, with a focus on hyperthermia-mediated drug delivery and potential future applications.

Hyperthermia-Mediated Drug Delivery

Hyperthermia, in the context of drug delivery and thermal therapy, refers to the application of heat resulting in tissue temperatures greater than normal physiologic temperature. In general, hyperthermia can be divided into mild ($\sim 40^{\circ}$ – 45° C) and ablative ($\sim 50^{\circ}$ – 100° C) regimes in which bioeffects are governed by a time-temperature Arrhenius continuum (thermal dose). Commonly used methods for generating local hyperthermia include the use of radiofrequency,²⁰ microwaves,²¹ laser,²² or superficial hot water applicators.²³ Temperature-sensitive DDS can be used as an adjuvant to thermal ablation to reduce the potential for tumor regrowth in regions of sublethal thermal damage such as at the ablation margin.²⁴ In addition, mild hyperthermia can be used to trigger drug release²⁵ within heated tissue and may be used just before subablative or ablative temperature elevation, potentially resulting in a “drug depot” effect whereby drug is concentrated in target tissues following local vascular shutdown.^{26,27} Mild hyperthermia and ablation can also be combined to treat large or conjoined tumors, or geographically distributed tumors that might not otherwise have local or regional interventional oncology options (ie, because of size, number, or distribution).

HIGH-INTENSITY FOCUSED ULTRASOUND

High-intensity focused ultrasound (HIFU) represents a noninvasive alternative to more traditional hyperthermia applications by tightly focusing ultrasonic waves from an external transducer to generate localized temperature elevation in target tissues (Fig. 3). The use of HIFU to generate heat in target tissues is particularly advantageous, as it can be focused deep within the body and can achieve both mild and ablative hyperthermia. The interaction of propagating ultrasound waves with tissue can result in thermal and mechanical bioeffects^{28–30} that can enhance extravasation, uptake, or stimulate drug release from temperature-sensitive or pressure-sensitive DDS.³¹ Both thermal and mechanical bioeffects can also be used to enhance intracellular drug delivery and tissue permeability.³² Furthermore, HIFU-mediated bioeffects can be tuned and controlled by adjusting the device power, frequency, duty cycle, timing, and other settings.

The use of MR imaging for image guidance of HIFU therapy, referred to as MR-HIFU, provides high-resolution anatomic imaging, and the ability to monitor HIFU-mediated temperature changes and tissue displacement. To date, MR-HIFU has been primarily used for the ablation of symptomatic uterine leiomyomata.^{33,34} However, it is currently under investigation for several oncologic applications including treatment of benign breast

fibroadenomas,³⁵ malignant breast carcinoma,³⁶ and prostate cancer,³⁷ palliative treatment of painful osseous metastases,³⁸ and ablation of brain tumors.³⁹ Moreover, MR-HIFU is being investigated as a treatment for neurologic disorders (eg, epilepsy, essential tremor, neuropathic pain, and Parkinson disease),^{40–42} and as an immunomodulator to inhibit local tumor recurrence and metastases following ablation.⁴³ MR-HIFU has also been shown to improve drug delivery to the brain by modulation of the blood-brain barrier (BBB).⁴⁴

Temperature-Sensitive Liposomes

Developments in ultrasound applicators and delivery techniques and in MR imaging–based temperature monitoring and control methods^{45–48} have made MR-HIFU–mediated mild hyperthermia an intriguing modality for noninvasive hyperthermia therapies in combination with drug delivery. A particularly attractive strategy for facilitating tumor-localized drug delivery consists of applying mild hyperthermia in combination with intravenous administration of TSLs.^{49–51} When heat is applied to the tumor, circulating TSLs in transit through the tumor vasculature rapidly release the drug, resulting in high intravascular drug concentrations that promote extravasation and penetration into the tumor interstitium (Fig. 4).⁷

TSLs optimized for drug release at mild hyperthermic temperatures between 39.5° C and 41° C are known as low-temperature–sensitive liposomes (LTSLs). Various preclinical studies have demonstrated substantial reductions in tumor volume using LTSLs in combination with mild hyperthermia when compared with conventional therapy or nonthermally sensitive liposomes.^{50,52,53} Recently, an LTSL formulation containing doxorubicin underwent a phase III clinical trial for the treatment of hepatocellular carcinoma in combination with radiofrequency ablation (RFA).⁵⁴

MR-GUIDED DRUG DELIVERY

MR imaging offers several advantages over other imaging techniques, such as ultrasonography and computed tomography, which make it ideal for guidance of drug delivery. First, variation between tissue-specific MR parameters enables excellent contrast between soft tissues, and between normal and abnormal morphology/pathology, enhancing precision of the treatment plan. However, MR imaging is devoid of ionizing radiation, which is of particular importance because repeated imaging is usually necessary to monitor and guide drug delivery and to assess tumor progression. Furthermore, MR imaging can be used to obtain anatomic, functional, and metabolic information via volumetric and multiplanar imaging. Recently, MR imaging has been used in the planning, monitoring, and posttreatment assessment phases of LTSL drug delivery in combination with HIFU.⁵⁵ Fig. 5 depicts the use of MR-HIFU in combination with LTSLs.

Treatment Planning

Treatment planning for hyperthermia-mediated drug delivery can be performed using MR images displayed within a graphical user interface (GUI) that provides tools for precise delineation of the target tissue (Fig. 6). The treatment plan is directly overlaid on the anatomic images, defining, for example, lower and upper temperature thresholds at targeted

locations. The GUI provides comprehensive visualization of the therapy plan and real-time progress, allowing for intraprocedural adjustments in response to changing conditions or new information acquired during the procedure.

Planning can also involve coregistration and fusion of multiple imaging modalities that best depict the tumor margin or relevant anatomy in relation to the treatment plan. For example, ultrasonography or PET can be combined with MR imaging to perform simultaneous multimodality imaging to enhance tumor detection or margin delineation with fused therapy guidance.⁵⁶ An example of therapy planning for MR-guided drug delivery is depicted in Fig. 7.

Monitoring and Real-Time Guidance

To account for inpatient and outpatient variability in intratumoral drug accumulation and distribution, direct imaging of drug delivery or an appropriate surrogate marker may be used to guide therapy adjustments in real time. For example, MR imaging can be used to monitor heat deposition, tissue perfusion, or tissue displacement, and other bioeffects that direct and also predict drug distribution from triggered DDS. Moreover, a suitable surrogate of drug delivery, such as a contrast agent coloaded inside the DDS, can allow for a spatiotemporal estimate of drug release and intratumoral distribution.^{51,57} Whether these imaging parameters can serve as effective surrogates for drug distribution remains an open question.

MR Thermometry

Tissue temperature can be measured using MR imaging, providing important feedback for the guidance and adjustment of parameters or locations of hyperthermia treatment. Several MR parameters are temperature sensitive, including the T_1 and T_2 relaxation constants and water proton resonance frequency.⁴⁶ The proton resonance frequency shift (PRFS) method⁵⁸ has been shown to deliver the best temperature sensitivity, providing a temperature standard deviation of less than 1° C at a temporal resolution less than 1 second and a spatial resolution of roughly 2 mm.⁵⁹ In addition, the PRFS method is almost independent of tissue type and has excellent linearity of temperature dependency in nonadipose tissues.^{46,59} On the other hand, the PRFS of adipose tissue does not linearly depend on temperature. Fat suppression or spectrally selective excitation techniques can be applied to preferentially image water protons,^{60,61} allowing for accurate PRFS-based thermometry in tissues containing both fat and water protons.⁶² An example of PRFS-based temperature monitoring during MR-HIFU mediated drug delivery in an animal model is depicted in Fig. 7.

Other MR thermometry methods may be used instead of, or in addition to, PRFS-based methods to further enhance the accuracy of the temperature measurements, or perform thermometry in adipose tissues.^{46,63,64} Although tissue motion also may affect temperature measurements, exact measurements may not always be a practical requirement.

Tissue Displacement

In addition to mild hyperthermia and thermal ablation, HIFU can also be used in a pulsed mode to produce mechanical bioeffects without significant heat deposition.⁶⁵ For instance, acoustic cavitation and acoustic radiation forces may be produced that induce tissue

displacement, and can be used as stimuli for targeted drug delivery.³² Additional potential bioeffects include alterations to endothelial gaps, extravasation, interstitial pressures, membrane permeability, or even nuclear uptake and transfection. How best to optimally combine these differing mechanisms for MR-HIFU drug delivery remains speculative and of intense interest.

As certain MR imaging methods are sensitive to tissue displacement on the order of micrometers, MR imaging can be used to monitor HIFU-induced spatiotemporal pressure variations in tissue. This technique is known as MR-guided acoustic radiation force imaging (MR-ARFI).⁶⁶ One advantage of MR-ARFI is the ability to localize and characterize the HIFU focal spot in situ using relatively low energy deposition and without causing any irreversible tissue changes. Thus, it can be used as a “test shot” to ensure the accuracy of spatial targeting,⁶⁷ or adjust the targeting or calibration, to assess and improve the HIFU focusing quality,⁶⁸ and estimate the acoustic pressures and intensities within the target location.⁴⁴ This information may be useful in calibrating target or treatment location, and the amount of deposited drug or MR imaging contrast agent.

Drug Release

Few methods exist for the in vivo assessment of drug release, dosing, and distribution at the intratumoral level. However, MR contrast agents may be used as drug surrogates when encapsulated in liposomes. These imageable LTSLs (iLTSLs) can provide information regarding the location of drug release, drug coverage of the tumor, and drug concentration following hyperthermia-mediated delivery. In this approach the desired drug dose and spatial distribution are prescribed, and an image-guided applicator manipulates heat in the target region to achieve the desired drug dose coverage. This technique exploits the interactions between MR contrast agent and water that determine T1 shortening and signal enhancement to identify membrane disruption and drug/contrast release from iLTSLs.^{57,69} HIFU⁷⁰ and other heating modalities⁷¹ have been used to precisely regulate the spatiotemporal distribution of heat and, consequently, direct and adjust drug delivery. This process, whereby heat is used to selectively distribute a drug within a tumor under MR imaging guidance, is referred to as “drug dose painting.”^{57,69} Precise observation of drug distribution can help to identify undertreated areas and allow for adjustments to be made to the treatment plan, including the addition of other ablative approaches.

For mild hyperthermia-mediated drug delivery with iLTSLs, MR imaging can be used to evaluate T1-weighted signal intensity before and after iLTSL injection, and to capture contrast agent release in real time or during and after each HIFU exposure. An example of the use of this technique is depicted in Fig. 8. At present, the magnetic susceptibility effects of iLTSLs on PRFS-based MR thermometry and the theoretic risks of toxicity attributable to contrast agent dechelation⁷² with hyperthermia pose challenges for drug dose painting.⁷³ However, mild hyperthermia-induced release of LTSL-encapsulated doxorubicin without contrast is under investigation in preclinical and phase I trials.⁷⁴

Posttherapy Assessment and Optimization

Standard T1-weighted and T2-weighted MR imaging methods, with or without the use of contrast agents, can provide volumetric assessment of posttherapy tumor regression or growth.⁵⁵ Additional MR imaging methods can be used to examine posttherapy changes in tumor vascularization or tumor blood volume. For example, diffusion-weighted (DW) imaging can be used to evaluate changes in tumor diffusion and heat-induced tissue damage. Similarly, contrast-enhanced (CE) imaging can be used to locate and characterize the extent of nonperfused volumes or volumes of lower perfusion following drug delivery therapies that exploit, for example, ablative hyperthermia or the drug depot effect (Fig. 9). The thermal lesions induced by ablative hyperthermia appear as hypointense (nonenhancing) regions in T1-weighted CE imaging because of the reduced delivery of contrast agent to these nonperfused regions (see Fig. 8).^{75–78} Good correlation has been shown between histologic and CE imaging assessments of regions of thermal coagulation.^{75,76}

Dynamic contrast-enhanced MR (DCE-MR) imaging can be performed to acquire a series of MR images before, during, and after the administration of an intravascular MR contrast agent such as Gd-DTPA (gadopentetic acid). DCE-MR imaging depicts the wash-in and wash-out contrast kinetics within tumor extravascular and intravascular compartments, and provides important insight into bulk tissue properties that may be used to guide additional therapy planning.

PRECLINICAL WORK AND FUTURE CLINICAL APPLICATIONS

Significant preclinical work in recent years has been dedicated to elucidating potential clinical applications of MR-guided drug delivery, including mild hyperthermia-mediated drug delivery to solid tumors and using HIFU as a means for enabling reversible opening of the BBB to enable drug delivery to cerebral tissues.

Hyperthermia and Tumor Drug Delivery

Heat-mediated drug release from TSLs has been the subject of several recent clinical trials. A phase I dose-escalation clinical trial evaluated the safety and feasibility of doxorubicin-loaded TSLs in combination with RFA in patients with primary and metastatic liver cancer.⁷⁹ This paradigm was further examined to define the impact and indications for this combined therapy in a phase III trial with more than 700 patients.⁵⁴

More recent preclinical studies aim to determine whether MR-HIFU-mediated hyperthermia with imageable heat-sensitive liposomes may serve as an effective noninvasive means for delivering chemotherapeutic agents to solid tumors while enabling real-time monitoring and temporospatial control of drug release.^{51,80,81} Many outstanding questions remain to be addressed concerning the feasibility, efficacy, and applicability of MR-HIFU-mediated hyperthermia for tumor drug delivery, such as: the optimal means for loading a range of tumor specific chemotherapeutic agents within liposomes; whether there may be drug-specific heating algorithms to ensure maximal drug release and concentration within solid tumors; whether repeated treatments are safe and feasible in patients with cancer; and identification of the enduring systemic consequences of systemic liposomal administration.

The long-term goal may be to expand the indications for patients with locally dominant disease for whom there are currently few or no ablative treatment options. Drugs limited by narrow therapeutic windows may be reevaluated if MR-HIFU can improve tumor localization and distribution, serving to improve therapeutic efficacy while minimizing systemic toxicities. Whether MR-HIFU hyperthermia radiation sensitization may play a role in combination therapies also remains speculative.

Blood-Brain Barrier Disruption

MR-guided, pulsed HIFU (pHIFU)-mediated BBB disruption shows promise for drug delivery in the brain.^{44,82} For example, following pHIFU treatment, BBB disruption was detected in F98 glioma-bearing rats using intravenously injected Evans blue dye (EB).⁸² This study demonstrated an enhanced tumor-to-contralateral brain ratio of EB, suggesting that pHIFU exposure may increase drug delivery to brain tumors.⁸² The effect of pHIFU on microvascular disruption was studied in greater detail by Marty and colleagues,⁴⁴ using MR contrast agents of different hydrodynamic diameters. These investigators estimated the molecular size cutoff and duration of BBB opening following HIFU-mediated BBB disruption as a basis for potential optimization of nanoparticle design and delivery. Similar measurements were made by O'Reilly and colleagues⁸³ using an MR imaging contrast agent and variable sonication parameters along with the Definity microbubble contrast agent. This study showed that even very short ultrasound bursts (3 μ s) and low burst repetition rates (1–2 Hz) were capable of disrupting the BBB (Fig. 10).

Research concerning the role of pHIFU in disruption of the BBB, with or without coadministration of microbubbles, is ongoing. Continuing investigation aims to control the release of microbubbles and their associated risks (eg, unstable cavitation) when deployed in proximity to the cerebrovasculature, and to time BBB disruption in relation to drug administration for maximal concentration of drug in the central nervous system.

SUMMARY

MR imaging-guided drug delivery is a promising strategy for facilitating or augmenting targeted drug delivery to solid tumors. MR imaging may be used for screening, planning, monitoring, or postprocedural assessment of treatment outcome. MR-guided HIFU is a particularly promising technique for augmentation of drug delivery in certain patients with cancer with unmet clinical needs and without availability of other local image-guided minimally invasive treatment options because of the size, scope, or distribution of disease. However, further research is needed to clarify HIFU drug delivery mechanisms, optimize HIFU parameters and MR imaging methods, and define roles and timing in combination therapies with other ablative energies, chemoembolization, or radiation. Similarly, the effects of mechanical or hyperthermic HIFU on drug release, transit time, wash-out, and extravasation are poorly defined, and present a fertile ground for research into the bioeffects of HIFU. The benefits of MR-HIFU-mediated local drug delivery for avoidance of systemic toxicities could define a clear pathway toward routine clinical use for many patients with cancer. In addition, although speculative, MR-HIFU-mediated, noninvasive drug delivery (the “drug paintbrush”) could open a new door to a novel interdisciplinary therapy for

designated patients with cancer. MR imaging–guided drug delivery therapies are also being investigated for treatment of difficult-to-treat anatomies by modulation of the tumor microenvironment or by improved delivery of systemically administered therapies (eg, via opening of the BBB). Along with other emerging MR imaging–guided treatment strategies, this may enable customization of therapy to better account for tumor heterogeneity and circumvent common barriers to effective drug delivery.

Acknowledgments

This work was supported by the Center for Interventional Oncology in the Intramural Research Program of the National Institutes of Health (NIH). NIH and Celsion Corp. have a Cooperative Research and Development Agreement (CRADA). NIH and Philips Healthcare have a CRADA supported by NIH Grant # Z1A CL040015-06. Dr A. Partanen is a paid employee of Philips Healthcare. The content of this article does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

References

1. Mikhail AS, Allen C. Block copolymer micelles for delivery of cancer therapy: transport at the whole body, tissue and cellular levels. *J Control Release*. 2009; 138:214–23. [PubMed: 19376167]
2. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Adv Drug Deliv Rev*. 2013; 65(1):36–48. [PubMed: 23036225]
3. Kopecek J. Polymer-drug conjugates: origins, progress to date and future directions. *Adv Drug Deliv Rev*. 2013; 65(1):49–59. [PubMed: 23123294]
4. Chari RV, Miller ML, Widdison WC. Antibody-drug conjugates: an emerging concept in cancer therapy. *Angew Chem Int Ed Engl*. 2014; 53(15):3796–827. [PubMed: 24677743]
5. Maeda H. Tumor-selective delivery of macromolecular drugs via the EPR effect: background and future prospects. *Bioconjug Chem*. 2010; 21:797–802. [PubMed: 20397686]
6. Bazak R, Hourri M, El Achy S, et al. Cancer active targeting by nanoparticles: a comprehensive review of literature. *J Cancer Res Clin Oncol*. 2015; 141(5):769–84. [PubMed: 25005786]
7. Manzoor AA, Lindner LH, Landon CD, et al. Overcoming limitations in nanoparticle drug delivery: triggered, intravascular release to improve drug penetration into tumors. *Cancer Res*. 2012; 72:5566–75. [PubMed: 22952218]
8. Dreher MR, Liu W, Michelich CR, et al. Tumor vascular permeability, accumulation, and penetration of macromolecular drug carriers. *J Natl Cancer Inst*. 2006; 98:335–44. [PubMed: 16507830]
9. Yuan F, Leunig M, Huang SK, et al. Microvascular permeability and interstitial penetration of sterically stabilized (stealth) liposomes in a human tumor xenograft. *Cancer Res*. 1994; 54:3352–6. [PubMed: 8012948]
10. Gao W, Chan JM, Farokhzad OC. pH-Responsive nanoparticles for drug delivery. *Mol Pharm*. 2010; 7(6):1913–20. [PubMed: 20836539]
11. McCarley RL. Redox-responsive delivery systems. *Annu Rev Anal Chem (Palo Alto Calif)*. 2012; 5:391–411. [PubMed: 22708903]
12. Kumar CS, Mohammad F. Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. *Adv Drug Deliv Rev*. 2011; 63:789–808. [PubMed: 21447363]
13. Dicheva BM, Koning GA. Targeted thermosensitive liposomes: an attractive novel approach for increased drug delivery to solid tumors. *Expert Opin Drug Deliv*. 2014; 11(1):83–100. [PubMed: 24320104]
14. Spratt T, Bondurant B, O'Brien DF. Rapid release of liposomal contents upon photoinitiated destabilization with UV exposure. *Biochim Biophys Acta*. 2003; 1611(1–2):35–43. [PubMed: 12659943]

15. Chauhan VP, Stylianopoulos T, Boucher Y, et al. Delivery of molecular and nanoscale medicine to tumors: transport barriers and strategies. *Annu Rev Chem Biomol Eng.* 2011; 2:281–98. [PubMed: 22432620]
16. Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. *Nat Rev Clin Oncol.* 2010; 7:653–64. [PubMed: 20838415]
17. Minchinton AI, Tannock IF. Drug penetration in solid tumours. *Nat Rev Cancer.* 2006; 6:583–92. [PubMed: 16862189]
18. Mikhail AS, Eetezadi S, Ekdawi SN, et al. Image-based analysis of the size- and time-dependent penetration of polymeric micelles in multicellular tumor spheroids and tumor xenografts. *Int J Pharm.* 2014; 464:168–77. [PubMed: 24440400]
19. Lai CY, Fite BZ, Ferrara KW. Ultrasonic enhancement of drug penetration in solid tumors. *Front Oncol.* 2013; 3:204. [PubMed: 23967400]
20. Fatehi D, van der Zee J, de Bruijne M, et al. RF-power and temperature data analysis of 444 patients with primary cervical cancer: deep hyperthermia using the Sigma-60 applicator is reproducible. *Int J Hyperthermia.* 2007; 23(8):623–43. [PubMed: 18097850]
21. Juang T, Stauffer PR, Neuman DG, et al. Multilayer conformal applicator for microwave heating and brachytherapy treatment of superficial tissue disease. *Int J Hyperthermia.* 2006; 22(7):527–44. [PubMed: 17079212]
22. McNichols RJ, Kangasniemi M, Gowda A, et al. Technical developments for cerebral thermal treatment: water-cooled diffusing laser fibre tips and temperature-sensitive MRI using intersecting image planes. *Int J Hyperthermia.* 2004; 20(1):45–56. [PubMed: 14612313]
23. Boreham DR, Gasmann HC, Mitchel RE. Water bath hyperthermia is a simple therapy for psoriasis and also stimulates skin tanning in response to sunlight. *Int J Hyperthermia.* 1995; 11(6):745–54. [PubMed: 8586897]
24. Ahmed M, Moussa M, Goldberg SN. Synergy in cancer treatment between liposomal chemotherapeutics and thermal ablation. *Chem Phys Lipids.* 2012; 165:424–37. [PubMed: 22197685]
25. Ranjan A, Jacobs GC, Woods DL, et al. Image-guided drug delivery with magnetic resonance guided high intensity focused ultrasound and temperature sensitive liposomes in a rabbit Vx2 tumor model. *J Control Release.* 2012; 158:487–94. [PubMed: 22210162]
26. Gasselhuber A, Dreher MR, Partanen A, et al. Targeted drug delivery by high intensity focused ultrasound mediated hyperthermia combined with temperature-sensitive liposomes: computational modelling and preliminary in vivo validation. *Int J Hyperthermia.* 2012; 28:337–48. [PubMed: 22621735]
27. Hijnen, NM., de Smet, M., Heijman, E., et al. Hyperthermia mediated drug delivery combined with ablation improves therapeutic efficacy of MR-HIFU thermal therapy. *FUS Symposium; Bethesda (MD).* October 12–16, 2014;
28. Fry WJ, Wulff VJ, Tucker D, et al. Physical factors involved in ultrasonically induced changes in living systems: I. identification of non-temperature effects. *J Acoust Soc Am.* 1950; 22(6):867–76.
29. Hill, CR., Bamber, JC., ter Haar, GR. *Physical principles of medical ultrasonics.* 2nd. West Sussex, England: John Wiley & Sons Ltd; 2004.
30. Bailey M, Khokhlova V, Sapozhnikov O, et al. Physical mechanisms of the therapeutic effect of ultrasound (a review). *Acoust Phys.* 2003; 49(4):369–88.
31. Bibi S, Lattmann E, Mohammed AR, et al. Trigger release liposome systems: local and remote controlled delivery? *J Microencapsul.* 2012; 29(3):262–76. [PubMed: 22208705]
32. Gourevich D, Dogadkin O, Volovick A, et al. Ultrasound-mediated targeted drug delivery with a novel cyclodextrin-based drug carrier by mechanical and thermal mechanisms. *J Control Release.* 2013; 170(3):316–24. [PubMed: 23770006]
33. Tempamy CM, Stewart EA, McDannold N, et al. MR imaging-guided focused ultrasound surgery of uterine leiomyomas: a feasibility study. *Radiology.* 2003; 226(3):897–905. [PubMed: 12616023]
34. Kim YS, Keserci B, Partanen A, et al. Volumetric MR-HIFU ablation of uterine fibroids: role of treatment cell size in the improvement of energy efficiency. *Eur J Radiol.* 2012; 81(11):3652–9. [PubMed: 21959213]

35. Hynynen K, Pomeroy O, Smith DN, et al. MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study. *Radiology*. 2001; 219(1):176–85. [PubMed: 11274554]
36. Furusawa H, Namba K, Nakahara H, et al. The evolving non-surgical ablation of breast cancer: MR guided focused ultrasound (MRgFUS). *Breast Cancer*. 2007; 14(1):55–8. [PubMed: 17244995]
37. Chopra R, Colquhoun A, Burtnek M, et al. MR imaging-controlled transurethral ultrasound therapy for conformal treatment of prostate tissue: initial feasibility in humans. *Radiology*. 2012; 265(1):303–13. [PubMed: 22929332]
38. Liberman B, Gianfelice D, Inbar Y, et al. Pain palliation in patients with bone metastases using MR-guided focused ultrasound surgery: a multicenter study. *Ann Surg Oncol*. 2009; 16(1):140–6. [PubMed: 19002530]
39. McDannold N, Clement GT, Black P, et al. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery*. 2010; 66(2):323–32. [PubMed: 20087132]
40. Martin E, Jeanmonod D, Morel A, et al. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Ann Neurol*. 2009; 66(6):858–61. [PubMed: 20033983]
41. Jeanmonod D, Werner B, Morel A, et al. Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. *Neurosurg Focus*. 2012; 32(1):E1.
42. Tyler WJ, Tufail Y, Pati S. Pain: noninvasive functional neurosurgery using ultrasound. *Nat Rev Neurol*. 2010; 6(1):13–4. [PubMed: 20057495]
43. Haen SP, Pereira PL, Salih HR, et al. More than just tumor destruction: immunomodulation by thermal ablation of cancer. *Clin Dev Immunol*. 2011; 2011:160250. [PubMed: 22242035]
44. Marty B, Larrat B, Van Landeghem M, et al. Dynamic study of blood-brain barrier closure after its disruption using ultrasound: a quantitative analysis. *J Cereb Blood Flow Metab*. 2012; 32:1948–58. [PubMed: 22805875]
45. Mougenot C, Quesson B, de Senneville BD, et al. Three-dimensional spatial and temporal temperature control with MR thermometry-guided focused ultrasound (MRgHIFU). *Magn Reson Med*. 2009; 61(3):603–14. [PubMed: 19097249]
46. Denis de Senneville B, Quesson B, Moonen CT. Magnetic resonance temperature imaging. *Int J Hyperthermia*. 2005; 21(6):515–31. [PubMed: 16147437]
47. Köhler MO, Mougenot C, Quesson B, et al. Volumetric HIFU ablation under 3D guidance of rapid MRI thermometry. *Med Phys*. 2009; 36(8):3521–35.
48. Enholm JK, Köhler MO, Quesson B, et al. Improved volumetric MR-HIFU ablation by robust binary feedback control. *IEEE Trans Biomed Eng*. 2010; 57(1):103–13. [PubMed: 19846364]
49. Yatvin M, Weinstein J, Dennis W, et al. Design of liposomes for enhanced local release of drugs by hyperthermia. *Science*. 1978; 202:1290–3. [PubMed: 364652]
50. Needham D, Anyarambhatla G, Kong G. A new temperature-sensitive liposome for use with mild hyperthermia: characterization and testing in a human tumor xenograft model. *Cancer Res*. 2000; 60(5):1197–201. [PubMed: 10728674]
51. Negussie AH, Yarmolenko PS, Partanen A, et al. Formulation and characterisation of magnetic resonance imageable thermally sensitive liposomes for use with magnetic resonance-guided high intensity focused ultrasound. *Int J Hyperthermia*. 2011; 27:140–55. [PubMed: 21314334]
52. Kong G, Anyarambhatla G, Petros WP, et al. Efficacy of liposomes and hyperthermia in a human tumor xenograft model: importance of triggered drug release. *Cancer Res*. 2000; 60(24):6950–7. [PubMed: 11156395]
53. Yarmolenko PS, Zhao Y, Landon CD, et al. Comparative effects of thermosensitive doxorubicin-containing liposomes and hyperthermia in human and murine tumours. *Int J Hyperthermia*. 2010; 26:485–98. [PubMed: 20597627]
54. Celsion. Phase 3 study of ThermoDox with radiofrequency ablation (RFA) in treatment of hepatocellular carcinoma (HCC). *ClinicalTrials.gov* [Internet]. Available at: <https://clinicaltrials.gov/ct2/show/NCT00617981>. Accessed February 1, 2015

55. Staruch RM, Hynynen K, Chopra R. Hyperthermia-mediated doxorubicin release from thermosensitive liposomes using MR-HIFU: therapeutic effect in rabbit Vx2 tumours. *Int J Hyperthermia*. 2015; 31(2):118–33. [PubMed: 25582131]
56. Curiel L, Chopra R, Hynynen K. Progress in multimodality imaging: truly simultaneous ultrasound and magnetic resonance imaging. *IEEE Trans Med Imaging*. 2007; 26(12):1740–6. [PubMed: 18092742]
57. Ponce AM, Viglianti BL, Yu D, et al. Magnetic resonance imaging of temperature-sensitive liposome release: drug dose painting and antitumor effects. *J Natl Cancer Inst*. 2007; 99(1):53–63. [PubMed: 17202113]
58. Ishihara Y, Calderon A, Watanabe H, et al. A precise and fast temperature mapping using water proton chemical shift. *Magn Reson Med*. 1995; 34(6):814–23. [PubMed: 8598808]
59. Quesson B, de Zwart JA, Moonen CT. Magnetic resonance temperature imaging for guidance of thermotherapy. *J Magn Reson Imaging*. 2000; 12(4):525–33. [PubMed: 11042633]
60. Delfaut EM, Beltran J, Johnson G, et al. Fat suppression in MR imaging: techniques and pitfalls. *Radio-graphics*. 1999; 19(2):373–82.
61. Schick F, Forster J, Machann J, et al. Highly selective water and fat imaging applying multislice sequences without sensitivity to B1 field inhomogeneities. *Magn Reson Med*. 1997; 38(2):269–74. [PubMed: 9256107]
62. de Zwart JA, Vimeux FC, Delalande C, et al. Fast lipid-suppressed MR temperature mapping with echo-shifted gradient-echo imaging and spectral-spatial excitation. *Magn Reson Med*. 1999; 42(1):53–9. [PubMed: 10398950]
63. Winter, P., Lanier, M., Partanen, A., et al. MRI guided HIFU of visceral fat: effect of heating on T2 relaxation of fat. Milan (Italy): ISMRM; 2014.
64. Waspe, AC., Mougenot, C., Pichardo, S., et al. Simultaneous PRF and T1-mapping based MR thermometry for monitoring high-intensity focused ultrasound ablation of primary bone tumors. Salt Lake City (UT): ISMRM; 2013.
65. Larrat B, Pernot M, Aubry JF, et al. MR-guided transcranial brain HIFU in small animal models. *Phys Med Biol*. 2010; 55(2):365–88. [PubMed: 20019400]
66. McDannold N, Maier SE. Magnetic resonance acoustic radiation force imaging. *Med Phys*. 2008; 35(8):3748–58. [PubMed: 18777934]
67. Kaye EA, Chen J, Pauly KB. Rapid MR-ARFI method for focal spot localization during focused ultrasound therapy. *Magn Reson Med*. 2011; 65(3):738–43. [PubMed: 21337406]
68. Vyas U, Kaye E, Pauly KB. Transcranial phase aberration correction using beam simulations and MR-ARFI. *Med Phys*. 2014; 41(3):032901. [PubMed: 24593740]
69. Viglianti BL, Abraham SA, Michelich CR, et al. In vivo monitoring of tissue pharmacokinetics of liposome/drug using MRI: illustration of targeted delivery. *Magn Reson Med*. 2004; 51(6):1153–62. [PubMed: 15170835]
70. Gröll H, Langereis S. Hyperthermia-triggered drug delivery from temperature-sensitive liposomes using MRI-guided high intensity focused ultrasound. *J Control Release*. 2012; 161:317–27. [PubMed: 22565055]
71. Needham, D., Ponce, AM. Nanoscale drug delivery vehicles for solid tumors: a new paradigm for localized drug delivery using temperature sensitive liposomes. In: Group TF, , editor. *Nanotechnology for Cancer Therapy*. Boca Raton, FL: CRC Press; 2007. p. 678-719.
72. Port M, Idee JM, Medina C, et al. Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. *Biometals*. 2008; 21(4):469–90. [PubMed: 18344005]
73. Hijnen N, Elevelt A, Pikkemaat J, et al. The magnetic susceptibility effect of gadolinium-based contrast agents on PRFS-based MR thermometry during thermal interventions. *J Ther Ultrasound*. 2013; 1(1):8. [PubMed: 25516799]
74. University of Oxford. Targeted chemotherapy using focused ultrasound for liver metastases (TARDOX). 2015. Available at: <https://clinicaltrials.gov/ct2/show/NCT02181075>. Accessed February 1, 2015

75. Hazle JD, Stafford RJ, Price RE. Magnetic resonance imaging-guided focused ultrasound thermal therapy in experimental animal models: correlation of ablation volumes with pathology in rabbit muscle and VX2 tumors. *J Magn Reson Imaging*. 2002; 15(2):185–94. [PubMed: 11836775]
76. Cheng HL, Purcell CM, Bilbao JM, et al. Prediction of subtle thermal histopathological change using a novel analysis of Gd-DTPA kinetics. *J Magn Reson Imaging*. 2003; 18(5):585–98. [PubMed: 14579402]
77. Rowland IJ, Rivens I, Chen L, et al. MRI study of hepatic tumours following high intensity focused ultrasound surgery. *Br J Radiol*. 1997; 70:144–53. [PubMed: 9135440]
78. Köhler MO, Denis de Senneville B, Quesson B, et al. Spectrally selective pencil-beam navigator for motion compensation of MR-guided high-intensity focused ultrasound therapy of abdominal organs. *Magn Reson Med*. 2011; 66(1):102–11. [PubMed: 21305602]
79. Wood BJ, Poon RT, Locklin JK, et al. Phase I study of heat-deployed liposomal doxorubicin during radiofrequency ablation for hepatic malignancies. *J Vasc Interv Radiol*. 2012; 23:248–55. [PubMed: 22178041]
80. de Smet M, Heijman E, Langereis S, et al. Magnetic resonance imaging of high intensity focused ultrasound mediated drug delivery from temperature-sensitive liposomes: an in vivo proof-of-concept study. *J Control Release*. 2011; 150:102–10. [PubMed: 21059375]
81. de Smet M, Langereis S, van den Bosch S, et al. Temperature-sensitive liposomes for doxorubicin delivery under MRI guidance. *J Control Release*. 2010; 143:120–7. [PubMed: 19969035]
82. Yang FY, Lin GL, Horng SC, et al. Pulsed high-intensity focused ultrasound enhances the relative permeability of the blood-tumor barrier in a glioma-bearing rat model. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2011; 58(5):964–70. [PubMed: 21622052]
83. O'Reilly MA, Waspe AC, Ganguly M, et al. Focused-ultrasound disruption of the blood-brain barrier using closely-timed short pulses: influence of sonication parameters and injection rate. *Ultrasound Med Biol*. 2011; 37(4):587–94. [PubMed: 21376455]

KEY POINTS

- MR imaging can enable planning, monitoring, real-time control, and posttherapy assessment of tumor-targeted drug delivery.
- Use of MR imaging to guide the combination of hyperthermia and thermosensitive drug delivery systems constitutes an effective approach for enhancing drug delivery to tumors.
- MR-guided high intensity focused ultrasound (MR-HIFU) is a particularly promising technique for improving delivery of systemically administered therapies and potential modulation of the tumor microenvironment.

Fig. 1.
Examples of drug delivery systems: micelles (A), liposomes (B), polymer-drug conjugates (C), and antibody conjugates (D).

Fig. 2.
MR imaging as part of drug delivery paradigm.

Fig. 3. Schematic of high-intensity focused ultrasound producing localized, elevated temperatures deep within the body, without heating or damaging surrounding tissues.

Fig. 4.

In vivo release of doxorubicin from TSLs using intravital fluorescence microscopy in a murine sarcoma window chamber model. Endothelial cells are shown in green and doxorubicin in red. HT, hyperthermia. (*Adapted from* Li L, Ten Hagen TL, Hossann M, et al. Mild hyperthermia triggered doxorubicin release from optimized stealth thermosensitive liposomes improves intratumoral drug delivery and efficacy. *J Control Release* 2013;168:147; with permission.)

Fig. 5. MR-HIFU in combination with LTSLs. A combination of MR imaging, HIFU heating, and software-based automated temperature feedback control is used to plan, monitor, and control the treatment in real time. LTSLs are used to deliver the drug at the target location.

Fig. 6. Graphical user interface of an MR-HIFU therapy console (Sonalleve, Philips Healthcare, Vantaa, Finland), demonstrating delineation of target tissue for MR-guided, hyperthermia-mediated drug delivery. The treatment plan is overlaid on the anatomic MR images and includes definition of lower and upper temperature limits for automated temperature feedback control. The blue and green circular overlays indicate therapy targets and the currently active target, respectively.

Fig. 7.

Planning and temperature mapping for hyperthermia-mediated drug delivery. (A, C) a rabbit Vx2 tumor (hyperintense) identified (*white dashed line*) on planning MR imaging. A target (green overlay) selected for therapy is shown. (B, D) Temperature maps (color scale) overlaid on dynamic magnitude images (gray scale) during hyperthermia-mediated drug delivery. Mild hyperthermic temperatures were maintained in the target region using a temperature feedback control algorithm. A and B depict the coronal imaging plane; C and D depict the sagittal imaging plane. (Adapted from Partanen A, Yarmolenko PS, Viitala A, et al. Mild hyperthermia with magnetic resonance-guided high-intensity focused ultrasound for applications in drug delivery. *Int J Hyperthermia* 2012;28:324; with permission.)

Fig. 8.

MR signal intensity before and after iTSL injection and MR-HIFU heating. Signal intensity (A) before, and (B) after iTSL injection. (C) A temperature elevation map during heating. (D) Signal intensity after 40 minutes of heating. Contrast agent release is limited to the heated region. A, B, and D depict T1-weighted MR images. (From Partanen A. Magnetic resonance-guided high intensity focused ultrasound mediated mild hyperthermia and drug delivery. Helsinki (Finland): University of Helsinki; 2013. p. 36; with permission.)

Fig. 9.

Transurethral prostate HIFU in animal model shows (A) CE imaging of nonperfused regions, (B) DW imaging with diffusion changes in ablated regions, (C) cytokeratin-8–stained tissue with areas of nonviable tissue, and (D) real-time cumulative thermal dose estimates. (From Partanen A, Yerram NK, Trivedi H, et al. Magnetic resonance imaging (MRI)-guided transurethral ultrasound therapy of the prostate: a preclinical study with radiological and pathological correlation using customised MRI-based molds. *BJU Int* 2013;112(4):512; with permission.)

Fig. 10.

(*Left*) Contrast-enhanced T1-weighted MR image of a rat brain after HIFU-mediated BBB disruption. (*Right*) T2-weighted MR image of the same rat brain showing enhancement, indicating edema at the sonicated locations. *Arrows* indicate sonication locations. *Numbers* indicate different delays between cycles: (1) 300 μ s; (2) 600 μ s; (3) 1 s; (4) 60 μ s, (5–8) 6 μ s. (From O'Reilly MA, Waspe AC, Ganguly M, et al. Focused-ultrasound disruption of the blood-brain barrier using closely timed short pulses: influence of sonication parameters and injection rate. *Ultrasound Med Biol* 2011;37(4):590; with permission.)