

# Future perspectives for intraoperative MRI

Ferenc A. Jolesz, MD

*Division of MRI and Image Guided Therapy Program, Department of Radiology, Brigham and Women's Hospital,  
Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA*

Intraoperative MRI was introduced in 1993 [1]. Since then, it has been generally accepted as a valuable image guidance tool for neurosurgery, but it still applies relatively immature and diverse technologies; its clinical indications are not well defined, and its potential impact on everyday neurosurgical practice is not yet fully recognized. The reason for the early acceptance of intraoperative MRI is that it is not a so-called “disruptive technology,” which necessitates the total transformation of a medical specialty. It has been easy to accept intraoperative guidance by MRI because it uses the same imaging modality for localization during surgery as it does for preoperative diagnosis. It also improves the now universally used intraoperative navigation by real-time, interactive, near-real-time imaging, with frequent volumetric updates. These can compensate for the unavoidable intraoperative deformations and brain shifts. The main reason for the relatively slow proliferation of this technology is not necessarily the high cost of MRI systems but the lack of clear definition of the requirements of the various types of intraoperative MRI systems. Neither the configuration nor the field strength of the MRI systems, nor their integration with the current conventional operating room environment and with multiple therapy devices, has been determined yet. It is also unclear whether intraoperative MRI is applicable only for tumor resection control or if it is relevant for any other neurosurgical procedure.

To realize the potential benefits of intraoperative MRI, one has to understand all the possible implications of this new approach. In a fundamental way, visualization beyond the exposed surface is an unrealized dream of

surgeons who are looking at the “operational field” but de facto dealing with the “operational volume.” Although the introduction of surgical microscopes changed the scale of dimensions, it did not reveal all three dimensions. It is obvious that the introduction of MRI in the operating room has expanded the limits of the surgeon's view of the operational field from two dimensional (2D) to three dimensional (3D). Intraoperative MRI also augmented the surgeon's eye via its portrayal of a more effective tissue definition than direct visual examination. Nevertheless, 3D volumetric imaging and MRI-based contrast mechanisms have already been used for MRI-guided tumor resection by conventional navigational systems. The main reason why intraoperative MRI was introduced to neurosurgery was to make up for deformation and to avoid incorrect localization and targeting. Therefore, the main advantage of intraoperative MRI is frequent image updates for neuronavigation.

Intraoperative serial imaging accounts for intraoperative shifts, or deformations, and demonstrates a progressively updated representation of the actual anatomy. The analysis of these data may tell us in the future how frequently we have to update the images during surgery and how much morphologic information it is necessary to correct for these deformations. With these data, we can answer one of the fundamental questions of image-guided neurosurgery, that is, whether elaborate and frequently repeated intraoperative imaging is necessary or if computer simulations supplemented by some intraoperative measurements can correct the unavoidable brain shifts.

Thus far, the greatest impact of intraoperative MRI is in glioma surgery [2,3]. The usefulness of MRI in localizing infiltrative tumor spread is obvious. Nevertheless, it is not clear that better

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E-mail address: [jolesz@bwh.harvard.edu](mailto:jolesz@bwh.harvard.edu)

localization of the MRI-visible tumor margins can result in more effective tumor removal, and if it does, whether the outcome will be better. The main issue is to get MRI diagnostic sensitivity to define exact tumor margins, which may be an unachievable goal in the case of malignant brain tumors. Nonetheless, using multiparametric MRI not only helps to define tumor margins but can be used for functional tissue characterization. Functional MRI (fMRI), diffusion MRI, diffusion tensor imaging (DTI), magnetic resonance angiography (MRA), and magnetic resonance spectroscopy (MRS) can definitely help to achieve accurate and safe tumor resections and decrease the rate of complications of brain tumor surgery. There is a well-grounded rationale for using not only anatomic but functional parameters for surgical planning, but it has not yet been established that these time-consuming imaging tasks have to be done during surgery. Nonrigid registration of preoperative-to-intraoperative images may provide a solution. This solution has to be based on correct models of brain deformation; otherwise, it cannot be used for surgical guidance.

Some of the MRI-measurable physical or physiologic parameters (eg, temperature, diffusion, perfusion, flow) are especially useful for intraprocedural monitoring of interventions like thermal ablations or endovascular procedures. These quantitative parameters should be obtained using dynamic imaging sequences, or they cannot be used for the control of energy depositions or the detection of functional responses to vascular insults. This dynamic imaging requirement imposes serious requirements for MRI hardware and software. The closed-loop control also mandates the full integration of therapy devices with MRI, which is the reason why the future development of intraoperative MRI requires advances in imaging techniques and a series of further integration steps. The hardware and software components and the imaging features of MRI have to be integrated into the operating room environment. The various surgical instruments, tools, and therapy devices have to be strongly coupled with the software and hardware components of the imaging systems. In the future, intraoperative MRI has to be a fully integrated module of a complex image-based therapy delivery system.

### **Intraoperative imaging paradigms**

Magnetic field strength and open configuration are conflicting physical features of intraoperative

MRI systems. Because of this inherent contradiction, there is a need for a trade-off between image quality and access to the patient. The various imaging paradigms and magnet-table arrangements that have been introduced into clinical practice and tested have dealt with this contradiction in different ways and have provided various compromises and solutions.

The first intraoperative magnet is a result of a compromise between field strength and access. The concept of a vertically open-configuration intraoperative midfield magnet was developed by engineers from General Electric Medical Systems (Milwaukee, Wisconsin) and by the members of Brigham and Women's Hospital Image Guided Therapy Program. The system was deployed in Boston in 1991. That prototype system, nicknamed, "double doughnut," (as a product introduced as SIGNA SP; General Electric Medical Systems) consists of two cylindric magnets to create inversely overlapping external magnetic fields between them. An open imaging volume is formed between the two magnet bores [1]. The effective field strength of the system is at 0.5 T. This unique design allows relatively unrestricted and constant access to the patient's anatomy but provides only limited flexibility in patient positioning. In this arrangement, the table is across the magnets or positioned perpendicularly, providing some flexibility to access the head. The head can be accessed by two neurosurgeons, and the operative microscope can be integrated into the system.

The patient stays constantly within the imaging volume, and images are obtained repetitively or serially. Intraoperative guidance based on optical tracking and navigation for neurosurgical procedures (biopsies and open brain surgeries) is accomplished by near-real-time interactive MRI or with serial acquisition of volumetric image updates [4,5]. For other nonneurosurgical applications at various anatomic sites, the concept of frameless stereotaxy was applied as a suitable targeting method. The navigational aspects of this system were further augmented by the integration of a complex display and visualization platform, the 3D Slicer [6,7].

The 3D Slicer was originally developed to support image-guided neurosurgery performed in magnetic resonance therapy by providing real-time reformatting of a recently acquired volumetric image in response to interactive manipulation of a sterilized probe in the operative field. Since its initial development, the 3D Slicer (Surgical Planning Lab, Boston, Massachusetts and Artificial

Intelligence Lab, Cambridge, Massachusetts) has evolved into a general purpose platform for the analysis of collections of volumetric images as well as 3D models derived from such images. The 3D Slicer was designed to stay away from the 2D slice-by-slice view of imaging data by integrating 2D and 3D image data with geometric anatomic models and additional information, such as pointers and annotation. The 3D Slicer has been used to provide visual information in the operating room to guide neurosurgical procedures. Its basic infrastructure provides for modular extension, which has been used, for example, to provide an additional duplicate “slave” image of the user interface for display on a second screen in the operating room or to display the virtual image of tracked probes inside the open magnet.

The display and visualization platform also has a general capability for ensuring the accuracy of coordinate systems and organizing the transformations between various reference frames. It provides rigid and nonrigid registration methods for multimodality fusion between preoperative image data and intraoperative image data. This system will eventually include models of specific tracked instruments, such as the Ojemann stimulator, a bipolar cautery, and a suction device. The ultimate goal of this platform is to provide standardized methods for exchanging spatial coordinates among various therapy and imaging systems and to capture spatial-temporal events.

This design of the vertically open-configuration magnet and the related paradigm is still the most preferable solution for intraoperative imaging, especially for open surgeries. When the idea was conceived, technical factors limited the field strength and consequently constrained the gap between the two magnet components. As a result, image quality and resolution were suboptimal, and the surgeon’s mobility was compromised in the narrow space. With advanced magnet-building technology, this exact configuration can be recreated at much higher field strength and with a substantially wider gap. In a less restricted environment, with more physician mobility and more flexible head positioning, this configuration still offers the best possible solution for MRI-guided neurosurgery. At a higher field strength (1 T and greater), spatial and temporal resolution can be improved to allow not only better anatomic detail but multiparametric functional imaging (eg, fMRI, DTI, MRA, MRS) during surgeries.

With improved hardware and software (eg, stronger gradients, dynamic-adaptive imaging

sequences, parallel or multichannel methods), images could be obtained extremely rapidly, even continuously, without interrupting the flow of surgery. Even in this current intraoperative magnet, where the patient is always within the imaging volume, the intraprocedural imaging takes a considerable time and suspends the surgery. The surgeon’s hand motion, occasional movement of surgical instruments, and radiofrequency (RF) noise from bipolar coagulation cause various artifacts that destroy the images. Using special imaging methods, incessant imaging that is relatively insensitive to motion, magnetic susceptibility, or brief electromagnetic noise can be implemented [8]. This potential technologic breakthrough can remove one of the major obstacles of intraoperative imaging—the neurosurgeon’s unintentional but inherent resistance to suspend surgery or change the normal flow of the ongoing operation.

The ultimate solution for unlimited patient access is a so-called “flat” or “tabletop” magnet with an external remote magnetic field [9]. The advantage of this completely open configuration is full access to the head and maximal flexibility in head positioning. The major disadvantages are the inherently limited field strength, the relatively small homogeneous imaging volume, and the relatively large size of the magnet under the operating room table, which may prevent the surgeon from reaching the surgical field with his or her hands and by the microscope.

After the introduction of the first intraoperative MRI system, which was designed explicitly for image-guided neurosurgery, several other groups began to use existing commercially available magnet configurations for neurosurgical guidance. Low- and midfield strength, horizontal open-configuration magnets [3,10–12], and closed-configuration higher field magnets [12,13] were placed in operating rooms or in interventional suites, which were modified for the needs of neurosurgery. The magnets that were originally designed only for diagnostic imaging were adapted to image guidance. Most of the efforts concerned the MRI table, which had to be revised or redesigned to make it well suited for brain surgery and MRI.

Using these primarily diagnostic MRI systems, the imaging paradigms are more or less constrained by the actual magnet configuration. In all versions, the surgical procedure has to be done outside the magnet. Because the head is not within the imaging volume, the table has to move or swing in and out from the magnet. To avoid

major modification of the operating room equipment and to get around the need for table motion, two commercial magnets were introduced. In both solutions, the magnet moves toward the head. The high-field (1.5-T) version is ceiling mounted, and during imaging sessions, it is pulled around to the operating room table [14]. The small low-field (0.12-T) magnet is mounted on the regular operating room table. It is partially open like the “double doughnut,” with a gap that allows the magnet to slide around the head when imaging is needed [15,16].

As far as field strength is concerned, these two magnet designs represent the two diverging directions in intraoperative MRI. It is obvious that the higher the field, the better is the image quality, but the lower field solution is less costly and more adaptable to the operating room environment. The high-field magnet offers various imaging sequences (eg, MRA, MRS, diffusion) and functional imaging methods (eg, fMRI, perfusion), and the image is acquired much faster. At the lower field strength, there are fewer problems with safety and device compatibility. Midfield magnets offer some compromise, but finding the middle ground may not be acceptable for either side. Most surgeons' preference for the higher magnetic field is driven by the current advances in diagnostic neuroimaging, where the modern trend is pointing toward 3 T. Besides higher spatial and temporal resolution, the higher field offers the advantages of high-quality and low signal-to-noise MRA, fMRI, and DTI, which are now natural components of surgical planning (Fig. 1) [17,18]. Most neurosurgeons would like to have these features available during surgery. Advocates of low-field intraoperative MRI believe that the relatively low-quality images are still sufficient to define tumor margins and detect the shifts and deformations during surgery. Those who believe in the power of computer technology and in the advances of automated or semiautomated image processing may accept the midfield compromise. Nonrigid registration of preoperative high-field images to lower quality intraoperative ones may permit the use of MRI data that are available only at high fields. When biopsies or surgeries are performed under low or midfield intraoperative guidance, the preoperative high-field images can be registered to the low-field intraoperative data [19]. This augmentation of intraoperative imaging with information obtained before surgery shows promise. Multimodality guidance using not only multiple MRI-derived data but positron emission

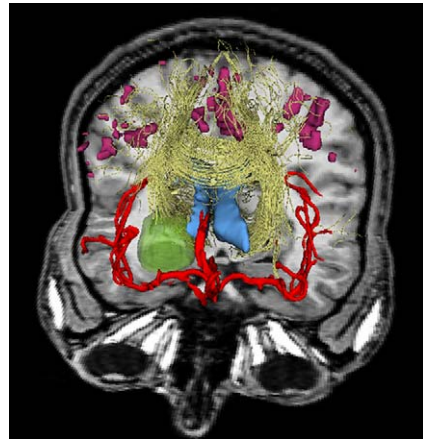


Fig. 1. Multimodality image fusion for surgical planning in a case of right temporal low-grade glioneural tumor. Three-dimensional (3D) tractography (yellow) derived from diffusion tensor imaging–MRI is rigidly registered with preoperative 3D spoiled GRASS and functional MRI (fist-clenching task). The 3D model of cortical activation is displayed in pink and the tumor is displayed in green.

tomography (PET), CT, and magnetoencephalography (MEG) should be an intrinsic part of surgical navigation. The preoperative data that are warped to the deformed intraoperative anatomy will reduce the rate of complications by providing an intraoperative model for real-time surgical planning at the operating room table that is essential for intraoperative decision making.

Field strength is not the only criterion when choosing magnet type. The flexibility in patient positioning and the surgeon's mobility are also critical; this is the main reason why neurosurgeons are adamant about using full-feature operating room tables. Good positioning of the head is critical for most open-brain surgery, and the use of surgical microscopes is also essential. These factors all influence the choice of imaging paradigms and the future design and ergonomics of image-guided operating rooms.

### Potential benefits in intraoperative MRI

Surgical guidance augments and supports the surgeon in performing procedures by reinforcing the knowledge of the patient's anatomy and by providing explicit visualization of intraoperative changes in the anatomy. This results in improved surgical decision making. Surgeons make decisions in the operating room based on the information that is available to them at that site at

that time. Often, they do not have the luxury of time to reflect on these decisions. By providing surgeons with the most up-to-date morphologic data, combined with all the available image-based information, their decisions will inevitably lead to better patient care. Real-time accurate information will provide the surgeon with the means and confidence to remove diseased tissue while minimizing the margins of healthy tissue excised. This not only improves tumor resection control but facilitates management of complications.

Controlling the blood flow is the most technically challenging and time-consuming aspect of many operations, which often involves tedious dissection to ensure a vessel, nerve, or other critical structure is not inadvertently severed. The introduction of higher field MRI systems (up to 3 T) will make vascular imaging suitable for guiding vascular surgeries and endovascular interventions. It has already been shown that intraoperative diffusion imaging can detect early ischemic damage during surgery and can be used to monitor vascular procedures [20]. Diffusion MRI can be complemented with perfusion MRI, and surgeries and embolization of vascular malformations can be made safer by keeping an eye on the brain while the blood vessel is manipulated. In aneurysm surgeries, 3D visualization of the lesion can help by showing the position of clips and the relation to the neck of the aneurysm and related blood vessels from angles other than those the microscope provides.

If surgeons knew the exact location of all the vital structures within the operational volume, it would significantly increase the speed of dissection. Reducing operating time will decrease operating room costs and postoperative complications, thus improving patient outcomes. The union of 3D planning with real-time intraoperative guidance will optimize surgical techniques and reduce morbidity and treatment times. Some of the most important examples of these potential improvements are the intraoperative use of fMRI and DTI to prevent damage to critical cortical functions and pathways of essential connectivity, the use of PET or MRI perfusion data to distinguish necrotic from viable tumor tissue, and the use of diffusion MRI to recognize vascularly compromised tissues. Even more substantial advances are foreseeable in the future if tumor-seeking contrast agents or tumor-tagging biomarkers are introduced into neurosurgery.

To take better advantage of intraoperative MRI, several important steps should be taken.

Among the steps necessary to realize the full potential of this technology, the most important are integration of intraoperative MRI scans with preoperative images obtained by other imaging modalities (multimodality fusion) and integration of the MRI methods with therapy devices/robots to transform open neurosurgical procedures into image-guided surgeries by changing surgical techniques and approaches. Without these advances, no major effect on disease outcome can be expected (Figs. 2 and 3).

One of the greatest benefits of intraoperative MRI is that the progress of brain deformations can be followed by serial intraoperative imaging [21,22]. Using this continuously updated information, preoperative images can be warped to the true anatomic position using nonrigid registration methods. Most of the specialized sequences (eg, fMRI, DTI, MRA) that are routinely used for surgical planning and intraoperative decision making can be obtained at high fields before surgery. Similarly, non-MRI images (eg, CT, PET, single photon emission computed tomography, MEG) can be adapted to intraoperative

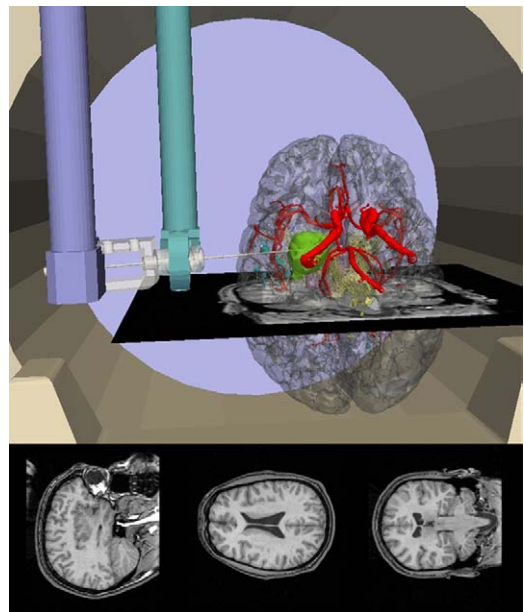


Fig. 2. Illustration of the interface between the 3D Slicer and the surgical robotic assistant. The robotic arm holding the biopsy needle is driven to the target (green) with the assistance of the 3D Slicer. The spatial position of the robotic arm and biopsy needle is tracked in real time and displayed in the 3D Slicer, along with image data.





Fig. 3. The robot attached to the open MRI scanner.

brain images. This multimodality fusion is eventually incorporated by all commercial navigational systems but their use is limited because of the inability to map the images they provide correctly to the actual brain anatomy. These complex imaging data sets should be available during surgery and warped to the actual anatomy. In the future, intraoperative MRI systems will be able to display them concurrently with the real-time acquired MRI scans. With low-field intraoperative systems, this method can also be used to improve image quality. High-resolution images obtained before surgery and acquired at high fields can be warped into low-quality and low-field MRI scans. This “single modality image augmented fusion” can provide highly accurate image guidance. Structures that are invisible at lower field strengths because of lack of resolution and a low signal-to-noise ratio can be brought to light and can improve the surgeon’s visualization and targeting. The combination of functional and anatomic images can improve the decision-making process, reduce complications, and result in improved outcomes.

Preoperative optimization of surgical approaches and trajectories is part of surgical planning. The preoperative plans usually consider all the available imaging data and combine them into a multimodality model. A simulation of surgery that includes multiple access routes and

trajectories can supplement this model. This multimodality model and the related predetermined simulation strategy can be registered to the patient (usually with rigid registration); during surgery, additional “on the fly,” modifications can be made by applying nonrigid registration to the changing anatomy. For preoperative data analysis, there is sufficient time for extensive and, presumably, more accurate, examination. In contrast, intraoperative data must be analyzed at a faster rate to reach a decision during the procedure. The surgical plan is interactively adapted to the intraoperative situation, and the real-time surgical planning assists surgical decision making. The predetermined plan of tumor removal can be compared with the actual resection to evaluate how the image guidance helped the surgeon to execute the original surgical strategy. This complex intraoperative interactive planning process is currently still cumbersome, however. In the future, more advanced image processing, visualization, and display techniques will be used in combination with software tools that emulate cutting, suction, coagulation, and other surgical manipulations.

The other important technical development that might follow the more widespread use of intraoperative MRI is related to the more complete integration of therapy devices into the interventional/intraoperative MRI environment. Fully integrated image-guided therapy delivery systems will be able to use localizing, targeting, and monitoring methods and will also be able to use quantitative image-based measurements to control various therapeutic procedures, such as robotic surgeries and image-guided thermal ablations. The use of image-derived quantitative parameters for the closed-loop feedback control of devices is a significant future development that may substantially change current neurosurgical practice. There have been early attempts to combine robots with intraoperative MRI [23] and to use intraoperative MRI to control thermal ablation devices (Fig. 3) [24–26].

One of the more ordinary consequences of intraoperative image guidance would be the transformation of traditional brain surgery into image-guided surgery. With more accurate and complete volumetric data, neurosurgeons should be able to operate more securely, with a faster and more economic approach. Thus far, there has been no reason for a more assertive and less cautious approach when intraoperative MRI is used. There is no indication of increased easiness, and no data

suggest any decrease in the time of surgeries. This is despite the improved navigation and better understanding of functional anatomy and spatial relations. The improved distinction between normal and pathologic tissue and enhanced appreciation of the related anatomy have not yet led to novel approaches or overall re-evaluation of current surgical strategies. It is anticipated, however, that the changes in surgical visualization and navigation will eventually change the current practice of neurosurgery. As a direct consequence of improved image guidance, new surgical techniques, strategies, and approaches will be introduced into neurosurgical practice.

So far, there are few changes in neurosurgical techniques that can be attributed to image guidance. One of the potential changes involves positioning, however. Head position is an important aspect of brain surgeries. Head position and craniotomy location define the surgical approach to the target lesion and influence several aspects of surgery, such as localization, targeting, access, and visualization. In intraoperative MRI target definition, localization is augmented by MRI tissue contrast and visualization is complemented by MRI. As a direct consequence, tumor explorations can be changed and head position and craniotomy locations can be modified or customized. Similarly, surface visualization provided by surgical microscopes and volumetric MRI could be supplemented by endoscopes, and their role could be redefined in the context of intraoperative MRI. Instruments like flexible endoscopes, which traditionally had to be controlled by direct eyesight, can be located and positioned by MRI and can be tracked and inserted beyond the surface, where visual assessment of their position is not possible. Beyond surface visualization is especially important when thermal ablation probes (laser optical fibers, RF antennas, or cryoprobes) are introduced into the brain. In thermal ablation interventions, the human eye cannot provide guidance and the correct positioning of the probes as well as the monitoring of energy depositions is controlled by MRI. Consequently, if image-guided positioning is applied, the instruments can be manipulated by robots or other mechanical devices. MRI-guided robotic devices have been developed and tested in open-magnet configurations [23]; in the future, similar devices can be used in closed-configuration high-field systems.

Currently, most intraoperative MRI guidance is for the removal of malignant (low- and high-grade) brain tumors. In these image-guided

procedures, MRI tissue characterization ability is exploited. MRI is used to delineate tumor margins and to detect residual tumor. It is obvious that MRI's high sensitivity may help to achieve more complete resection of tumors. Nevertheless, even MRI is limited in accurately delineating the entire spread of an infiltrative glioma, and most of the resection represents only debulking. Thus far, there is no definitive evidence that MRI-controlled extensive glioma resection results in any change in clinical outcome. The MRI guidance definitely improves the technical execution of surgery by providing 3D visualization, better understanding of spatial relations, and better delineation of critical functional anatomy. This advantage should eventually help not only malignant but benign tumor resections. Full comprehension of the operational volume versus the operational field, the appreciation of depth and distances, and the visualization of structures under the surface should eventually change the way surgeons approach intracranial pathologic findings.

### Unresolved issues in intraoperative MRI

Images can be obtained during surgery in a serial fashion to provide image updates about the changing brain anatomy. Imaging, however, is time-consuming, and time is essential in surgery. Imaging not only interrupts the flow of surgeries but adds substantial extra nonsurgical time to the overall duration of the procedure. On the one hand, there is the surgeon's intuition to minimize the time for imaging, and on the other hand, there is the surgeon's need for accurate guidance. These two competing issues result in a compromise that defines the actual number of imaging sessions. Today, this important decision depends on the surgeon's instinct or preference and is not based on any scientific optimization method. It is unclear how much information is needed to correct intraoperative shifts and deformations and how often data acquisitions should take place to drive such an adjustment reliably. If intraoperative deformations and shifts follow a predictable course, computer-based simulation and modeling would help to reduce the need for image updates. The exact sampling interval required to update intraoperative images correctly depends on the particular deformation pattern, which presently cannot be foreseen before surgery. Without a relatively short sampling interval, the dynamic course and spatial extent of brain shift cannot be fully appreciated. Ideally, frequent or even continuous

volumetric imaging is the only method that can guarantee accurate and real-time image guidance. Although MRI provides more information about brain morphology, other imaging modalities, such as stereo video systems, laser surface scanning devices, ultrasound, and CT, can also be used during surgery to reveal the changing anatomy. These methods may show changes of surface or internal anatomy during surgery, but the information they provide is not sufficient to provide full intraoperative guidance. Nonetheless, these methods can be used to reduce the need for frequent MRI updates. They can signal a significant degree of shift that indicates new volumetric updates. They can also be used for computer simulations that can model brain deformations. At present, neither the knowledge of the biomechanical properties of the brain nor the capabilities of computer simulation is sufficient to predict the various deformation patterns seen during surgery; therefore, the use of this adaptive model is limited.

In the future, we can use a series of imaging methods and processing algorithms to capture intraoperative changes during neurosurgery. Real-time automated segmentation methods will provide updated 3D models of the brain [21,27–29]. The combination of rigid and nonrigid registration methods, active surface-matching techniques, and the application of biomechanically more accurate models of brain deformation will eventually help to decrease the sampling rate needed for the full appreciation of changing brain anatomy during surgery. If a sufficiently accurate biomechanical model exists, the volumetric deformation field can be computed and used for intraoperative modeling.

The unpredictable nature of brain deformation is caused by extrinsic factors like retractors or by intrinsic factors like edema or hemorrhage. As a result of these unsystematic events, serial imaging cannot be substituted for simulation. Intraoperative MRI is a prerequisite of reliable and accurate intraoperative navigation.

### MRI-guided thermal ablations

Previous clinical studies of thermal ablation in the brain have involved the use of focused ultrasound surgery (FUS) through an open skull, microwave, laser-induced ablation, and so-called “cryosurgery.” Most studies have shown that thermal ablation of various brain lesions is feasible and safe. Relatively large lesions were treated with minimal morbidity. Unlike thermal ablation

(eg, laser surgery, RF surgery, cryosurgery), FUS works without the introduction of a thermal probe, and if it is done through the intact skull, it is noninvasive. The converging ultrasound beams pass through the brain to the target, without damaging the intervening tissue and provides a small enough spot size (as small as 1 mm) for precision. The noninvasive nature of ultrasound surgery has special appeal in the brain, where the ability to treat or destroy deep tissue volumes without disturbing the overlying tissues is critical.

It was recognized several decades ago that converging focused ultrasound beams can be applied as a surgical technique to treat neoplastic tissue, particularly deep in the brain. FUS applies localized high temperatures to induce cell damage as result of protein denaturation and subsequent coagulation necrosis. The clinical application of this well-researched method was delayed because of the lack of a noninvasive imaging system to provide targeting and temperature monitoring in real time (see Fig. 4). MRI's excellent anatomic resolution, high sensitivity for tumor localization, and unique ability to image temperature changes all make FUS possible. Today, the full integration of MRI and FUS enables real-time, image-controlled, noninvasive, soft tissue coagulation in the breast and pelvis, and the clinical feasibility of MRI-guided FUS has been proven [30,31].

In neurosurgery, the clinical applicability of FUS is somewhat limited in the presence of bone and air or in gas-containing cavities in the skull. The bone has a high absorption and acoustic impedance compared with soft tissues. At bone–soft tissue interfaces, approximately one third of the incoming energy is reflected back, which may allow unacceptably high temperatures to develop within the bone. The loss of acoustic energy can be offset by focusing, but the focus can shift from the targeted location because of variations in skull thickness and refraction. The solution is to adjust the focus by applying corrections to the phase of the ultrasound source. Skull thickness can be estimated from CT of the head, and phased-array transducer elements can be independently controlled to adjust the phase and refocus the distorted beam [24,32,33]. The currently developed brain treatment system (Insightec, Dallas, Texas) overcomes acoustic aberrations of the ultrasonic beam using automated planning software based on a set of CT scan images.

MRI-guided FUS has major advantages over surgery and radiation therapy for the treatment of benign brain tumors. High-field MRI provides



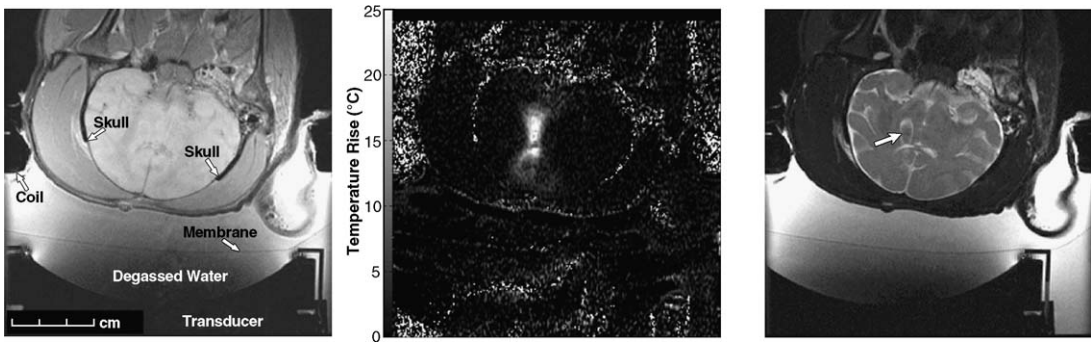


Fig. 4. (*Left*) Proton-density image of the brain of a rhesus monkey with a craniotomy. The monkey was placed on its back, and a bag of degassed water was used for acoustic coupling. (*Center*) Map of the temperature rise (generated from phase-difference gradient echo images) induced during a 10-second 63-W ultrasound exposure in the internal capsule just lateral to the thalamus. The peak temperature at the focus was greater than  $90^{\circ}\text{C}$ . The gap in the heating shown is caused by the ventricle, where there was no ultrasound absorption. A spherically curved transducer (radius of curvature/diameter =  $10/8$  cm, frequency = 1.5 MHz) produced the ultrasound field. (*Right*) T2-weighted image showing the resulting thermal lesion.

enough anatomic detail for correct targeting and real-time closed-loop control of temperature, and the deposited thermal dose ensures safe and effective treatment for benign tumors. The most serious shortcoming of thermal ablative treatment of malignant tumors is the lack of precise target definition by MRI. The surgical concept of a well-defined tumor mass is incorrect; instead, we deal with spatially disseminated tumor cells that may spread beyond the reach of the thermal treatment. This is a serious handicap for conventional and minimally invasive approaches. If a cure is not anticipated, however, a less invasive procedure is more justified for palliation.

MRI-guided FUS can be a major advance for functional neurosurgery. High-resolution MRI-defined anatomic regions can be targeted with high accuracy, and lesions of various sizes can be created. In combination with fMRI and DTI, functional changes can be monitored and changes in connectivity can be detected. There is some experimental evidence that lower power FUS may reversibly change nerve conductivity and/or neuronal function and can be used for functional testing before making permanent lesions.

In addition to tissue coagulation, the sharply demarcated thermal lesions have a zone around them that shows blood-brain barrier (BBB) leakage to larger molecules. This method could be used to open the BBB for chemotherapy or targeted drug delivery, but it is unpredictable and difficult to control. If BBB opening is mediated by heat, it is associated with potentially irreversible tissue

destruction. Another more promising mechanism of ultrasound tissue interaction, cavitation, can also induce focal BBB opening. It is reproducible and reversible, and there is no neuronal damage within or around the sonicated area [34,35].

Cavitation refers to the collapse of rapidly developed gas bubbles at the focal point as a result of oscillations of pressure of the ultrasound field. Cavitation energy can be generated by preformed gas bubbles (ie, ultrasound contrast agents) injected into the blood stream just before the sonication. The collapse of a bubble is associated with a large concentration of energy, which creates high pressure, propagating a shock wave. This leads to direct mechanical tissue effects that change the cell membrane and vascular wall permeability. If the bubbles are intravascular, any adverse effects to the adjacent brain tissue is minimal, and the power levels used are orders of magnitude lower than that required for generating tissue ablation or the cavitation threshold. At the lowest power levels used, the sonications did not cause neuronal damage to the brain, and the BBB opening is completely reversible within 24 hours [35].

The opening of the BBB allows larger molecules to enter the brain [36]. This can have a significant clinical impact on the feasibility of local, noninvasive, targeted drug delivery or gene therapy. Specifically, FUS could provide targeted access for chemotherapy and gene therapy and allow the use of recombinant proteins, monoclonal antibodies, or antisense oligonucleotides as pharmaceutical agents for the brain. It could even

provide a vascular route for implanting cells in the brain. The anatomically targeted and controlled opening of the BBB at a desired location would permit novel noninvasive methods of treating central nervous system diseases, such as brain tumors, seizures, and movement disorders. Using large molecular size peptides, neuroactive proteins, and various antibodies, new innovative therapeutic interventions should be available for dealing with organic brain diseases and mental disorders. In addition to the coagulative- and cavitation-based effects, high-energy acoustic beams can be used to occlude or block blood vessels [37,38]. Ultrasound techniques are therefore being developed to stop the bleeding resulting from trauma or catheterization (hemostasis) and for selectively blocking blood vessels. Blood vessel occlusion may be useful for the nonsurgical and nonendovascular treatment of arteriovenous malformations and for tumor treatment by interrupting blood flow to a tumor.

### Image-based therapy delivery systems

Image guided thermal ablation requires the integration of therapeutic devices with imaging systems. This integration is a prerequisite of image-guided therapy, because location and feedback control of the energy disposition call for a fully integrated system. We are entering a new area of combined diagnostic and therapeutic applications involving advanced technology. There are still unresolved problems, the most important of which is the lack of sufficient data to establish the clinical efficacy of the minimally invasive techniques under trial. The few MRI-guided thermal ablations already performed contribute to the evaluation of the feasibility of these techniques.

Therapy systems must be linked with imaging systems to form complete therapy delivery systems. The successful deployment of these systems depends on a multidisciplinary team composed of surgeons, interventionalists, imaging experts, and computer scientists. Such an environment is radically different from the conventional operating room. Most notably, the surgeon's view of the surface of the operational field is complemented by images showing what is beyond the visible surface. This feature of MRI, in turn, leads to dramatic changes in surgical approaches and methods driven by a close integration of image-based information with surgical procedures. This new integrated setting, recently coined "The Operating Room of the Future," is not yet

optimized and is the subject of intense research. The overall goal of image-guided therapy delivery systems is to integrate all the accessible information (preoperative and intraoperative imaging data) into a single complete operational therapy delivery system.

Images contain information used for diagnosis and therapeutic interventions—applications that are inextricably linked because of the close interplay between the process of diagnosis and therapy. Nevertheless, there are fundamental differences between the requirements for a diagnostic workup and an imaging study directed toward a therapeutic procedure. For correct diagnosis, specificity has greater significance than sensitivity. For therapy, sensitivity should be a fundamental feature. Images of the highest quality are requisite to accurate localization, targeting, and defining of instrument trajectories. All available imaging modalities, especially x-ray fluoroscopy, have been exploited in this regard. More recently CT, ultrasound, and MRI have been introduced into the operating room for intraoperative image guidance. At the same time, with the advance of computerized image processing and visualization tools, image guidance systems have been incorporated into various surgical and radiation oncology applications. These systems make use of images acquired before surgery to create anatomic models. The models, in turn, provide localization, targeting, and visualization of the 3D anatomy. Preoperative models, however, should be modified as the procedure progresses and the anatomy changes. The only feasible means of detecting physiologic motion, displacements, or deformations is via intraoperative or intraprocedural imaging. Monitoring of dynamic changes induced not by motion but by a variety of other functional or physical parameters may be altered or modified during interventional or surgical procedures. Although the primary goal of monitoring is to follow and update anatomic changes in position, other types of dynamic information (ie, flow, perfusion, cortical function) can also be extremely useful in optimizing this process. Although these therapy delivery systems can be tailored to different clinical applications, successful implementation depends almost entirely on interdisciplinary collaboration, an infusion of the most current surgical and radiologic methods, and cutting-edge biomedical engineering principles aimed at combining imaging and therapy devices. Few would argue that MRI-guided therapy is not the quintessential example of a truly interdisciplinary

noninvasive approach to the diagnosis and treatment of disease.

### Summary

MRI-guided neurosurgery not only represents a technical challenge but a transformation from conventional hand-eye coordination to interactive navigational operations. In the future, multimodality-based images will be merged into a single model, in which anatomy and pathologic changes are at once distinguished and integrated into the same intuitive framework. The long-term goals of improving surgical procedures and attendant outcomes, reducing costs, and achieving broad use can be achieved with a three-pronged approach:

1. Improving the presentation of preoperative and real-time intraoperative image information
2. Integrating imaging and treatment-related technology into therapy delivery systems
3. Testing the clinical utility of image guidance in surgery

The recent focus in technology development is on improving our ability to understand and apply medical images and imaging systems. Areas of active research include image processing, model-based image analysis, model deformation, real-time registration, real-time 3D (so-called “four-dimensional”) imaging, and the integration and presentation of image and sensing information in the operating room. Key elements of the technical matrix also include visualization and display platforms and related software for information and display, model-based image understanding, the use of computing clusters to speed computation (ie, algorithms with partitioned computation to optimize performance), and advanced devices and systems for 3D device tracking (navigation).

Current clinical applications are successfully incorporating real-time and/or continuously updated image-based information for direct intraoperative visualization. In addition to using traditional imaging systems during surgery, we foresee optimized use of molecular marker technology, direct measures of tissue characterization (ie, optical measurements and/or imaging), and integration of the next generation of surgical and therapy devices (including image-guided robotic systems). Although we expect the primary clinical thrusts of MRI-guided therapy to remain in neurosurgery, with the possible addition of other areas like orthopedic, head, neck, and spine

surgery, we also anticipate increased use of image-guided focal thermal ablative methods (eg, laser, RF, cryoablation, high-intensity focused ultrasound). By validating the effectiveness of MRI-guided therapy in specific clinical procedures while refining the technology that serves as its underpinning at the same time, we expect many neurosurgeons will eventually embrace MRI as their intraoperative imaging choice.

Clearly, intraoperative MRI offers several palpable advantages. Most important among these are improved medical outcomes, shorter hospitalization, and better and faster procedures with fewer complications. Certain economic and practical barriers also impede the large-scale use of intraoperative MRI. Although there has been a concerted technical effort to increase the benefit/cost ratio by gathering more accurate information, designing more localized and less invasive treatment devices, and developing better methods to orient and position therapy end-effectors, further research is needed. Indeed, the drive to improve and upgrade technology is ongoing. Specifically, in the context of the real-time representation of the patient's anatomy, we have improved the quality and utility of the information presented to the surgeon, which, in turn, contributes to more successful surgical outcomes. We can also expect improvements in intraoperative imaging systems as well as increased use of nonimaging sensors and robotics to facilitate more widespread use of intraoperative MRI.

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