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A View from the Outside In

Image-Guided Therapies Quickly Becoming a Foundation of Medical Care

By Leslie Mertz

In today's operating rooms, surgeons are more likely to be scrutinizing a computer screen than examining a patient's opened chest or abdominal cavity. In just a few short years, imaging techniques such as computed tomography (CT), magnetic resonance (MR) tomography, and ultrasound have graduated from tools that help a doctor diagnose a health condition to tools that can actually guide therapy.

Doctors are currently using these imaging techniques to navigate the brain during neurosurgery, to perform virtual colonoscopies, and to pinpoint the location and size of malignant tumors to help ensure their complete removal. This is just the beginning, according to experts in the field.

Research is under way to expand the use of image-guided therapies so that surgeons can perform heart-valve replacements and other cardiovascular procedures without having to cut the chest cavity. Additional studies are ongoing to use image-guided therapy for pancreatic and other cancers that are now difficult or nearly impossible to treat and for the development of new drug delivery systems that will transport chemotherapeutic agents to the target site, and only to the target site, thereby drastically reducing a patient's drug dose and the associated side effects.

"There's a pretty wide range of therapies that can fall under the description of image-guided therapies, but the main idea is that you have some kind of medical imaging modality that is used during an intervention therapy," said Dieter Haemmerich, Ph.D., associate professor of pediatrics at the Medical University of South Carolina. He described the main imaging technologies as follows:

- CT, which uses X-rays to obtain data that are constructed into cross-sectional or other images
- MR imaging (MRI), which uses a magnetic field and radio waves to produce images
- ultrasound imaging, which uses ultrasonic waves to create representations of internal body structures.

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"Using these various technologies, sometimes in concert, image-guided therapy has begun to infiltrate many areas of medical care, with cancer and cardiovascular treatment being two of the major beneficiaries," Haemmerich said.

Finding the Way

The primary job of image-guided therapy is to provide a useful and detailed picture of the inside of the body. In cancer treatment, it means finding a tumor and determining its exact boundaries.

"I see image-guided therapy as being something where we take tomograms—either a CT scan or an MR scan, maybe even a positron emission tomography (PET) scan—and match that to the physical space of the patient, and then show the surgeon where they are as they treat the patient," said Robert L. Galloway, Jr., Ph.D., professor of biomedical engineering, professor of surgery, professor of neurosurgery, and director of the Center for Technology Guided Therapy at Vanderbilt University. In other words, he explained, the tomograms are a series of stacked image slices that, when reconstructed on a computer, produce a three-dimensional (3-D) image that the doctor uses as a map when performing a procedure on the patient. "That lets them see where they are, for instance, relative to a tumor, and it also lets them see where they are relative to blood vessels that they want to miss, because an awful lot of this is not only hitting the target, but missing things you don't want to hit."

> **Of the structures of interest to the surgeon, the most critical are arteries and veins.**

A key part of that is registration, or how the image relates to physical space. "Although the doctor may have a rotatable, rendered image on the computer screen, the screen itself is still inherently two-dimensional (2-D)," he said. "So how do you convey 3-D information? Even if they had 3-D glasses, they are at best two-and-a-quarter-dimensional, because if I'm looking at you on a 2-D movie screen, I can't see the back of your head no matter what. I know where you are in the room, but I don't know what's on the back of your head, and I sure as heck don't know what's inside of your head, so I'm not seeing 3-D at all there. I have no problem imagining 3-D, but I just have trouble visualizing it."

The single leading step in image-guided therapy is therefore registration between image space and physical space, he said. "We try to provide that information in such a way that the surgeon can construct the 3-D image in his or her head and determine the relative positions of the structures in the patient." Of the structures of interest to the surgeon, he said, the most critical are arteries and veins. "Surgeons are not really afraid of tissue; they're terrified of blood vessels." A mistaken cut of a major vessel can be fatal. That is an issue with tumor surgery, because large numbers of blood vessels are typical of fast-growing tumors.

A number of researchers from around the world are approaching the problem of registration, often using relatively fixed points in the patient's own anatomy, such as certain forked blood vessels, or specified points on the surface of the body to correlate the image to the patient. Galloway and his research group are taking a different track. They're dragging a tracked probe over an organ's surface and using that as a reference for the computer image.

He said, more work is necessary, noting that interdisciplinary efforts will drive a solution. "We need engineers who work with surgeons," he said. "This is about design."

Especially Tough Cancers

It was only a few years ago that a small group of researchers, including Galloway, had what he called the "bizarre idea" of using image guidance in neurosurgery. "Today, it's the standard of care," he remarked. "If you do an intracranial procedure today and you don't use an image-guided surgery system, you have to show cause as to why you didn't use one. It's become a billion dollar a year business."

He thinks the same will be true of many medical procedures in the near future. "If you think about minimally invasive surgery, what you're doing is going in and repairing or taking something out, and at the same time, exposing as little healthy tissue to the therapeutic process as possible," Galloway said. "To do that in anything is not simple. To do that in those places where the stakes are high—in the brain and also in abdominal organs that are heavily vascularized—guidance really matters."

Liver cancer is a case in point. Although it is the second leading cancer killer worldwide, and despite the fact that surgery is the most effective treatment, the vast majority of liver cancer patients do not undergo surgery.

The reason is that liver surgery is very difficult. For one thing, liver tumors are often adjacent to major blood vessels. "In the United States, we're particularly fond of our fatty foods, and me in particular, so the chances of me getting colon cancer are higher," Galloway said. "The problem is the metastatic disease that comes along with it and infiltrates the liver. Because it's bloodborne—that is, you've got tumor cells from your colon transporting via the vascular system—the tumors tend to grow near the bigger blood vessels. So the surgeon is afraid to go in and cut something out near a major blood vessel, because they're worried about cutting in that blood vessel and killing the person on the table."

On top of that, liver surgery is trickier than brain surgery, he said. Part of the issue is that the liver and other abdominal organs slouch, shift, and otherwise change shape during surgery. "The brain rests in a rigid skull, which helps. It does deform, but it doesn't fold over on itself or anything like that," he said. "When you move into abdominal organs, however, now you're dealing with things that can deform, things that are much more free to move than the brain is, so you've got to bring a better level of engineering sophistication to the problem in order to be able to correct for those sorts of things."

Despite the considerable challenges of registration between image space and physical space in abdominal organs, and the proximity of liver tumors to blood vessels, surgery is still the best possible option, and image guidance is the way to make it possible, he said (Figure 1). "We know that surgery is the best outcome. There's

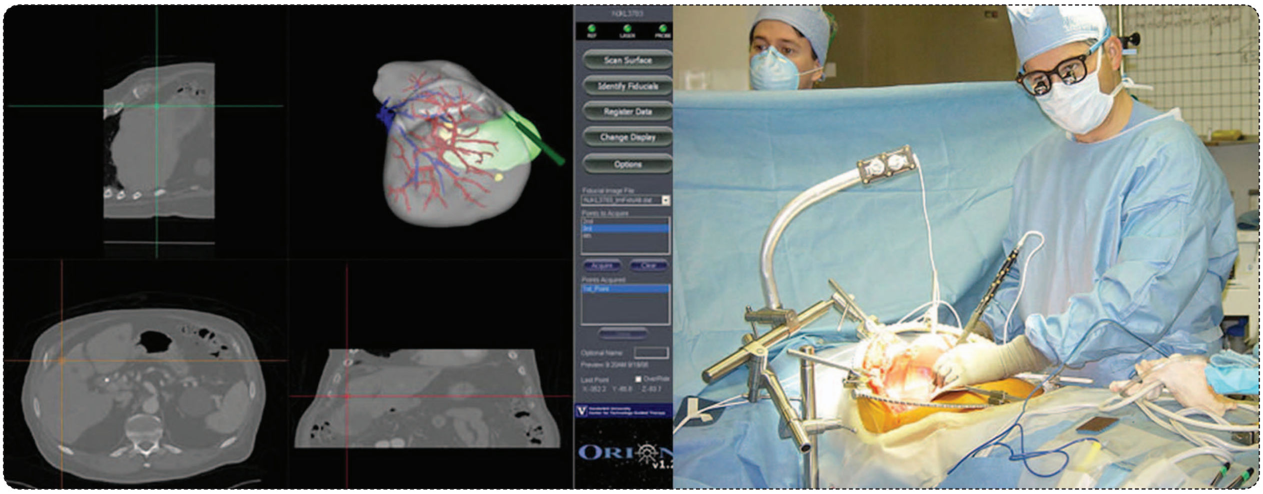


FIGURE 1 A surgeon consults a display generated by the image-guided system developed at Vanderbilt University to perform liver surgery. Liver surgery is especially difficult for several reasons, including the number of blood vessels in the organ. Image guidance helps surgeons avoid the vessels. (Photo courtesy of Dr. Robert L. Galloway and Dr. William Chapman.)

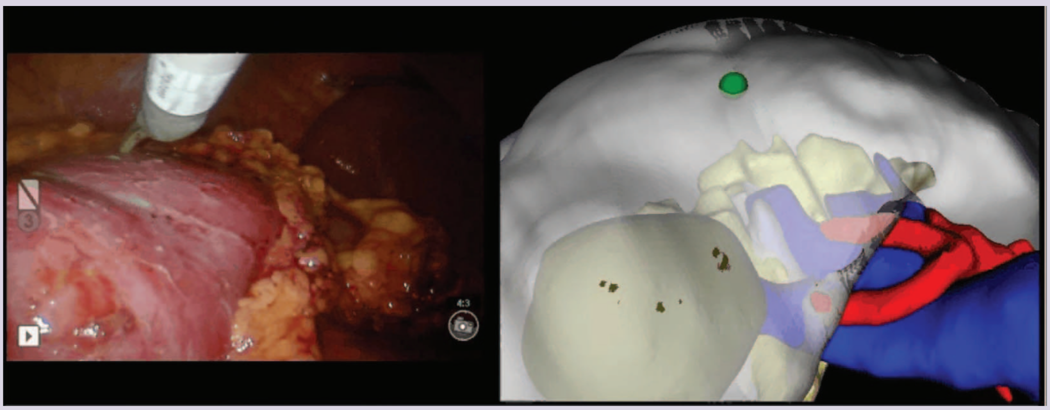
nothing else that even comes close, so if we can do that and make that possible, make that safer, then we know that we've got a win."

Kidney cancer presents its own obstacles. Conventional treatment for kidney cancer is to remove the entire affected kidney, because a person can survive on just one. "That's just two major blood vessels and the ureter that you need to control, so it's pretty straightforward surgery," he said. The complication arises when the surgeon opts to remove only the cancerous part of the organ. "Once you cut into a kidney, then things get surgically much more complex, because you've got blood vessels and you've got a collecting system and you've got to get all that straightened out," he explained. But it's worth the effort. "If you're down to one kidney, you had better not ever become hypertensive and you'd better not be in a car wreck. Conversely, if you've got one-and-a-half kidneys or 1.7 kidneys, then you've got a little more reserve, and the quality of your life is going to be much better." For those reasons, he said, partial nephrectomies may become more common as image-guided procedures mature (Figure 2).

Surgeons are not really afraid of tissue; they're terrified of blood vessels.

Treatment for pancreatic cancer is on the horizon, too—thanks to a new blood test that promises to detect the cancer much earlier than current tests. "Nobody asked before how you could operate on a pancreas because by the time you figured out that somebody had pancreatic cancer, they were pretty much dead," he said. He expects that image-guided surgery will become the standard of care there, too.

In all three cases, he said, "The trick, of course, is getting surgeons who are trained in how to make certain decisions



(a) (b)

FIGURE 2 (a) The traditional laparoscopic view of the kidney when using the da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, California). (Photo courtesy of Dr. Robert Galloway and Rowena Ong.) (b) Work done at Vanderbilt University adds image guidance to the system via the operating room image-oriented navigation (ORION) system and allows the surgeon to see structures beneath the surgical tool as they operate.

and how to do certain procedures, and get them to think a little bit outside of the box." Functional engineering is also critical. "The absolute dumbest thing an engineer can do is walk up to a surgeon and tell them that what they are doing isn't good enough, because where do we get off with that? So it has to be an engineer-and-surgeon team working on this, or else we're going to create something really goofy, or we're going to create something that is only marginally different," he asserted.

Overall, he said, "Sure, we all want the magic bullet. If you get cancer and can take a pill and the cancer would go away, wouldn't that be wonderful? In the meantime, engineers can help make surgery both possible and less damaging."

Putting on the Heat

Image-guided technologies are finding a place in heat-ablation procedures that turn up the temperature on tumors until their cells die. Haemmerich is conducting research on the use of electric current to heat tissues, a procedure known as *radio frequency* (RF) ablation, which is already in use clinically. "In this case, a catheter is run through a small incision in the skin, and inserted into the tumor using image guidance. Then, the tumor and the surrounding tissue are heated and destroyed by heat. The heat is used to directly kill the cancer." It is not always 100% successful, he said. "One limitation is still that sometimes you kill most of the tumor but not all of it, and then the tumor grows back. This research is to try to get better heating devices to uniformly kill the whole tumor."

A mistaken cut of a major vessel can be fatal.

Although heat ablation with current devices does not destroy the whole tumor all the time, it is still a beneficial procedure with excellent success rates particularly for smaller tumors of less than 3 cm in diameter. When paired with chemotherapy or radiation therapy, it can provide additional advantages.

"With chemotherapy, it's often difficult to treat the center regions of the tumor, because there's not much blood flow in the center," Haemmerich said, noting that the chemotherapeutic drugs are carried through the bloodstream. "That means that some cancer cells may still survive there. With the heat-based methods, the lack of blood flow is no problem, and you can kill the center of the tumor very easily. Afterward, the chemotherapy is much more effective, because you have already destroyed a large part of the tumor, including the center where the chemotherapy doesn't reach."

Nonlethal heat and radiation is also a winning combination, because the heat makes the tumor cells more susceptible to radiation, said Neal Kassell, M.D., professor of neurosurgery at the University of Virginia and chair of the Focused Ultrasound Surgery Foundation. The foundation specializes in MR-guided ultrasound. "The type of ultrasound that people are familiar with is for diagnosis, but there is a field of therapeutic ultrasound that includes ultrasound-guided and MR-guided ultrasound. Some indications are better treated with MR-guided, and some are adequately treated with ultrasound-guided," he said.

"One advantage of MR-focused ultrasound is that you can measure temperature with MR thermometry, which is important when you use temperature as a way to determine whether you have effectively treated tissue. You can't do that with ultrasound," Kassell said.

In addition, MR-focused ultrasound provides far better imaging capabilities, said Mark Hurwitz, M.D., director of regional program development for the department of radiation oncology at the Dana-Farber Brigham and Women's Cancer Center at Harvard Medical School. "MR provides more information about the target as well as the tissue the focused ultrasound beam is passing through. We can find exactly where the nerves, vessels and organs are in terms of planning the treatment." Once the procedure is complete, he said, he can also employ MR to ensure that the tumor was ablated and that healthy tissue sustained no damage.

Hurwitz is currently studying how effectively MR-guided ultrasound, as well as combined radiation and ablation, treats bone metastasis and prostate cancer. He is also the principal investigator of a large phase III trial on bone metastasis. While he can't discuss the phase III results yet, he noted that earlier trials showed very good pain-reduction results with more than a third of patients reporting partial relief and another third reporting complete relief.

Besides the use of image-guided heat to enhance radio sensitivity and kill tumor cells, it is now part of several additional therapies, such as thermal ablation to destroy areas of the brain as a treatment for neuropathic pain and essential tremor and to destroy blood clots, he said.

Straight to the Heart

Another huge area for image-guided therapy is in the cardiovascular realm. A common procedure that uses imaging is the implantation of stents, small expandable tubes used to open blocked blood vessels, said Haemmerich. "For that, you need some kind of imaging to tell you where you are and where you want to go. That's how you place the stents and then confirm that they are at the location you want them to be."

One of the researchers who is pushing the envelope is Robert J. Lederman, M.D., senior investigator in the division of intramural research at the National Heart, Lung, and Blood Institute (NHLBI). He is also director of cardiovascular intervention at the National Institutes of Health (NIH) and heads its Image-Guided Cardiovascular Intervention Fellowship Program. "I've been working now for a decade to do something that's very difficult, and that's to use MRI instead of X-ray to guide catheter procedures." The problem with X-ray, the current standard of care, is that it provides only quick glimpses of the target area, he said. "When we work under X-ray, we can't really see what we're doing except for a few moments when we occasionally inject contrast to fill up the blood space." However, with MRI, a doctor can not only continuously see the blood and the soft tissue, but he or she can also see in real time how their own medical devices are interacting with tissues.

He is especially interested in using real-time MRI to perform radiation-free heart catheterization in children. He is not alone in his desire to reduce radiation exposure in children. A national campaign, called Image Gently, notes that children are more sensitive to imaging radiation than adults are and warns that cumulative radiation exposure may have adverse effects over time.

As MR-guided catheterization research progresses, some issues must be resolved, he noted. One of the most pressing is the design of the catheters themselves. Lederman explained that catheters, which were made for X-ray use, simply don't show up on MRI. In addition, he said, "Long, conductive devices can heat up under MRI, and almost all catheters are long and conductive." In answer, his and other laboratories at the NHLBI are working on MRI-compatible catheter prototypes, as well as imaging techniques tailored to guide treatments and not just diagnoses. "These are very complex and expensive undertakings that can be a little off-putting to industry, so we're using our government labs to jumpstart the process."

Large numbers of blood vessels are typical of fast-growing tumors.

As that work continues, Lederman is involved in another big project: doing heart-valve replacements without cutting open the chest. "One really exciting line of work in our lab is to access the beating heart through the chest wall, but without surgery and without arresting the heart. Then we can put a large port directly into the ventricular cavity from the outside—without surgical exposure—and put in a large prosthesis like a mitral valve replacement. Those devices are gigantic! Or, we can put in a valve prosthesis for aorta. When we're done, we could close the hole remotely, without opening the chest."

This work is in the developmental stages. "We're proceeding step-wise," he said, noting that he has conducted some animal testing and has only recently started to perform simple MRI-guided heart catheterization procedures in humans. "One of my goals in life is to provide non-surgical alternatives."

Several trends in cardiovascular work are worth watching, he said. One is MRI generated and very detailed anatomical maps to the patient's body. Such maps would allow medical professionals to perform faster catheterization procedures with less X-ray exposure to the patient. "We are working to replace 'static' roadmaps with dynamic roadmaps that morph dynamically to correct for cardiac and respiratory motion," he said.

"Another trend is 3-D ultrasound, whether through the chest wall, through a transesophageal probe (that is inserted through esophagus to view the heart), or using ultra-miniaturized imaging ultrasound probes that are put directly inside cardiac chambers," he said.

He also noted that some laboratories are pursuing real-time MRI for use in treating cardiac arrhythmia. "Currently, cardiac electrophysiologists burn small sections of myocardium (heart muscle) to treat cardiac rhythm disorders," he said. This blocks the electric current that drives the incorrect heart contraction and resolves the arrhythmia. "When they do this procedure, however, they can't see the target tissue. MRI would be attractive, because it would allow physicians to interactively assess the target tissue while they work. They could watch it heat up. They could confirm that they are destroying the desired short circuits while they work."

Edging into Orthopedics

Besides cancer and cardiovascular treatment, image-guided therapies are becoming more prevalent in orthopedic surgeries, such as minimally invasive knee replacements. The technology not only can provide the operating physician with a preoperative view of the affected joint but may also allow the operating physician to make adjustments during procedures so that joints can be aligned more precisely.

Health-care costs do come into play with image-guided orthopedic procedures, however, because many such procedures are already very successful without image guidance, noted Galloway. "There have been a lot of times when I'm approached by somebody about image guidance, and I ask, 'Will the information provided by guidance help you?' If they hesitate or if they answer, 'Well yes, sometimes,' then it's probably not worth doing," he said.

"You want to be a little bit aware of the cost of technology in health care. If we can do something with image guidance, and it means somebody goes home with 1.8 kidneys instead of one, that's a win. That's a huge win. If you double the price of having a knee operation and only one in a hundred

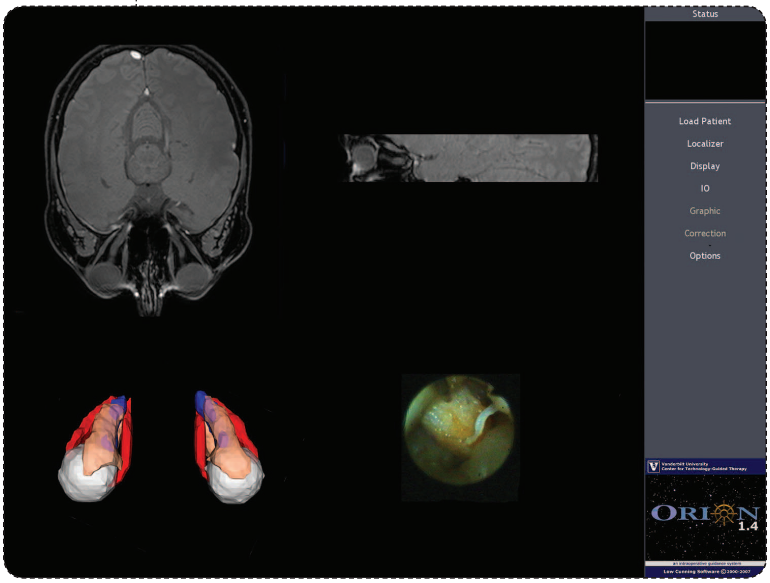


FIGURE 3 Image guidance is also used in drug delivery. Here, the ORION system developed at Vanderbilt helps guide drug delivery to the back of the eye. The image in the lower right quadrant is a live endoscopic feed. (Photo courtesy of Dr. Robert Galloway and Dr. Louise Mawn.)

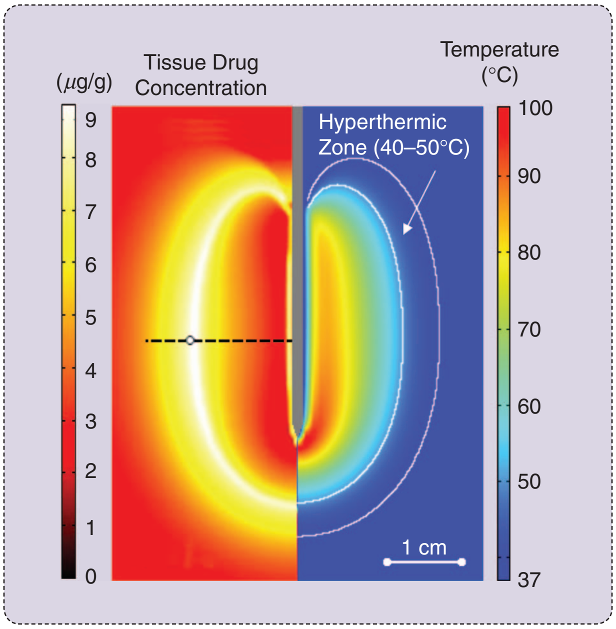


FIGURE 4 Image guidance can also assist drug delivery. Chemotherapy drugs can be encapsulated in liposomes, which are spheres made of lipids. The tiny spheres, which range from 100–200 nm in size, are heated to release their contents. By selectively heating certain areas of the body, the drugs are delivered only at the site of a tumor. Heating is accomplished via electric current in a procedure known as RF ablation. The figure at the left shows tissue drug concentration if RF ablation is combined with liposomes and demonstrates the complementary effect of killing of the center regions of tumors by heat alone (more than 50 °C), while depositing drugs in the surrounding region for additional treatment effect. (Image courtesy of Dieter Haemmerich.)

people need it, then you really don't need us," he commented.

Studies are currently under way to determine whether image guidance provides sufficiently improved outcomes, such as less pain and faster recovery, to warrant their costs.

> Although heat ablation with current devices does not destroy the whole tumor all the time, it is still a beneficial procedure.

Zeroing in Drugs

While it may not be an obvious connection, research into methods of drug delivery is also tapping imaging technology (Figures 3 and 4). When cancer patients receive chemotherapy today, drugs flood the entire body and the patients experience various side effects. "You're kind of hoping that enough goes into the tumor," Haemmerich said. "There's currently a lot of research going on in terms of getting chemotherapy specifically into the tumor, and also getting radiation more concentrated in the region where the tumor is located. The idea is to get more into the tumor and to get less everywhere else in the body to reduce the side effects."

One way to do this is by encapsulating the chemotherapy drugs in tiny spheres called liposomes, he said, and he is conducting research to make it possible. "These are 100- to 200-nm spheres made of lipids. If we heat them above a certain threshold, they release their contents, which are the chemotherapy drugs. That way, we can locally heat tissue and locally deliver the chemotherapy." The remaining, unheated liposomes circulating in the body are eventually degraded by the liver and kidney, and their contained drugs are never released into the bloodstream.

In his research, Haemmerich is conducting computer simulations to learn the temperatures needed and the duration of heat needed to melt the liposomes and maximize the drugs delivered to the tumor. "This is not clinically used yet, but there is a lot of interest currently in using that method."

Kassell agreed. "Focal or targeted drug delivery is a huge area," he said. Research is also under way on another delivery vehicle, called microbubbles, which burst under application of focused ultrasound. "They're not temperature-sensitive. They're sensitive to the ultrasound pressure, which causes them to burst and release their payloads." The result is the same: drugs are delivered only to the target area, and systemic side effects are drastically reduced or eliminated.

For liposomes, ablation of tumors and other uses, MR-guided focused ultrasound is here to stay, Kassell said. "There is the potential for focused ultrasound to revolutionize therapy to the same degree that MR scanning revolutionized diagnosis," he said. "It could be the ultimate in minimally invasive surgery; a new way to deliver drugs, which means it could change drug therapy; and an alternative for much of radiotherapy. In doing so, it could be used to treat a broad spectrum of serious medical disorders and thereby improve the lives of millions of people worldwide."

Image-guided procedures have already nosed their way into medical care, added Galloway. "Image-guided neurosurgery is now the standard of care. I would put the number of such image-guided procedures that we've done just at Vanderbilt in the hundreds, if not the thousands, and other hospitals internationally and across the United States are also doing them." Multiple hospitals are beginning clinical testing on image-guided liver and kidney surgeries, and he said Vanderbilt hopes to do the first glaucoma treatment using image-guided therapy next spring.

"So the work goes forward," he said. "We can never get enough NIH funding to have the people in place to work on this, but it's going forward."

Leslie Mertz (LMERTZ@nasw.org) *is a freelance science and medical writer and author as well as an educator.*