Imaging tools act as an extra pair of eyes for the surgeon.

DR DANIEL RUAN AND DR JAYENDER JAGADEESAN

SURGERY

The eyes of the operation

Real-time imaging of a patient's body is guiding surgeons and radiologists past healthy tissue to the diseased cells.

BY JESSICA WRIGHT

In 1988, when David Jaffray was a summer student, he watched as a team of surgeons prepared to treat a child with brain cancer, aiming carefully planned radiation treatment at a fuzzy X-ray image.

"I thought to myself, a huge amount of effort has gone into designing the treatment for this child, and we have all this technology and all these people standing around trying to get this right, and we can't see what we're doing," says Jaffray, a medical physicist at the Princess Margaret Cancer Centre in Toronto, Canada. He has worked ever since to engineer solutions to this problem.

Jaffray's experience shows that in many ways, doctors work in the dark. A suspicious lump of cancer looks exactly like the rest of the breast, for example. The prostate can hide a tumour that can evade multiple biopsies. But what the human eye cannot see, precision medical imaging can — whether it's magnetic resonance imaging (MRI) or computed tomography (CT), for example. For the past twenty years, researchers have worked to turn these scans into maps that reveal the hidden insides of a patient's body, guiding surgery or radiation therapy.

In 2003, Jaffray helped design the first radiation machine with a built-in CT scanner. This equipment allows radiologists to trace the outline of the tumour before each dose. The resulting confidence that they can avoid healthy tissue has allowed doctors to increase the dose of radiation. In the brain, imaging reveals not just the structural outlines of a tumour, but which parts can be cut out without dire consequences. And researchers are working to adjust these maps during surgery, so they update in real-time, moving and shifting along with the patient.

TUMOUR TOPOLOGY

Image guidance is particularly valuable for cancer treatment because it addresses the primary challenge: how to remove every last bit of a tumour while damaging as little healthy tissue as possible. Imaging during a breast cancer lumpectomy, for example, allows surgeons to remove the small 'breadcrumbs' of cancer that are often left behind, significantly reducing the risk of recurrence, says radiologist Ferenc Jolesz, director of the National Center for Image-Guided Therapy at Brigham and Women's Hospital in Boston, Massachusetts.

In the early 1990s, Jolesz pioneered the use of MRI in operations, taking scans during brain surgery for the first time. When this was successful, it became clear that the best way to guide treatment would be to combine as many forms of imaging as possible, says Jolesz. In September 2011, a grant from the US National Institutes of Health led to the Advanced Multimodality Image Guided Operating (AMIGO) suite — a three-room operating suite that includes an MRI scanner, a CT and positron emission tomography (PET) scanner, and an advanced three-dimensional ultrasound and navigation system.

Researchers are exploring how to combine the resources at AMIGO to refine treatments. Imaging during surgery can address the problem of overtreating early-stage tumours, such as those found during routine lung CT scans on smokers. Small lumps are difficult to locate so surgeons may end up removing large pieces of lung tissue that will never grow back, says Raphael Bueno, a thoracic surgeon at Brigham and Women's Hospital. As part of an ongoing clinical trial, Bueno has devised a method to use a CT scan to guide the placement of a small

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hook-like device in the lesion. The hook is attached to surgical thread that reaches out of the lung. During surgery the thread acts as a guide, allowing Bueno to snip out only the affected tissue.

But nowhere is accurate targeting more essential than in the brain, where the neurons that control key functions may snake past a tumour or through the target site of epilepsy surgery. What's more, a tumour can reorganize the brain's function, shifting the neuronal connections. To address this, surgeons are developing ways to glean information from MRI scans — such as functional MRI (fMRI) or diffusion tensor imaging (DTI) — that map not only the brain's structure, but also its function.

Functional MRI highlights the parts of the brain that receive the most blood when patients perform a task, revealing which regions may be involved in certain functions. And DTI analyses the diffusion of water molecules in the brain that orient in the same direction as the long tracts of neurons. Researchers can turn these data into maps that paint brain tracts different colours according to their direction, identifying information highways once invisible to surgeons.

Using these scans to inform surgery has dramatically improved patients' outcomes, says Christopher Nimsky, a neurosurgeon at the University of Marburg in Germany. "Ten or twenty years ago we accepted that we would cause 10% or 15% new neurological deficits after surgery." Thanks largely to the use of imaging during surgery, he says, that figure is "now down to 2% or 3%, even in the complicated cases."

The functional maps, which doctors have begun to use routinely in the past five years, help them decide which patients would be too impaired by surgery to make it worthwhile. But they also give doctors the confidence to pursue more aggressive surgery in certain cases. Using DTI may reveal that although a tumour is in a functional region, it sits further away from essential neuronal connections than the surgeon originally thought, allowing them to remove more of the tumour or surrounding region.

These technologies were originally designed as research tools. Turning the data into maps that report on the location of important brain regions is complex and in many ways subjective. "The challenge is cutting to the core of what information the surgeon really needs," says Alexandra Golby, a neurosurgeon and researcher at Harvard Medical School in Boston, Massachusetts. "The clinician wants to ask, is that tract behind the tumour or running [through] the tumour? Which tracts am I likely to encounter on my way in? Is this area connected to that area?"

Many surgeons now routinely use Slicer, an open source software tool introduced in 1999 that combines structural MRI scans with fMRI and DTI data in three dimensions[1]. Shown all at once, the tracts produced by DTI analysis look "like a bowl of spaghetti", says Golby. In 2011, Golby added a module to Slicer that allows surgeons to isolate any of the tracts that pass through a boundary they have defined around the tumour. Surgeons can also highlight a particular spot in the brain, and view only those tracts that pass through it. During the operation, these maps may be combined with the surgical navigation guidance system, which uses structural data to show surgeons where they are in the brain.

One crucial feature is that the outlines traced on imaging scans accurately reflect the boundaries of the tumour. In fact, different scans, such as CT and MRI, may not even match each other, says Kristy Brock, a medical physicist at the University of Michigan in Ann Arbor. It's fascinating to see how different the tumours look on all these things," she says.

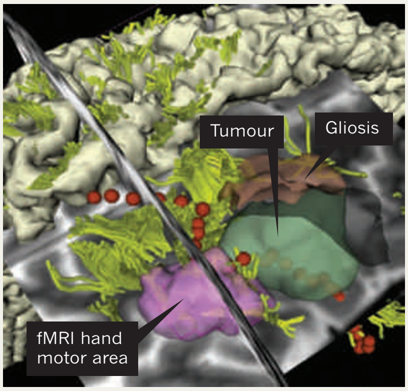
To get a better understanding of these outlines, Brock is working alongside radiologists, oncologists, surgeons and pathologists in a new field called correlative pathology. In one study, Brock and her colleagues took images of the liver before and after it was surgically removed. They then sliced it into sections, photographing each one to create a three-dimensional picture. Finally, they used histology to stain cancer cells a different colour from the rest of the tissue so they could identify the cancer at the cellular level in each slice[2]. By combining these layers of information, researchers can get closer to understanding how accurately MRI defines the boundaries of a tumour, says Brock. They can also compare different imaging technologies to determine which scan, or combination of scans, most accurately represents reality.

MAPPING IN REAL TIME

For even more precision, however, an imaging system should take into account the significant changes that occur during surgery. Once the skull is open, cerebrospinal fluid leaks out and the brain bulges from the skull. And as the surgeon cuts into the tissue, there are even more changes. With an MRI machine in the operating theatre, doctors can match the tract reconstructions with the shifting reality of a brain in an open skull.

LOCATE AND DESTROY

A 3D reconstruction using data from several imaging technologies reveals a tumour.



ALEXANDRA GOLBY; SONIA PUJOL, AND ISAIAH NORTON, BRIGHAM AND WOMEN'S HOSPITAL

The challenge is to take the surgical scan as quickly as possible and line it up accurately with the pre-surgical images, says Gavin Winston, a neurologist at University College London. Winston is aiming to do this for the optic radiation, a vision tract that often passes through the site targeted for epilepsy surgery. He has developed computer adjustments that allow doctors to take a second DTI scan during surgery and line this up with the existing DTI tracts in a matter of minutes[3].

This innovation can have real benefits for the patient's quality of life. Many patients opt for epilepsy surgery with the hope of qualifying for a driving licence. But damage to the optic radiation can impair their vision so much that they still can't drive, Winston says. His team has used this technique on 12 patients so far, and all 12 were able to drive after surgery.

> ***"It's fascinating to see how different the tumours look on all these things."***

But taking an MRI or DTI scan during surgery is extremely difficult, says Golby. "You have to stop, get the metal out of the way, and then move the patient into the scanner, or move the scanner over the patient," she says. "We've come to take it for granted that we can get these gorgeous pictures of the insides of people's bodies, but it takes a huge technical tour de force to do so." Golby is developing simpler methods to keep surgeons updated. One option is to use ultrasound, which is easy to use and cheap. Ultrasound provides much sparser data than MRI, she says, but may be sufficient to tell the surgeon when something significant has changed in the brain.

All these approaches allow researchers to consider each patient's biology and to base treatment on their unique response. "The idea that treatments can be more precise by integrating imaging is sort of obvious," says Jaffray. "But the technological advance that allows us to do that in a non-invasive way is pretty remarkable," he adds, considering how much the tumour changes shape over time. He envisages "fleets of multimodal treatment machines" that can make these adjustments consistently — systems that will, in effect, bring superhuman vision to those seeking to repair the human body. ■

Jessica Wright *is a freelance science writer based in New York City.*

1. Golby, A. J. *et al. Neurosurgery* **68**, 496–505 (2011).
2. Milot, L. *et al. Radiology* **254**, 747–754 (2010).
3. Winston, G. P. *et al. Epilepsia* **52**, 1430–1438 (2011).