



Maximilien Vermandel and his team deliver photodynamic therapy to a patient who has undergone surgery to remove a brain tumour.

MEDICAL DEVICES

Lighting up the brain

To combat brain cancer, neurosurgeons and oncologists will have to get creative. The latest innovations rely on light and electricity to fight the disease.

BY CASSANDRA WILLYARD

Seven years ago, Kenneth Coughenour started feeling dizzy and strange. “I felt like I was in a fog,” he says. His wife urged him to stay home, but Coughenour had meetings at the hospital in Gallipolis, Ohio, where he works as a recruiter. His physician told him it might be the lingering effects of a sinus infection, but sinus medication didn’t make him feel any better. Then, about a week after Coughenour first developed symptoms, he

collapsed in the shower. “My whole right side went paralysed,” he says. The paralysis lasted only a couple of minutes, and Coughenour managed to get dressed. But he collapsed again while walking out the front door. That’s when his wife called an ambulance.

A scan revealed a golf-ball-sized tumour that turned out to be a glioblastoma, a particularly aggressive, fast-growing brain cancer with a poor prognosis. And there was more bad news: Coughenour’s tumour was buried deep in his brain, making conventional brain

surgery impossible.

Coughenour was shocked. Earlier that week he had joked, “it’s probably just a brain tumour”, but he never actually believed it. At the time, Coughenour was just 48 years old and an avid biker. He’d never had any serious health problems.

The hospital sent Coughenour by ambulance 380 kilometres north, to the Cleveland Clinic in Ohio. Gene Barnett, a neurosurgeon there, confirmed that he couldn’t remove Coughenour’s tumour, but he might be able to kill it using

a procedure called laser interstitial thermal therapy (LITT). Barnett could drill a pencil-sized hole in Coughenour's skull, direct a laser beam into his brain and destroy the cancerous tissue using heat.

Barnett operated just days later, and the procedure went well. Coughenour also received chemotherapy and radiation therapy. Still, because of the severity of the disease, his doctors didn't expect him to survive much longer than a year. Glioblastoma nearly always recurs. Coughenour, however, defied the odds, remaining cancer-free for almost seven years. But in August, he found out that the cancer had returned.

Brain cancer is notoriously difficult to treat, but that has only made researchers more inventive. "There's a great deal of ongoing innovation for that very reason," Barnett says. LITT is just one of a handful of promising brain-cancer treatments that fall outside the conventional surgical and pharmacological therapies. Researchers are also using lasers to activate cancer-destroying drugs. And other groups are testing the use of electrical fields to interrupt the division of cancer cells. Although many of these therapies seem promising, researchers are still trying to determine exactly how effective they are, and which patients might benefit.

LASER FOCUS

Scientists have been studying the potential of using lasers to burn away solid tumours for decades, but "it was an idea that was ahead of the technology", Barnett says. There were two main problems. First, researchers had no way of monitoring how much tissue the laser was destroying. And second, the probe's bare fibre-optic cables would get so hot that they would char the surrounding tissue — and that singed tissue would insulate the rest of the cancer tissue from further damage. As a result, it was difficult to destroy the tumour.

Then, in the mid-1990s, a technology called magnetic-resonance thermometry became available. This enabled surgeons to track temperature changes in brain tissue during surgery. "You were monitoring the kill zone you were creating in real time, so that you could actually shape and create a lesion that matched the tumour you were trying to go after," says neurosurgeon Eric Leuthardt, director of the Brain Laser Center at Washington University's School of Medicine in St Louis, Missouri. Around the same time, researchers developed cooled probes, which solved the charring issue.

Today, two LITT systems are available for neurosurgery. A system developed by Visualase in Houston, Texas, and now sold by the medical-device company Medtronic in Minneapolis, Minnesota, was the first to be approved by the US Food and Drug Administration (FDA), in 2007. NeuroBlate from Monteris Medical in Plymouth, Minnesota, received clearance two years later. The two systems differ in how they direct light and how they use magnetic-resonance thermometry, but "the basic principle is the same", Barnett says. "Given enough

heat and enough time, you can kill tissue reliably." Both systems are approved as medical devices. "It's a tool, as opposed to a treatment or a therapy," says Emily Smith, marketing director for Monteris, but she adds that the company hopes to pursue FDA approval for specific indications in the near future.

LITT's main advantage over conventional surgery is that it's minimally invasive. Rather than removing a portion of the skull to access the tumour (a craniotomy), the surgeon needs only to drill a small hole. That shortens the recovery time. But neurosurgeons still prefer to remove tumours with a scalpel when it's feasible. For craniotomies, "we have many, many years of surgical data that tell us who benefits and when and why", says Shawn Hervey-Jumper, a neurosurgeon at the University of California, San Francisco. LITT doesn't have the same evidence base.

Researchers are still trying to sort out which patients might benefit from LITT. Since 2005, the standard of care for patients with glioblastoma has been surgery followed by 6 weeks of concurrent chemotherapy and radiotherapy, and then 6–12 months of maintenance chemotherapy. This is sometimes called the 'Stupp protocol' after Roger Stupp, a neuro-oncologist at Northwestern University's Feinberg School of Medicine in Chicago, Illinois, who headed the team that discovered its effectiveness. Leuthardt and Barnett, who both consult for Monteris, typically use LITT to treat recurrent tumours or those that are difficult or impossible to reach using conventional surgery. But there have yet to be any clinical trials comparing LITT to craniotomies, or chemotherapy and radiation.

Although LITT is minimally invasive, it can still cause side effects. The procedure tends to cause swelling and inflammation, which can

lead to neurological problems that are usually temporary but sometimes permanent. Conventional surgery causes inflammation, too, but because the tumour has been removed, there is more space for tissues to swell, whereas LITT leaves behind dead tissue. And although LITT seems like an obvious solution for deep tumours that can't be reached easily with a scalpel, Hervey-Jumper points out that these are also places where swelling can cause serious problems. "It has to be applied with caution," he says.

And there's another concern. In October 2017, Monteris issued a recall of the NeuroBlate system after the company noticed that, under certain rare circumstances, the probe could overheat and cause damage. According to Smith, this occurred in two cases. In May 2018, the FDA advised health-care providers to "strongly consider treating patients using alternative procedures if available".

Researchers are working to address some of these challenges. Monteris has developed an improved probe to correct the overheating issue, which should be available by the end of 2018. Barnett is excited about the possibility of marrying LITT to a brain-mapping technique called resting-state magnetic resonance imaging (MRI). This technology, which is more accurate than the widely used functional MRI, would allow researchers to create a map of the brain before surgery. With that map in hand, surgeons might be able to use LITT to remove tumours situated near areas that are important for speech and other crucial cognitive functions, he says.

COMBINATION THERAPIES

Lasers can destroy tumours, but they can also activate compounds or open up pathways into inaccessible areas. Leuthardt, for example, is

NOVOCURE



A patient wears the Optune device, which delivers low-voltage electric fields to the brain.

examining the possibility of combining LITT with new cancer-fighting drugs. His research suggests that LITT makes the blood-brain barrier more permeable for 4–6 weeks after surgery (E. C. Leuthardt *et al.* *PLoS One* **11**, e0148613; 2016), which could allow drugs that don't normally cross into the brain to penetrate (see S46). He and his colleagues are conducting a phase I clinical trial to determine whether they can take advantage of this unique window. LITT might also improve the efficacy of immunotherapies. Because the procedure leaves behind dead tissue, and because it creates a burn, “you actually may amp up the body's immune response to tumour antigens”, Leuthardt says.

Another technique, photodynamic therapy (PDT), relies on a light-activated drug called a photosensitizer. These drugs accumulate disproportionately in tumours and, when exposed to a specific wavelength of light, produce free radicals that destroy the cells. The idea is that the photosensitizer could be administered a few days before surgery. Once the tumour has been removed, the surgeon would shine a laser into the cavity to kill off any malignant cells that remain.

Because the photosensitizer accumulates only in cancer cells and the drug is activated only where the light shines, “what you have is this nice combination that avoids all systemic side effects, so you can be much more aggressive against the cancer”, says Harry Whelan, a neurologist at the Medical College of Wisconsin in Milwaukee. “Photodynamic therapy is kind of like a drug with a switch.”

The technology has been around for decades, but its development has progressed slowly. “It's kind of an orphan technology,” says Whelan. He thinks it's time for a fresh look: he and his colleagues have launched a phase II trial to test one photosensitizer called porfimer sodium (Photofrin) in patients with recurrent glioblastomas and other high-grade gliomas.

Meanwhile, Maximilien Vermandel, a medical physicist at Lille University Hospital in France, and his colleagues have developed a PDT device that consists of a laser inserted into an expandable, liquid-filled balloon. After the surgeon removes the brain tumour through conventional surgery, the balloon is inserted into the remaining cavity and inflated. The balloon expands to fit the shape of the cavity, allowing light to reach all the margins at once. The light diffuses through the liquid and activates a photosensitizer called 5-aminolevulinic acid. The hope is that any remaining cancer cells that weren't removed surgically will be destroyed when the light from the laser balloon hits them. The researchers are currently running a ten-patient trial to test the technology (C. Dupont *et al.* *Neurosurgery* <https://doi.org/10.1093/neuros/nyy324>; 2018).

Barnett points out two disadvantages of PDT. The procedure still requires open surgery to shine light onto the cancerous cells, and the light penetrates only a short distance into the brain. Although it can wipe out tumour cells

on the margins of the tumour cavity, “you really don't get a deep kill”, he says.

But Vermandel points out that 85% of all glioblastoma relapses occur in the first 5 millimetres of tissue surrounding the cavity. Vermandel is used to scepticism. His colleagues often tell him that PDT has already been evaluated and shown to be ineffective. But previous studies did not include standard-of-care therapies such as radiation and chemotherapy, he says. The ten-person trial he and his colleagues have launched, which has already enrolled nine people, will.

Evanthia Galanis, an oncologist at the Mayo Clinic in Rochester, Minnesota, notes that high-grade gliomas infiltrate the surrounding tissue. That's why a cure is so difficult to achieve. Both LITT and PDT kill cancer cells at the site of the tumour, but they don't have any impact on distant tumour cells. So whether these local therapies will improve long-term outcomes is still an open question, she adds.

ELECTRIC SHOCK

Some novel therapies, however, do treat the whole brain. Oncology company Novocure in St Helier, Jersey, has developed a system to deliver alternating electric fields to the brain to curb cancer growth. The therapy, called Optune, consists of an array of electrodes that attach to the scalp. Electric fields interfere with the ability of microtubules to form and pull apart DNA, and disrupt cell division. Because most brain cells aren't dividing rapidly, the technology doesn't harm other parts of the brain. “It's probably one of the more exciting areas right now,” Hervey-Jumper says.

Stupp first encountered the technology when Novocure showed it to him in the mid-2000s. Although sceptical, he agreed to help design studies to test the device's performance. The team first tested Optune in patients with recurrent glioblastoma. Half of the participants in a phase III trial received standard-of-care systemic therapies, and half received Optune alone. “What we could show at the end is the outcome is about the same,” Stupp says. But in 2017, the results of a second phase III trial in patients with newly diagnosed glioblastoma made a much bigger splash.

In the second trial, 695 patients were randomized to the Stupp protocol or the Stupp protocol plus tumour-treating electric fields (R. Stupp *et al.* *JAMA* **318**, 2306–2316; 2017). The group that received tumour-treating fields lived, on average, nearly five months longer than the group that received the standard of care alone. They also had a longer time before their cancer progressed, about seven months on average, compared with just four months for chemotherapy alone. At 2 years, 43% of patients who received Optune were alive, compared with 31% of patients in

“Given enough heat and enough time, you can kill tissue reliably.”



Kenneth Coughenour and surgeon Gene Barnett.

the standard-of-care group. “I was convinced the day I saw the survival curves,” Stupp says.

Side effects are typically mild, including itchiness where the electrodes attach. The main drawback is that patients must have their heads shaved and use the device 18 hours a day. That can be an irritation for some patients. “The fact that they're wearing this device can be quite obvious,” Galanis says. But at Northwestern, where the treatment is offered to all people with glioblastoma, “most patients will actually go for it”, says Stupp.

Optune received FDA approval in 2015 on the basis of an interim analysis of the phase III trial data. And in March 2018, the US National Comprehensive Cancer Network, which produces clinical-practice guidelines for cancer treatment, recommended Optune in combination with chemotherapy as a treatment for patients with newly diagnosed glioblastoma.

Leuthardt finds the idea of manipulating biology with electric fields rather than molecules exciting. “That's really a new way of thinking about biology,” he says. “I think you're going to see a lot more where that comes from.”

Any advances that improve or lengthen the lives of patients with brain cancer would be welcome news. Even with the best treatments, the prognosis for patients with glioblastoma is dismal. Coughenour knows that. But after almost seven years of clean scans, he was sure he had beaten the disease. Still, he remains optimistic. He started immunotherapy treatment in September. If that doesn't work, there might be other new therapies to try. Coughenour is counting on the inventiveness of the research community to help move the needle. ■

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