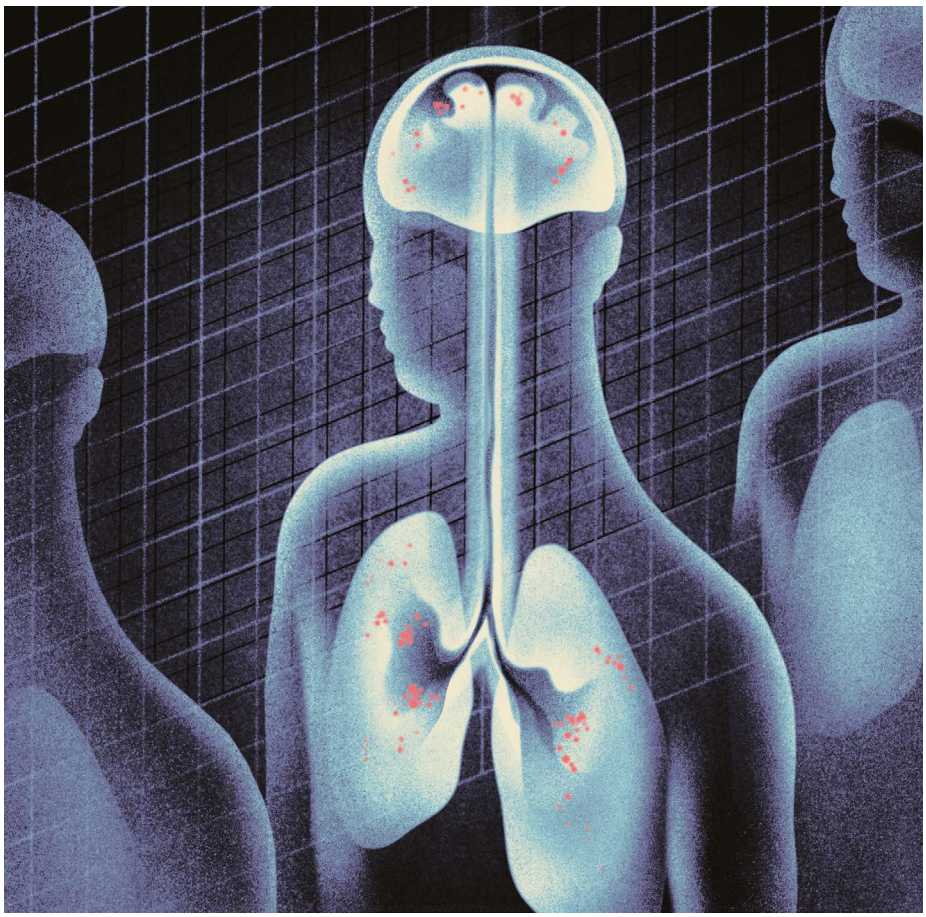
A deadly spread to the brain

Lung cancer commonly advances to the brain, leading to distressing neurological symptoms and a poor chance of survival. Better treatments are emerging for the disease, but will they help people with brain tumours? **By Natalie Healey**



DANIEL STOLLE

Lung cancer is bad enough if it doesn't spread to the brain. Only about one-fifth of people with lung cancer will live for five years after diagnosis. But for those who develop brain metastases, the already grim outlook is even worse. They will survive, on average, for less than six months.

When lung cancer reaches the brain it can cause headaches, seizures and paralysis. The tumours can also cause memory problems and mood swings – symptoms that frighten many people, according to Lizza Hendriks, a pulmonologist at Maastricht University Medical Center in the Netherlands. "People seem more afraid about metastasis in the brain compared to spread to other organs," she says.

Unfortunately, however, as many as 40% of people with lung cancer will develop brain tumours, and more brain metastases start out as lung tumours than any other type of cancer. But why the disease so often takes a journey to the brain has long been a mystery to clinicians.

Matthias Preusser, an oncologist at the Medical University of Vienna, says a nineteenth-century hypothesis proposed by English surgeon Stephen Paget is never far from his mind. In 1889, Paget wrote: "When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil." In reviewing hundreds of autopsy reports of women who died from breast cancer, Paget discovered that the disease most commonly spread to the liver, ovaries and bones. For breast-cancer cells, he surmised, these were the congenial soil.

Paget's 'seed and soil' findings were published[1] in *The Lancet*. His idea could help to explain why lung cancer is more likely than most to metastasize to the central nervous system. "It's possible the brain provides a 'soil' that is favourable to some types of cancers and they feel at home there for some reason," Preusser says.

Some modern-day evidence supports the idea, such as imaging work in mice that found that lung cancer flourishes in the brain by rapidly forming branches of blood vessels that provide sustenance[2]. But not everyone subscribes to the 130-year-old hypothesis. Another theory points the blame at nicotine from tobacco smoke (see 'Nicotine plays a dirty trick'). But whatever the mechanism, the spread from lung to brain is one of the most lethal forms of metastasis.

Radiate to eradicate

For many oncologists, the question is not what lies behind lung cancer's voyage to the brain but how to treat it when it gets there. Historically, the options have been limited. Oncologist Sarah Goldberg at Yale School of Medicine in New Haven, Connecticut, says obliterating a brain metastasis that has spread from the lung often requires the same approach as any other cancer in the central nervous system: kill it with radiation.

Whole-brain radiation therapy targets the entire organ, but eradicating the tumours comes at a cost. In the short term, the side effects include fatigue and nausea. "But longer term, the main concern is the cognitive side effects," says Goldberg.

Memory loss and other cognitive problems are common with this treatment and can be similar to the symptoms the therapy was intended to reverse. More worrying still is a rare phenomenon called radiation necrosis, which leads to the permanent death of the affected brain tissue and as a result causes symptoms such as seizures and personality changes. Targeted radiotherapy, often called stereotactic radiosurgery, spares a large proportion of the brain but does not always find and destroy all the tumours.

In the past five years, there has been a move away from whole-brain radiation to focus on

Nicotine plays a dirty trick

The tobacco-borne compound seems to smuggle lung cancer into the brain.

Cancer biologist Kounosuke Watabe at Wake Forest School of Medicine in Winston-Salem, North Carolina, thinks that metastatic brain tumours in lung cancer can be linked to whatever causes the disease in the first place, which for most patients is smoking. Cigarettes are responsible for more than 70% of lung cancer cases. Watabe and colleagues[6] examined data from nearly 300 people with lung cancer and found that tumours in the brain are more likely in those who smoke.

This is not a particularly surprising finding; scientists have long known that tobacco contains cancer-causing compounds. But Watabe then turned his attention to the more innocuous nicotine. "Nicotine is not a carcinogen per se, but it goes to the brain, and that's why people get addicted," he says. Giving nicotine to mice genetically engineered to be prone to lung cancer saw them develop more brain tumours than did a control group.

The reason for this, Watabe proposes, is that nicotine makes the brain a more receptive environment for lung cancer cells. The brain's microglia should destroy any potentially dangerous substances, but Watabe found that nicotine can bind to receptors on the microglia and drastically change their function. The compound switches the cells from an M1 (tumour-destroying) to an M2 (tumour-promoting) phenotype. The findings suggest that continuing to smoke after developing lung cancer, as up to 50% of smokers do, could increase the risk of brain metastases. Watabe also cautions that nicotine-replacement products (such as vaping, patches and gum) might not be the safest way to kick the habit.

One hopeful finding is a compound that could block nicotine's effect on the brain's microglia cells. Parthenolide, a naturally occurring substance found in a herb called feverfew, which is often marketed as a migraine remedy, seems to inhibit the tumour-promoting transformation in mice. But it is impossible to say whether it would do the same for humans until clinical trials confirm these initial animal findings. This will be the next step for Watabe's research.

systemic therapies, says Preusser. Some people who have brain metastases from non-small-cell lung cancer (NSCLC) – which accounts for about 85% of lung cancers – are now treated with the same drugs used to target the primary tumour in the lungs. The treatments are targeted at mutations such as epidermal growth factor receptor (EGFR) overexpression (found in 10–30% of white and up to 60% of Asian people with NSCLC) or anaplastic lymphoma kinase (ALK) translocation (roughly 5% of NSCLC cases), and they can be just as effective in the brain as in the lungs.

The revolution was slow in coming. Just a few years ago, people with brain metastases were commonly excluded from clinical trials for lung cancer drugs, says Hendriks. This meant that oncologists simply did not know whether targeted therapies could help if the cancer had spread to the brain. When early EGFR and ALK inhibitors for lung cancer were eventually tested, they did not always manage to cross into the brain. Some were stopped by the blood–brain barrier, a layer of endothelial cells that protects the neurons from potentially harmful substances in the blood.

Thankfully, newer ALK inhibitors, such as alectinib, ceritinib, brigatinib and lorlatinib, were designed to penetrate the barrier. And the EGFR inhibitor osimertinib reaches the brain more easily than older drugs in the same class. "A decade back, when someone developed brain metastases from lung cancer, survival would be in the ballpark of six to nine months," says neuro-oncologist Manmeet Ahluwalia at the Cleveland Clinic in Ohio. "Now, with these targeted therapies, the median survival is four to five years for patients who have ALK-driven lung cancer."

An immune attack

There is also much excitement around using immunotherapy drugs to treat lung cancer, which is Goldberg's focus. These harness the body's immune system to attack the cancer cells. Surprisingly for such large molecules, some are able to cross the blood–brain barrier. Goldberg and colleagues[3] found that pembrolizumab works as well in the central nervous system as in the rest of the body. "We were really encouraged by this," says Goldberg. "It shows us that it's not just the targeted therapies that can have activity in the brain, but immunotherapy can as well."

Pembrolizumab is an antibody that works by targeting a checkpoint protein called PD-L1, which normally calms down the immune system to prevent autoimmunity, for example. Tumours can thereby use PD-L1 as a kind of molecular invisibility cloak to evade the immune system (see page S10). Goldberg found that pembrolizumab elicits a response in tumours expressing even small amounts of PD-L1 (more than 1%), but larger trials comparing pembrolizumab and radiation are needed to see whether antibody therapy alone is enough to keep brain tumours at bay in lung cancer.

These developments provide more options for people with NSCLC whose cancer has spread to the central nervous system, but Ahluwalia does not think they will make radiation obsolete. He suspects that a combination of the two approaches will probably become best practice, where medication is given depending on the type of lung cancer, and targeted radiosurgery is used to mop up any brain tumours that do not respond.

It would be even better if brain metastases could be blocked from the start. Preclinical work is needed to understand the molecular mechanisms behind why they often develop in lung cancer. Preusser has contributed to a study[4] that tracked mutations in people with a common type of NSCLC called adenocarcinoma. The researchers found that brain tumours contained more copies of the *MYC*, *YAP1* and *MMP13* genes than did cancer in the lungs. And experiments using mice at University Hospital Hamburg-Eppendorf in Germany indicated that elevated levels of a gene encoding a cell adhesion molecule called ALCAM help lung cancer tumours to cosy up to the brain's vascular endothelium[5]. It follows that inhibiting these genes might stop lung cancer making itself at home in the central nervous system.

"It's not just the targeted therapies that can have activity in the brain but immunotherapy can as well."

Such research is still in its infancy, but Preusser says the findings suggest that Paget's seed-and-soil theory should not lie fallow. "At the moment we basically wait until brain metastases are there and then treat them. But my hope is that if we have a better understanding of how they form, we can prevent them from growing in the brain in the first place."

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