SARA MA, USC CSI-CANCER

Scientists can use liquid biopsies to determine whether lung cancer has started to spread round the body.

Liquid assets

Measurements of the number of circulating tumour cells in the blood could help oncologists to determine the best treatment for their patients with lung cancer and improve survival times. **By Benjamin Plackett**

Lung cancer research is finally beginning to benefit from a nineteenth-century medical discovery. Circulating tumour cells (CTCs) were first proposed[1] to be required for a cancer to spread by an Australian pathologist, Thomas Ashworth, back in 1869.

At the time, it simply was not possible to detect CTCs with any clinical precision because their concentrations in the bloodstream are so low. Typically, someone with lung cancer has just one to ten CTCs per millilitre of blood. "You're looking for a few CTC cells in tens of millions of blood cells," says Harry Groen, a thoracic oncologist at the University of Groningen Medical Centre in the Netherlands. "That's a tough thing to do."

CTCs are cells that have broken free of the primary tumour to circulate in the bloodstream. Their presence is an indication that the cancer could be spreading through the body. Techniques that have been developed in the past few years have improved the specificity and sensitivity of CTC assays, making the detection of circulating lung cancer cells more accurate. Doctors hope to use these liquid biopsies to enhance the way they monitor the progression or remission of lung tumours. This could be particularly useful after surgery, when scar tissue can make low-dose computed tomography (CT) scans difficult to read.

Several papers published this year show that higher CTC concentrations correspond to poor outcomes in people with lung cancer[2–4]. This is the first step towards making the technique part of routine clinical practice. But lung cancer specialists are already planning how to push the technology a step further. They hope to use CTC audits to predict the best treatment options for their patients with lung cancer and thereby improve the survival rate of what is the world's deadliest cancer.

Currently, a diagnosis of lung cancer begins with a CT scan followed by a biopsy to confirm it. The system works pretty well, but monitoring the lung cancer during and after treatment is more difficult, says Gary Kao, a radiation oncologist at the University of Pennsylvania in Philadelphia. "After treatment, be it surgery or radiation, CT scans are harder to read because the anatomy has been disturbed," he says. "You have parts of the lung which are underinflated, and you also have scarring."

As an alternative, researchers hope to use liquid biopsies that measure the concentration of CTCs in the blood to monitor the effects of treatment and warn of potential relapses. "I've been an oncologist for about 30 years and this is the most exciting time for lung cancer research in my career," says Kao.

PETER KUHN, USC MICHELSON CSI-CANCER

Making it count

Because CTCs are short-lived, their presence in small numbers is not a cast-iron guarantee that the disease is escalating rapidly. "You can have an early-stage disease that gives off CTCs, but it doesn't mean that person is doomed," says Kao. Before CTC levels can be used to track lung cancer, scientists must show that high CTC levels really do lead to an increased risk of relapse and a poor prognosis.

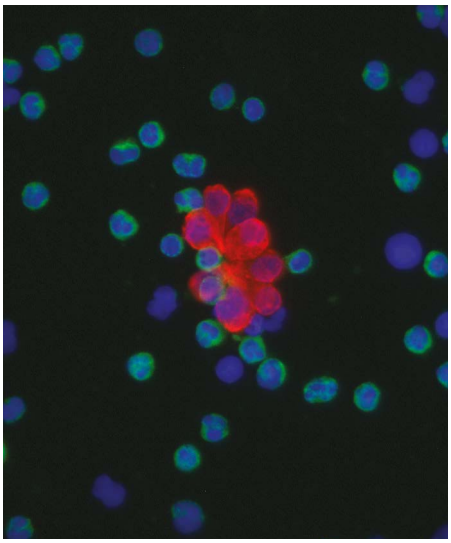
Earlier this year, Kao showed[2] that there is a link between CTC concentrations and patient outcomes. He studied 92 patients in the first stage of lung cancer who were about to be treated with radiotherapy, and measured their CTC levels before, during and up to two years after the treatment. He defined a positive result as the presence of five or more cells per millilitre of blood, although he concedes that this number was arbitrary. "We're building a sense of a threshold for lung cancer CTCs, but we're still trying to pin it down," he says. "I can't promise it won't change in the coming years."

The results showed, unsurprisingly, that higher CTC levels both before and after treatment were significantly associated with an increased risk of relapse.

A second study[5] took blood samples from 104 surgical patients at an early stage of lung cancer. The results confirmed that high CTC levels correspond with a lower survival rate. Noriyoshi Sawabata, a thoracic surgeon at Nara Medical University in Kashihara, Japan, who led the study, says the findings mean that CTC monitoring has a clinical future. "I would like to see CTC tests become routine as they correspond with patient outcome," he says.

Tailored treatments

There is plenty of evidence that high levels of CTCs in lung cancer are an accurate predictor of worse outcomes. "The essential question is then, of course, how does this change your management of the disease?" says Kao. He hopes that liquid biopsies will one day be able to identify the best therapy for each particular patient.



Circulating tumour cells (red, seen here with some immune cells) help cancer to spread.

"CTCs are a very strong way to monitor lung cancer but the problem is they aren't predictive, just prognostic," Groen says. "That means they tell you how bad or good things are, but most clinicians want something that also predicts the best way to treat it."

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Realizing the predictive potential of CTCs might require a series of studies that follow cohorts of patients with lung cancer who are given different treatments on the basis of their CTC levels. If such trials could consistently show that patients live longer when their CTC data are factored into treatment decisions, that would strongly favour making CTC measurements a routine intervention.

But these studies will take time, cautions Peter Kuhn, a medical biologist at the University of Southern California in Los Angeles, whose research focuses on how cancer spreads. "A liquid biopsy test as a specific decision-making diagnostic has to go through the same rigour of trials as a drug," he says.

Similar trials already underway for other cancers could act as a template for lung cancer. For example, a recent study[6] looked at 193 men with already-worsening prostate cancer. The researchers measured their CTC levels before doctors chose whether to prescribe either an androgen receptor signalling inhibitor (ARSI) or chemotherapy using the drug taxane (the doctors were not told the CTC results before they made their clinical plans). The patients were followed for up to three years after their treatment.

Patients with detectable levels of CTCs had a better chance of survival when treated with taxane as opposed to ARSIs. Conversely, patients whose CTC tests were negative had better survival rates when given ARSIs. The researchers concluded that results from CTC tests could be used to improve treatment choices for people with prostate cancer. Other studies of prostate cancer have shown similar results.

If studies of patients with lung cancer also find that the best treatment depends on their CTC levels, doctors can see whether this helps patients to live longer. But the studies will be more complicated than the one on prostate cancer, which considered only two therapy options. "We now have dozens of choices in most cancers," says Kuhn.

Before oncologists can be sure that liquid biopsies will improve their patients' chances of survival, they will need to explore almost every treatment option for every cancer in the same way. This will take time and money, and CTC tests are not cheap – one widely used assay costs US$350, for example.

"CTC examination probably has to be carried out again and again throughout the treatment of the cancer," says Sawabata, so the cost will soon mount up over the course of the therapy.

The road ahead for liquid biopsies in the treatment of lung cancer is a long one. But the first steps have already been made, with technology that can accurately measure CTCs and studies that show that high CTC levels correspond to poor outcomes.

If researchers continue to build on these findings, a more personalized approach for the treatment of lung cancer, based on the number of CTCs, could help to improve survival rates for a disease that continues to kill about two million people a year.

Benjamin Plackett is a freelance science journalist in London and the Middle East.

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