Cataloguing the genetic chaos in oesophageal cancer

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On the 27th of September 2013 Tracy Collinson's world turned upside down. Seemingly out of nowhere, her husband Nigel – father to their two young boys – was diagnosed with oesophageal cancer.

Just twelve weeks later he died in her arms.

It's a heartbreaking story and one that we hear all too often. More than half of all people diagnosed with oesophageal cancer survive less than a year. And although rates are increasing – particularly in men – survival has barely changed in decades.

It's a grim picture that urgently needs to change, which is why it's one of the cancers we're prioritising as part of our research strategy.

We've already written about some of the pioneering work we're funding to diagnose oesophageal cancer earlier, but that's not the only angle we're exploring.

A new study from Professor Charles Swanton and his team at the Francis Crick Institute, published in the journal *Cancer Discovery*, is unpicking the complex genetic chaos that underpins advanced oesophageal cancer, helping us to understand the disease in ever greater detail and pointing towards potential ways to treat it more effectively.

Tracking tumours through time and space

It isn't the first time we've covered the important and exciting research coming out of Swanton's lab. For example, we recently wrote about his work mapping the genetic diversity in different types of cancer, and he's pieced together the evolutionary histories of kidney, lung and bowel tumours.

This time he's turned his attention to oesophageal cancer. Led by clinical fellow Dr Nirupa Murugaesu, Swanton and his team have been studying the detailed genetic makeup of multiple samples from tumours in eight patients, taken before and after chemotherapy with the drug cisplatin.

By tracking the genetic changes in tumours across space – i.e. in several different regions of each tumour – and time (before and after chemo), the researchers have built a detailed picture of how each cancer has evolved within the body from a single faulty cell to an aggressive tumour.

So what did they find?

Unpicking the patchwork

As we've come to expect from studies in other cancer types, their analysis revealed that each tumour is made up of a patchwork of related but genetically distinct 'families' of cells – a phenomenon known as heterogeneity. All the groups share certain gene faults (mutations) in common, which were presumably present when the tumour first started, but each has its own genetic errors that arise as the cancer grows and changes within the body.

Taking a closer look at the data, a few interesting observations popped out.

Firstly, many of the mutations found across all cells within the tumours –

which must have arisen early on – bore the characteristic molecular fingerprints of acid damage, caused by stomach acid washing back up onto the cells at the bottom of the oesophagus. This is a known risk factor for oesophageal cancer, which is why anyone with persistent heartburn should get it checked out by their GP. However, alterations that came later and were only found in certain groups of cells seemed to have been caused by more general cell processes that had gone awry.

Importantly, these later mutations tended to be found in genes that can be targeted by currently-available 'smart' drugs, designed to home in on specific faulty molecules in cancer cells. But if the faults are only present in a subset of the cells, rather than the whole tumour, it means that these therapies are unlikely to completely eradicate the disease.

They also found that the tumours with more complex genetic patchwork, made up of many genetically diverse groups of cells, were more aggressive and less likely to respond to cisplatin chemotherapy than simpler cancers.

Driving drug resistance

Next, the team took a closer look at samples from five patients taken before and after cisplatin treatment.

The drug works by damaging the DNA in cancer cells, so they can no longer multiply and eventually die. But in some cases tumours can develop resistance to its effects, coming up with ways of repairing the damage and continuing to grow unchecked.

It's not surprising that Swanton and his team spotted the signature of cisplatin damage in the DNA from tumour samples after treatment. This suggests that chemotherapy itself was causing new mutations within the resistant tumours, potentially making a bad situation worse.

On the plus side, they also found many gene faults that were present throughout each cancer both before and after treatment, which could potentially be targets for new drugs.

Where next?

This study highlights a few different future directions that could help oesophageal cancer patients.

Firstly, the team's findings show that genetic testing could help doctors identify patients whose cancers have relatively little heterogeneity, and are therefore more likely to benefit from cisplatin. This means that people with more diverse, aggressive tumours would avoid treatment that's unlikely to work, along with the side effects of the drug and the risk of creating further genetic chaos.

This is something that needs testing in larger groups of patients, to see if it helps to get the right treatment to the right patient and increases survival.

It also means that we need to find alternative approaches for those patients who aren't suitable for chemotherapy. Targeted therapies are one idea – for example, there's some evidence that the drug Herceptin, which targets an overactive molecule on the surface of some cancer cells, might help a relatively small group of patients. But if, as Swanton's team have found, these faults tend only to be found in a fraction of all the cancer cells, they're not going to work that well.

Instead, we need to focus on finding therapies that target the mutations that are common to all the cancer cells in a person's body, in the 'trunk' of the tumour's family tree. Unfortunately, it's been very difficult to develop effective drugs that target these fundamental cancer drivers – such as p53 and Ras – but a few promising candidates are being tested in

clinical trials.

The researchers also noticed that single samples from a tumour revealed far less heterogeneity than multiple biopsies, which isn't unexpected as we already know from Swanton's previous work that the genetic makeup of individual tumours can vary over relatively small distances. This has implications for using genetic testing to guide personalised therapy, suggesting that only multiple samples will give a true picture of the levels of genetic diversity within a cancer.

More broadly, research like this is illuminating the previously impenetrable genetic chaos in cancer. The challenge now is to sift through all the data and look for underlying patterns that might allow doctors to predict how an individual patient's disease is likely to change over time – effectively writing what Swanton calls the 'rulebook' of cancer evolution.

And by understanding more about how tumours become resistant to therapy – and how treatments such as chemotherapy and radiotherapy affect them – we can start to use this knowledge to our advantage, predicting cancer's next move in advance and picking the best approach to beat it.

Figuring out the complex molecular changes that drive oesophageal cancer is a huge task. It feels like we're only starting to scratch the surface, but it's the only way we will truly understand the disease and be able to tackle it more effectively – and that can't come soon enough.

As Tracy Collinson says: "Nigel was a big character, full of positivity and energy and often was heard saying, 'just when you are about to give up, dig a bit deeper.'"

For the sake of Tracy and her family, and all the other families who have

lost their loved ones to this brutal disease, we will keep digging.

More information: "Tracking the genomic evolution of esophageal adenocarcinoma through neoadjuvant chemotherapy," *Cancer Discovery* (2015), DOI: 10.1158/2159-8290.CD-15-0412

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