Circulating tumour DNA as a prognostic tool in prostate cancer

Metastatic prostate cancer is associated with various changes occurring in the DNA. Sequencing tumour DNA from solid tumours is useful but challenging, mainly because sampling solid tumours is an invasive procedure. Dr Manish Kohli, from the Huntsman Cancer Institute at the University of Utah, uses circulating tumour DNA – DNA from tumour cells that freely circulates in the bloodstream and is therefore easily accessible – to identify genomic alterations and assess their clinical relevance in patients with different stages of prostate cancer. His team's findings, which was an international, multi-institutional collaboration as well as an academia-industry collaboration, may be helpful in prognosis and in selecting patients for treatment.

Prostate cancer is one of the most common cancers among men; it is estimated that about 1 man in 8 will be diagnosed with prostate cancer during his lifetime. Each year, globally, 1.26 million cases are reported.

The prostate is a walnut-sized gland found in men and located below the bladder. It produces a fluid that gets mixed with sperm to create semen. In most cases, when cancer develops in the prostate, it grows slowly and remains confined to the prostate gland. These types of cancers may not cause serious harm and may need minimal or even no treatment. However, if the prostate cancer is aggressive it can spread quickly. They are then referred to as metastatic prostate cancers.

ANDROGEN DEPRIVATION THERAPY

Androgens, such as testosterone, are hormones that promote the development and maintenance of the male reproductive system. These hormones are required for normal growth and function of the prostate. They act by binding to the androgen receptor, a protein that is expressed in prostate cells. Binding activates the androgen receptor, which then stimulates the expression of specific genes that cause prostate cells to grow.

However, androgens are also necessary for the growth of prostate cancer cells. Depriving cancer cells of androgens is therefore a way to fight prostate cancer. Androgen deprivation therapy (ADT) is coupled with radiotherapy (which aims to kill cancer cells with radiation) to treat prostate cancer. ADT consists in a chemical castration. It involves antiandrogens, drugs which block the androgen receptor, or inhibit or even suppress androgen production. As a result, levels of androgens are reduced, which prevents prostate cancer cells from growing.

DIFFERENT STAGES OF PROSTATE CANCER

Prostate cancer can be more or less aggressive. It can also evolve. The more it grows, the more difficult it is to stop, which is why an early diagnosis is always preferable.

Early in their development, prostate cancer cells need relatively high levels of androgens to grow. This makes them sensitive to ADT: decreasing androgen levels or blocking androgen activity effectively inhibits their growth. Such prostate cancers are called hormone sensitive. Eventually, however, prostate cancer treated with ADT can evolve. It acquires the ability to grow even when androgen levels in the body are extremely low or even undetectable. At this point, ADT is ineffective. We then talk about castration-resistant prostate cancers.

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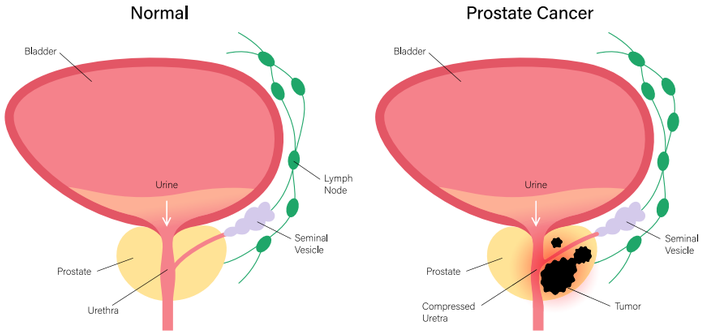


In most cases, tumour cells in the prostate grow slowly and remain confined to the prostate gland. However, if the prostate cancer is aggressive it can spread quickly, and may cause serious harm.

As prostate cancer evolves from hormone sensitive to castration resistant, it stops responding to ADT. This starts with a biochemical failure. Prostate-specific antigen (PSA) is a protein made by prostate cells (both normal and cancer ones). A small amount of PSA is found in blood. Measuring blood PSA levels is used as a screening test because, in case of prostate cancer, levels increase. ADT lowers PSA levels in hormone-sensitive prostate cancer. When cancer becomes castration-resistant, however, PSA levels increase again. This is when we talk about biochemical failure: biochemical failure is defined as rising blood PSA levels.

On an average estimate, nearly eight months after biochemical failure occurs, radiographic evidence appears on X-rays and CT scans. Following this, clinical symptoms start which worsen as more new metastases appear.

GENOMIC ALTERATIONS

Genomic alterations are changes that occur in the DNA. They can be mutations (changes in the DNA sequence of a gene), or amplifications or deletions of whole genes (genes are duplicated or cut out). These alterations accumulate and eventually transform healthy cells into cancer cells.

Genomic alterations that cause prostate cancer usually affect specific genes. Each stage of prostate cancer is associated to a range of potential genomic alterations that cause them. However, it is unknown how the genomic landscape evolves from hormone-sensitive to castration-resistant prostate cancer. It is also unclear how mutations impact clinical outcomes. Dr Manish Kohli and his team followed metastatic prostate cancer patients over 9 years with the aim to shed light on these matters.

The team performed blood circulating DNA measurements and followed hundreds of metastatic prostate cancer patients over several years using a targeted panel of 120 cancer genes (PredicineLDT® panel).

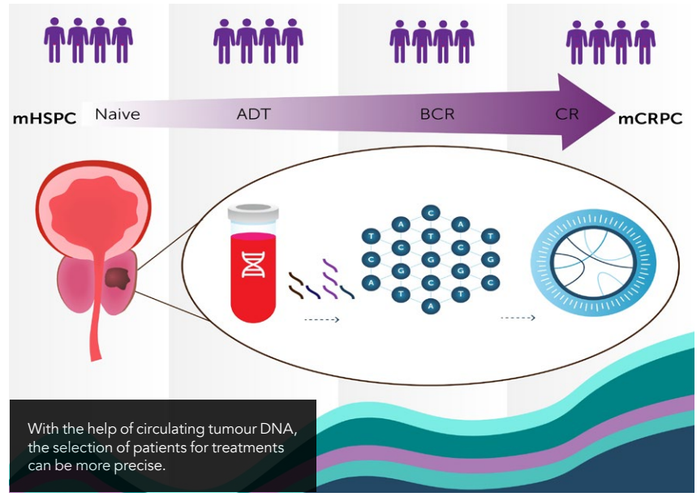
CHALLENGES IN TUMOUR SEQUENCING

To identify the genomic alterations involved in cancer, a biopsy is usually performed: a sample of the tumour is collected. This sample, which contains cancer cells, is then analysed. DNA from cancer cells is sequenced and compared to DNA from healthy cells so that differences can be identified.

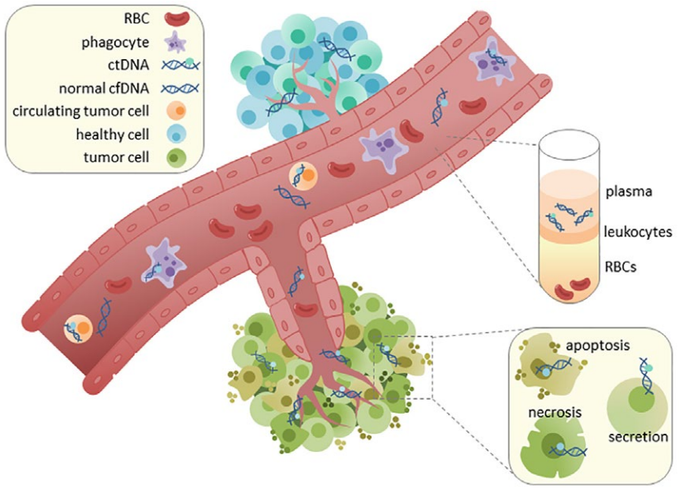
Using this technique, Dr Kohli's group has previously sequenced DNA from solid metastases in patients with castration-resistant prostate cancer. However, isolating DNA from solid tumours is challenging. Also, the biopsy itself is challenging as getting samples from solid tumours is an invasive procedure. It is so invasive that performing serial biopsies, which is necessary to study how the genomic landscape evolves, is unfeasible. These challenges can be addressed by using circulating tumour DNA instead of performing solid tumour biopsies.

CIRCULATING TUMOUR DNA

Circulating tumour DNA is DNA that originates from a tumour cell but, instead of being contained inside the cell nucleus, freely circulates in the bloodstream. The precise mechanisms are still unclear, but it is believed that fragments of DNA are released when a cancer cell dies.



With the help of circulating tumour DNA, the selection of patients for treatments can be more precise.



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Circulating tumour DNA is DNA that originates from a tumour cell but, instead of being contained inside the cell nucleus, freely circulates in the bloodstream. The release mechanism is unknown, though apoptosis, necrosis, and active secretion from tumor cells have been hypothesised.

While there are still unanswered questions about the presence of tumour DNA in blood, circulating tumour DNA is useful. These fragments of DNA can be collected through a simple blood collection. Because they reflect the tumour genome, they can be sequenced and used to identify genomic alterations. Monitoring tumour progression and the evolution of the genomic landscape is therefore possible with circulating tumour DNA.

The team followed hundreds of metastatic prostate cancer patients over years. Patients were divided into different groups depending on their cancer stage. They found that the quantity of circulating tumour DNA in blood was higher in patients with castration-resistant cancer than in those with hormone-sensitive cancer. This was associated with lower overall survival (length of time patients diagnosed with cancer are still alive).

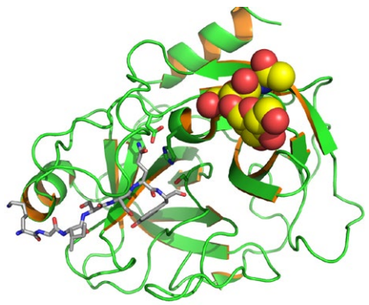
DNA CHANGES

Sequencing circulating tumour DNA from patients allowed Dr Kohli and his team to identify genomic alterations in each patient. Some genes are more likely to be affected than others. Genomic alterations also differ depending on cancer stage.

Among the most frequently altered genes are the androgen receptor gene (AR), tumour-suppressor genes, genes involved in cell division, in cell differentiation, and in DNA repair. Multiple mutations were identified in these genes, and a higher number of them was detected in patients with castration-resistant prostate cancer.

One of the most common genomic alterations is AR gene amplification: multiple copies of the gene are present in tumour DNA, leading to a potentially greater number of androgen receptors in tumour cells. This is mostly visible in patients with castration-resistant prostate cancer.

Dr Kohli and his team found correlations between genomic alterations and clinical outcomes.



Prostate-specific antigen (PSA) is a protein made by prostate cells. A small amount can be found in blood; in the case of prostate cancer, its levels in the blood increase. Measuring blood PSA levels is used as a screening test.

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Tumour-suppressor genes slow down cell division and repair DNA when alterations occur, and therefore hamper tumour progression. The team led by Dr Kohli observed that, in prostate cancer (both hormone-sensitive and castration-resistant), a number of these genes was deleted.

On the contrary, genes named proto-oncogenes modulate cell division and differentiation in a way that favours tumour progression. Dr Kohli's group detected amplifications of these genes in patients with both hormone-sensitive and castration-resistant prostate cancer.

CLINICAL RELEVANCE OF GENOMIC ALTERATIONS

Dr Kohli and his team found correlations between genomic alterations and clinical outcomes. The first finding is that, in patients with hormone-sensitive prostate cancer, ADT failure occurs sooner when the quantity of circulating tumour DNA is higher. Mutations in multiple DNA repair genes are also associated with shorter time to ADT failure and lower chances of survival.

In patients with castration-resistant prostate cancer, mutations in a tumour-suppressor gene named *TP53*, the deletion of tumour-suppressor gene *RB1*, and *AR* gene amplifications, correlate with poorer chances of survival.

PROGNOSIS AND SELECTING PATIENTS FOR TREATMENT

These findings indicate that circulating tumour DNA, which is easily collectible, can provide information about prognosis, cancer stage and treatment failure.

Until now, the selection of patients for treatments in addition to ADT has been guided using clinical prognostic factors such as the Gleason Score (a score commonly used to grade prostate cancer) and the presence or number of metastases. Dr Kohli's findings may allow this selection to be more precise in the future, thanks to the information provided by circulating tumour DNA.

Behind the Research

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Research Objectives

Dr Kohli's research provides insights into key genomic perturbations.

Detail

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Bio

Dr Manish Kohli presently holds the Jack R. and Hazel M. Robertson Presidential Endowed Chair at Huntsman Cancer Institute. Prior to this, he was Director of the DeBartolo Family Precision Medicine Institute at Moffitt Cancer Center in 2019 and Professor of Oncology at Mayo Clinic from 2008-2018. As a cancer clinician/researcher, Dr Kohli focuses on integrating biomarker(s), nano- biosensor development and clinical trials.

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Personal Response

What are your next research aims?

"After studying this mutational landscape across the spectrum of cancer progression in prostate cancer, our on-going research will now focus on individual aberrations that we have identified and develop tests that have clinical utility and value. Our overarching goal is to deliver cancer care in a way that is precise, based on individual patient-based aberrations and is low cost for the patient."

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