Not all high-grade prostate cancers are the same.

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By Dr Jacqueline Schmitt - Manager, Research Programs for PCFA

In a recent study, researchers have found that not all high-grade prostate cancers are the same. The research examined Gleason grade group 5 prostate cancers which are associated with aggressive disease and poor outcome and found that some cancers of this type were more aggressive than others based on differing patterns of gene expression. This is important work that may one day help clinicians decide how best to treat different subgroups of Gleason grade group 5 prostate cancers. The advantage of this is that men with less aggressive cancers may be spared the side effects of intensive treatment while those with more aggressive cancers receive intensive and more targeted treatment.

What does Gleason grade group 5 mean?

To determine a prostate cancer diagnosis, clinicians will perform several tests to ascertain how aggressive the tumour is and how likely it is to spread. This information will help them decide how to manage and treat the disease. Some of these tests include imaging (MRI or PSMA PET scans), biopsies (taking samples of prostate tissue for analysis), digital rectal exams and blood tests such as the PSA test. From these tests, the cancer stage and grade can be determined which provides an estimate of how quickly the cancer will grow and if it will spread.

The **Gleason grading system** is the most commonly used method for prostate cancer grading. Gleason grading is done on prostate biopsy samples. During a biopsy, a hollow needle is inserted into the prostate gland and a small sample of tissue is removed. Many samples are taken from different regions of the gland to help establish how much of the prostate is affected by cancer.

By examining thin slices of biopsy samples under a microscope, the pathologist can distinguish normal prostate tissue from prostate cancer. Normal prostate tissue has an ordered pattern of growth, but in cancer tissue, the pattern is not ordered because of the unpredictable way cancer cells grow. These different patterns, called **Gleason patterns**, are given numbers. Pattern 1 looks like normal prostate tissue - closely packed and well-formed glands. Pattern 3, which is the most

common, has recognisable glands but some abnormal cells. Pattern 5, which indicates the most aggressive cancer, has lots of invading cells and no recognisable glands. To work out the grade of the cancer, the pathologist determines the most common and second-most common patterns. The Gleason pattern numbers for these two are added together, to derive the final **Gleason score**. For instance, if the most common pattern is Gleason pattern 3, and the second most common is Gleason pattern 4, then the final Gleason Score is 3+4=7.

In Australia the Gleason system is the most commonly used grading system, but increasingly a new grading system called the **ISUP Grade Group** system is being used. This new system is a modification of the Gleason score system. It was developed in the United States based on research involving tens of thousands of men. It is easier to understand and is more accurate than the Gleason system for predicting how quickly the cancer will spread and the chance of death.

The ISUP Grade Group system uses five grades. Grade 1 is the least aggressive and Grade 5 is the most aggressive:

- **Grade group 1** (Gleason score 6 or less): Low risk; the cancer is slow growing and less aggressive
- **Grade group 2** (Gleason score 3+4 = 7): Intermediate favourable; the cancer is moderately aggressive
- **Grade group 3** (Gleason score 4+3 = 7): Intermediate unfavourable; the cancer is moderately aggressive
- **Grade group 4** (Gleason score 8): High risk; the cancer is fast growing and aggressive
- **Grade group 5** (Gleason score 9 or 10): The highest risk; the cancer is fast growing and aggressive

The ISUP Grade Group helps clinicians decide how best to manage and treat the cancer. More information on this grading system can be found in our previous blog article on this subject.

But not all Grade Group 5 cancers are the same.

Although Grade Group 5 cancers (Gleason score 9 and 10 cancers) have similar features when examined under a microscope, a recent study published in the journal European Urology suggests that they are quite different when their gene expression patterns are examined. This study was led by researchers at the University of California Los Angeles (UCLA).

In this study, researchers examined prostate cancer tissue samples from 2138 patients with Grade Group 5 prostate cancer. The researchers wanted to know if there were differences in gene expression patterns between the patient samples and if these differences affected the patients' prognosis and long-term outcome.

Gene expression patterns (profiles) are determined by looking at the products of genes called RNA. When a gene (made of DNA) is activated, it serves as a template to create an RNA molecule in a process called gene transcription. The RNA in turn serves as the template to create the specific protein product encoded by the original gene. Through examining the different types of RNA molecules present in a cell, researchers can define the expression pattern or profile for that cell. Comparing the gene expression profiles of normal cells with cancer cells, provides insight into the changes that occur in cancer cells that could be contributing to their behaviour.

The UCLA researchers compared the expression profiles of different patients with Grade Group 5 prostate cancer. To do this, they used sophisticated microdissection techniques to dissect cells from Gleason pattern 5 areas of prostate cancer biopsy tissue. They then extracted RNA from the cells which was used to determine the gene expression profiles. The scientist also used data and information available from a previous clinical trial called GRID (Decipher Genomics Resources Information Database) which was conducted from 2014 to 2017.

After comparing the expression profiles for 2138 patients, the researchers found four distinct groups or clusters based on specific expression profile information. Cluster 1, they referred to as a high genomic risk cluster. This cluster seen in 325 of the patients (15%) had expression profiles enriched for genes related to the cell proliferation, metabolic pathways, androgen response pathways, and DNA repair, and had a higher average genomic risk than the other clusters.

Cluster 2, with the lowest genomic risk, was seen in 383 of the patients (18%). This cluster was associated with expression of genes important for immune response and various other metabolic pathways.

Clusters 3 (624 men, 29%) and 4 (806 men, 38%) showed an intermediate pattern of gene expression compared to clusters 1 and 2. Cluster 3 had slightly higher expression of genes related to cell proliferation and metabolic pathways then cluster 4, while cluster 4 showed higher expression of immune related genes then cluster 3.

The researchers wanted to be sure that what they were observing was correct, so they examined the expression profiles of a separate group of 1921 patients. Again, they found four clusters with the high genomic risk cluster showing upregulation of pathways related to androgen receptor signalling, DNA repair, and proliferation, while the low genomic risk cluster showed upregulation of immune response pathways.

Finally, the researchers wanted to know if the different clusters would provide information on clinical outcome for prostate cancer. For this part of the study, they examined a third separate group of 201 men for whom the disease outcome was known. In these men, it was found that those in the high genomic risk cluster (Cluster 1) had significantly worse metastasis-free survival than the other clusters.

The researchers showed that Grade Group 5 prostate cancers can be divided into 4 different subgroups based on their gene expression profiles. They showed that those with expression profiles consistent with high genomic risk (cluster 1) had a poorer outcome and suggested that this group “may be the most likely to derive benefit from treatment intensification, and rational approaches may include the use of interventions active against the pathways that are dysregulated”. They conclude that further investigation into Grade Group 5 disease “and particularly into this aggressive subgroup, is clearly warranted”.

This important study shows us that not all prostate cancers are the same. Studies like this one and developments in precision medicine are bringing us closer to a future where treatments for prostate cancer are more personalised.