Biological markers identified as powerful predictors of prostate cancer relapse following radiotherapy

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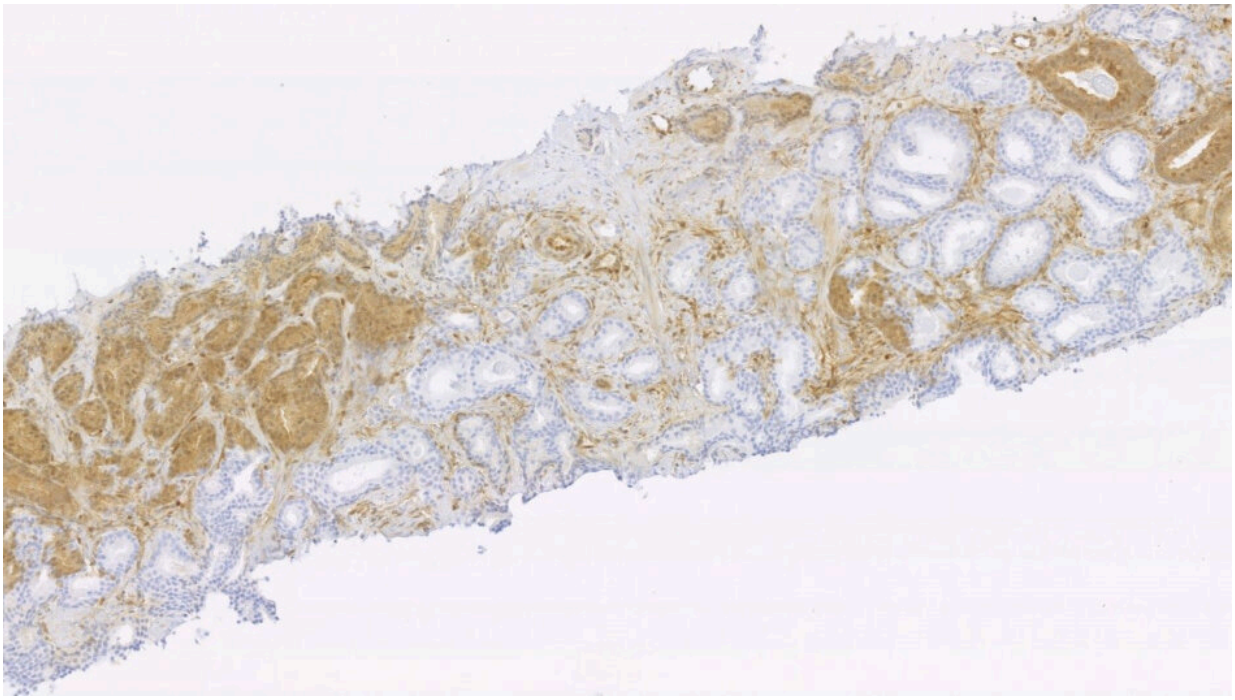

Prostate tumour biopsy sample from a patient showing areas with 'normal' PTEN protein (brown stained regions) and areas with loss of PTEN protein (blue unstained regions). Credit: Dr Anna Wilkins

Two key proteins linked to cell division can reliably predict disease recurrence in prostate cancer after radiotherapy treatment, according to

new research.

Using an inexpensive and widely available technique in the clinic, the researchers evaluated a range of proteins in prostate tumor biopsies and determined that the phosphatase and tensin homolog (PTEN) and geminin proteins are key markers associated with cancer relapse after radiotherapy.

Based on their results, the team at The Institute of Cancer Research, London, reported that patients with tumors showing loss of PTEN were almost three times more likely to experience recurrence than those with 'normal' PTEN. Similarly, the data showed a 70 percent increase in the likelihood of experiencing recurrence in patients with tumors that had a 10 percent increase in geminin.

The findings from this study could lead to the new biomarkers being adopted for routine use in the clinic to stratify patients into risk groups and guide treatment selection, ultimately helping to improve cure rates and reduce side effects in those considering radiotherapy for prostate cancer.

Prognostic indicators of recurrence

With more than 52,000 new cases and 12,000 deaths each year, prostate cancer is the most common cancer among men in the UK. Radiotherapy and surgery remain the gold standard treatments for localized prostate cancer. However, it is estimated that 20–30 percent of men will show signs of recurrence within five years of initial therapy, highlighting the need to improve treatments for these patients.

In this new study, published in *eBioMedicine*, the researchers analyzed diverse proteins that are present in prostate tumors, and involved in important cancer-related cellular processes such as cell division,

response to hypoxia (low oxygen), cell death, cell growth and inflammation, to assess if any of these markers could help to improve prediction of prognosis.

Using a technique known as immunohistochemical staining to visualize proteins in tumor biopsy sections, the researchers scored samples of patients with or without recurrence who were recruited to the phase III CHHiP trial—the largest ever global study of different radiotherapy schedules in localized prostate cancer.

The trial was managed by the ICR's Clinical Trials and Statistics Unit (ICR-CTSU) and led by Professor David Dearnaley, who headed the ICR's Clinical Academic Urology Team before his retirement in 2020 and Professor Emma Hall, Co-Director of the ICR-CTSU.

The team used the data from the samples to generate a model for estimating the prognostic value of each biomarker. They found that PTEN, a tumor suppressor that regulates cell growth and division, and geminin, a protein that inhibits DNA replication during cell division, could predict response to radiotherapy independently of other factors that are already used in the clinic.

Impact of radiotherapy schedules on tumor biology

The CHHiP trial established that a shorter, more dose intensive, or 'hypofractionated' radiotherapy schedule could provide the same therapeutic benefit for patients with prostate cancer as the conventional longer radiotherapy schedule.

Patient samples obtained from the CHHiP trial provided the researchers an opportunity to investigate whether tumor diversity should be used to select optimal radiotherapy schedules.

The results from the study provided important reassurance that the effectiveness of the radiotherapy schedule was not impacted by tumor diversity. They also confirmed that the PTEN and geminin biomarkers could predict recurrence irrespective of radiotherapy regimen.

Incorporation into clinical care

Predictive and prognostic biomarkers, such as the ones identified in this study, allow clinicians to stratify patients into distinct subgroups based on risk of disease or response to therapy.

Study senior author Dr. Navita Somaiah, leader of the Translational Breast Radiobiology Team at the ICR and clinical oncologist at The Royal Marsden, said, "Immunohistochemistry is a powerful, inexpensive, and widely available technique that could facilitate the clinical use of these biomarkers and help to meet the current unmet need for affordable prognostic tools in localized prostate cancer.

"The technique is feasible with small quantities of tumor material, which allows you to make the most out of the small prostate biopsies. It also has the potential for automated analysis in the future, making it an attractive tool for incorporating into clinical care."

A globally unique opportunity

Study lead Dr. Anna Wilkins, clinician scientist at the ICR and a consultant in clinical oncology at The Royal Marsden, said,

"To our knowledge, our study is the first to analyze such diverse protein markers in a single combined approach and to specifically pick out PTEN loss and the cell proliferation marker geminin as independent and powerful predictors of recurrence."

"The CHHiP trial was a globally unique opportunity to test whether radiotherapy schedules should be adjusted for tumor biology as it is the largest trial comparing shorter, intense radiotherapy treatment with longer, less intense treatment. Encouragingly, we found that biologically diverse tumors could be safely treated with shorter, kinder curative radiotherapy schedules."

"We are currently trying to train a computer to score PTEN loss and proliferative markers automatically, which would be very helpful to tailor individualized treatment in the clinic. There are new drugs being developed such as capivasertib—an AKT inhibitor discovered through collaborative work by the ICR and partners Astex Pharmaceuticals and AstraZeneca—that appear to work particularly well in prostate cancers with PTEN loss. So in the future, it could be possible for these drugs to be combined with radiotherapy to further improve cure rates."

"The work was only possible because of the enthusiasm of patients and cancer specialists across the country to support the study and the long-term follow-up needed to obtain these results."

Professor David Dearnaley, emeritus professor of uro-oncology at the ICR, said, "This exciting development could help many people who are about to receive radiotherapy treatment for localized prostate cancer. For patients who have these protein changes, and are therefore at increased risk of the cancer coming back, the tests could enable them to have more intensive, targeted treatments alongside radiotherapy, which could make a real difference in terms of achieving long-term control of their prostate cancer."

More information: Anna Wilkins et al, Multi-candidate immunohistochemical markers to assess radiation response and prognosis in prostate cancer: results from the CHHiP trial of radiotherapy fractionation, *eBioMedicine* (2023). DOI:

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