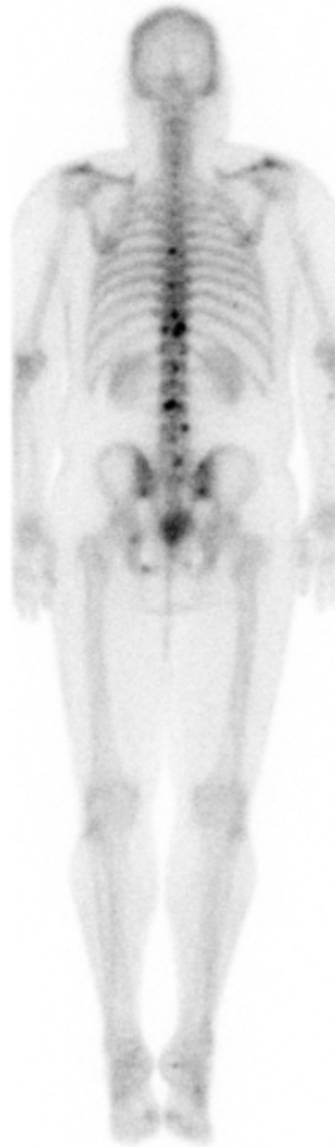


New Blood-Based Monitoring of Prostate Cancer

How can we better detect prostate cancer growth and predict resistance to therapy?

Prostate cancer is the second most common cancer in men, affecting an estimated 4 million people, and is the fifth leading cause of death worldwide. Unfortunately, difficulties in selecting the most appropriate therapy can complicate treatment decisions.

In metastatic prostate cancer, multiple novel therapies are now available that can slow disease progression and improve survival. But every cancer responds differently to different drugs, and there is a critical need for new methods to precisely identify the best treatment for each patient. Although tissue biopsies provide molecular and genetic information that can guide individualized treatment decisions, they are painful and inconvenient, particularly when cancer has spread to the bone. Blood-based liquid biopsy tests, however, are noninvasive and can be performed repeatedly and longitudinally with minimal discomfort to the patient.



Metastatic Prostate Cancer

Prognosis of prostate cancer is related to the sites that have been invaded and the extent of the metastases. The most common sites of metastases are bone and lymph nodes, though the majority of men with metastatic prostate cancer have the bone-only or bone-dominant disease. This image shows one man whose prostate cancer has spread primarily to the bone in his spine and pelvis. Bone biopsies are very painful, however, making it more challenging to monitor the cancer's spread.

For patients with localized prostate cancer, a major challenge is knowing whether a tumor is indolent or aggressive, and the risk of it spreading from the prostate to other parts of the body. Understanding this risk can help determine whether a prostate cancer needs to be treated. Conventional imaging techniques, such as CT scans, bone scans, and MRIs, often miss signs that the cancer has begun to spread. Examination of the prostate cancer biopsy provides an important measure of its aggressiveness, called the Gleason score, but this can be inaccurate due to the very small amount of tissue sampled from the prostate. Conversely, the prostate-specific antigen (PSA) blood test suffers from a high rate of false positives, since PSA is a protein that is expressed in cancer cells as well as benign prostate cells. Meanwhile, clinicians are reluctant to apply surgical and radiation therapies unless they are definitely needed, since these can cause incontinence, sexual dysfunction, and bowel problems, among other side effects.

Now, a recent study from researchers at the Massachusetts General Hospital Cancer Center addresses these risk-stratification and treatment-decision difficulties. David T. Miyamoto, MD, PhD, assistant professor of radiation oncology

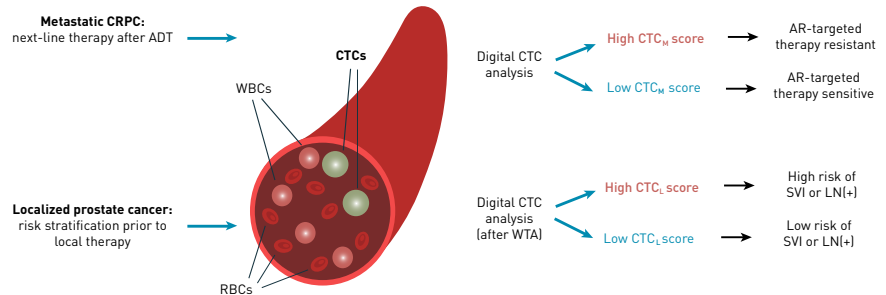
at Mass General Cancer Center, and a multi-disciplinary team of clinicians, molecular biologists, and bioengineers published in the March issue of *Cancer Discovery*¹ a new method to detect and characterize circulating tumor cells in the blood more accurately and efficiently than existing methods, with important implications for treatment decision making in prostate cancer.

REFINING CTC TECHNOLOGY

Circulating tumor cells (CTCs) are rare cancer cells that are shed into the blood from primary and metastatic tumors and circulate through the body. Because of their rarity and fragility, they are extremely difficult to isolate. A team of scientists at the Mass General Cancer Center had previously developed a microfluidic technology called the CTC-iChip to isolate CTCs gently and efficiently. But even after microfluidic enrichment with the CTC-iChip, distinguishing these CTCs from normal white blood cells remained a challenge, and required staining the cells with cancer-specific markers and spending long hours looking under the microscope.

In the new study, Dr. Miyamoto and his colleagues report a novel method to rapidly analyze CTC samples and to detect RNA-based molecular signatures within prostate CTCs.

Dr. Miyamoto and his team



Blood Biopsy With CTC iChip and Digital Droplet PCR

CTCs are isolated from the peripheral blood of prostate cancer patients using a microfluidic device called the CTC iChip, which filters out red blood cells (RBCs) and white blood cells (WBCs). For metastatic castration-resistant prostate cancer, digital CTC analysis scores help predict whether the cancer will resist abiraterone therapy. For localized cancer, whole transcriptome analysis (WTA) and CTC analysis yield scores that can predict whether the cancer will spread to seminal vesicles (SVI) and the lymph nodes (LN).

collected the blood of patients with both clinically localized and metastatic castration-resistant prostate cancer and used the CTC-iChip to isolate CTCs. They then analyzed these samples using droplet digital polymerase chain reaction (PCR), a highly sensitive method of RNA quantification. The team aimed to identify a genetic signal of cancer cells in the blood. In particular, they were looking for RNA transcripts from eight genes that are specifically expressed in prostate cancers. For each gene, a weight was generated on the basis of its expression to create scores for both metastatic and clinically localized prostate cancer.

The researchers found that expression in CTCs of one of the genes, HOXB13, predicts for worse survival in patients being treated with a drug called abiraterone,

which was approved in 2012 for the treatment of patients with metastatic castration-resistant prostate cancer. Combined expression of HOXB13 and another gene called AR-V7 provided even greater predictive value for cancer prognosis and response to treatment. Ultimately, the researchers will need to confirm the predictive power of these genes in a larger clinical trial to determine their true clinical utility, says Dr. Miyamoto.

BETTER BIOMARKERS FOR DISEASE PROGRESSION

Perhaps the most surprising and revelatory finding from the study was that some patients whose cancer seemed to be localized on imaging scans actually had CTCs in the blood. Additionally, the CTC score generated by genetic

(continued from page 2)

analysis was found to be a good predictor of whether the cancer had spread outside the prostate, such as to the seminal vesicles and the lymph nodes. If the CTC test is confirmed to be a better predictor of progression of disease than existing tools, such as the PSA test and standard pathologic features, it could help identify appropriate treatment options for patients, says Dr. Miyamoto. It might even become a secondary screening approach for prostate cancer in patients who have an elevated PSA, and thus reduce the number of unnecessary biopsies performed.

"For most localized prostate cancers, there are three choices: radiation therapy, removal of the prostate, or active surveillance," says Dr. Miyamoto. "There's a real need for biomarkers at this stage, to help patients and clinicians decide on the appropriate treatment."

¹ Miyamoto D, et al. An RNA-Based Digital Circulating Tumor Cell Signature Is Predictive of Drug Response and Early Dissemination in Prostate Cancer. *Cancer Discovery*, 2018;288-303.



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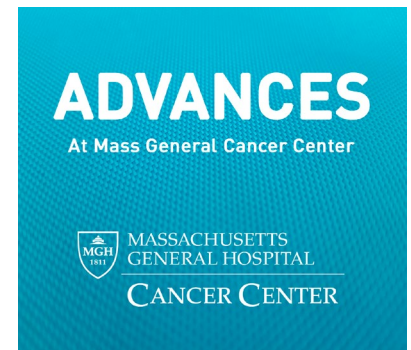
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