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ON THE COVER

Circulating Tumor Cell Assays: A Major Advance in Cancer Treatment

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Scientists have discovered a test that can **revolutionize** the way doctors evaluate and treat a cancer patient. This technology involves the detection and genetic assay of **circulating tumor cells** in the bloodstream.

These **circulating tumor cells** are the metastatic **seeds** that can break away from the primary site of cancer, and spread to other parts of the body. Understanding circulating tumor cells is critically important, since it is the spread of cancer to other parts of the body—and **not the primary cancer**—that is often responsible for the death of a person with cancer.



Up until now, medical science has been focused on the primary tumor, basing treatment decisions on the specific characteristics of the primary cancer cells. However, circulating tumor cells can be genetically **different** from the primary cancer. Treatments designed to attack the primary tumor could fail to destroy the circulating tumor cells.

Here, we'll examine **circulating tumor cell assays** and the **great potential** this technology offers to advance the medical approach to cancer. The basic **circulating tumor cell (CTC)** assays you'll learn about in this article are available in the United States and provide important data as it relates to how an individual's cancer is treated. The **Cleveland Clinic** has recognized this CTC test as the top medical innovation for the year 2009.

A more **advanced** version of the **CTC** test is available by sending one's blood to Germany, where a **genetic analysis** is performed to identify the expression of therapeutic targets and chemo-resistance markers **unique to an individual's circulating tumor cells**. That test will be described in the second article, but read this article first so you understand the powerful prognostic value of circulating tumor cell (CTC) blood testing.

MOVING FROM THE PRESENT TO THE FUTURE

The conventional approach to cancer has been to focus on the primary tumor. For example, with breast cancer the emphasis has been to examine the breast tumor for specific markers, such as estrogen receptor status and HER2 status. Treatment decisions are then made based on the presence or absence of these markers in the primary tumor. However, this approach may be misguided as research has demonstrated that circulating tumor cells (CTC) can be genetically different from the cancer cells in the primary tumor. One example is a study¹ in which 37% of breast cancer patients had CTC that were positive for HER2, even though their primary breast tumor was negative for HER2! Another study provided similar findings.² This research suggests that directing treatment towards the cancer cells of the primary tumor can, in some cases, be "barking up the wrong tree." For this reason, focusing on the metastatic cancer cells could lead to better results. CTC testing provides us with the means with which we can now focus our attention on these potential metastatic cancer cells.

IMPROVING PROGNOSTIC ACCURACY WITH CIRCULATING TUMOR CELLS

A crucial step in evaluating a cancer patient relies on establishing an accurate prognosis, which provides a prediction of the probable course and outcome of the disease. With a correct prognosis in hand, doctors can then design the most appropriate treatment for a person's cancer.

Currently, the ability to provide an accurate prognosis is far from perfect. To investigate if circulating tumor cell (CTC) testing can improve prognostic accuracy, German scientists studied 35 women with non-metastatic breast cancer who had their levels of CTC measured before they had received any treatment for their cancer.² Of these patients, 17 tested positive for CTC, while 18 tested negative for CTC. When the researchers looked at the prognoses of the two groups they found striking differences. The group that tested negative for CTC had a median overall survival of 125 months. The group with 5 or more CTC present in their blood had a median overall survival of only 61 months! The difference in survival of over 5 years between the two groups reveals the great importance that the presence and number of CTC had on the prognoses of this group of women with breast cancer. The findings of this study can have huge implications in how treatment is tailored for the individual with breast cancer. A key issue in breast cancer treatment is distinguishing at the outset which women have cancers that are low risk that do not require intensive treatment, and which women have a high risk of metastasis that requires aggressive treatment. This study provides a glimpse into the potential of CTC testing to provide a more accurate prognosis to allow doctors to distinguish high-risk from low-risk breast cancer patients.



In a related study, researchers at the University of Texas M. D. Anderson Cancer Center measured CTC in 151 women with metastatic breast cancer.³ These patients were also evaluated for other prognostic cancer markers, such as hormone receptor status, CA 27.29 (a blood marker that helps to measure the degree of breast cancer metastatic activity), and HER2 status. Those who had 5 or more circulating tumor cells (CTC) had a median overall survival of 13½ months. The median overall survival for those with less than 5 CTC was over 29 months. The researchers also discovered that the presence of 5 or more CTC had the highest predictive value compared to all other tumor markers! The researchers went on to boldly state that “circulating tumor cells have superior and independent prognostic value... ”

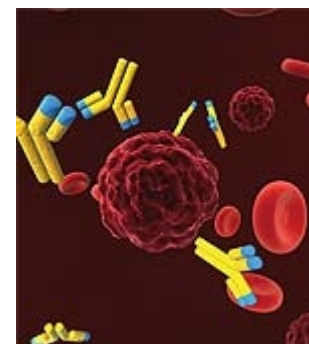
Furthermore, recent research indicates that CTC evaluation can be used to predict prognosis for men with prostate cancer. Researchers at Thomas Jefferson University compared the levels of CTC in 37 men with metastatic prostate cancer. Their findings were remarkable—for the men with 5 or more CTC, the median overall survival was only 8.4 months. For those men with less than 5 CTC the median overall survival was 48 months!⁴ Yet another study measured CTC in 55 men with a rising PSA after surgery for prostate cancer.⁵ A rising PSA after surgery is strongly predictive of prostate cancer recurrence.⁶ Radiation therapy was administered to 15 patients. Of these prostate cancer patients, 60% who were CTC positive had progression of their disease during radiation therapy, while there were **no disease progressions** in the CTC negative group!⁵ Additional studies have confirmed these results.⁷⁻⁸

PREDICTING WHO WILL BENEFIT FROM PROSTATE CANCER SURGERY

A central issue that men with prostate cancer, and their doctors, face is deciding if surgery (or other therapy) to eradicate the prostate is the best course of action. Surgery is most indicated when there is a strong likelihood that it will be curative. This is generally the case when the cancer is confined to the prostate gland.

Potential surgical failure can occur when the cancer has spread beyond the prostate gland. In this situation, surgery is not likely to cure the disease and many doctors will not recommend surgery.

Unfortunately, the surgeon often does not know the extent of the cancer before surgery is performed. However, in a landmark study, scientists at Columbia University in New York have discovered that CTC testing can predict which men with prostate cancer are likely to benefit from surgery.⁹ In this study, 138 men with prostate cancer scheduled for surgery to remove the prostate were tested for the presence of CTC in their blood. An eye-opening finding revealed that the men who were CTC positive were 12 times more likely to experience a potential surgical failure compared to those who were CTC negative. Moreover, the scientists determined that CTC status was superior to PSA levels and Gleason score at predicting potential surgical failure. In fact, every single person who was CTC positive with a PSA greater than 10 ng/mL had potential surgical failure. This compares to 76% of patients who were surgically cured with a PSA greater than 10 and who were CTC negative! All in all, CTC negative patients had an 87% chance for a surgical cure. The authors remarked that **“this assay might be a useful criterion in the counseling...of patients on the value of surgical treatment for prostate cancer.”**



CIRCULATING TUMOR CELL (CTC) ASSAYS

- Doctors and scientists have identified a test that promises to revolutionize the evaluation and treatment of cancer.
- By detecting the number of circulating tumor cells (CTC) in the bloodstream, doctors can gain important information about a patient's prognosis, which can be used to guide treatment decisions.
- Greater numbers of CTC in the blood have been linked with increased risk of metastasis as well as poorer prognosis and survival.

- CTC assays may offer higher predictive value than many commonly utilized tests such as measurements of hormone receptor status, CA 27.29, and imaging studies.
- Monitoring CTC levels may also provide valuable information about the efficacy of treatment and the risk of recurrence.

CIRCULATING TUMOR CELLS SUPERIOR TO IMAGING TESTS

Researchers have also discovered that CTC evaluation may be more accurate than standard imaging tests at predicting the prognoses of metastatic breast cancer patients. Traditionally, imaging tests have been used to evaluate the effectiveness of treatment in those with metastatic breast cancer. The response to treatment is often determined by measuring changes in tumor size with CT and MRI scans. In a groundbreaking study performed in 2006, metastatic breast cancer patients had imaging tests done before and 10 weeks after they began therapy.¹⁰ The results of the imaging tests were reviewed by two independent radiologists. CTC were measured 4 weeks after the start of therapy. The researcher's findings were astonishing—the group that responded to treatment based on imaging tests (i.e., the tumors got smaller) and had 5 or more CTC had a worse prognosis than the group with CTC counts less than 5 that showed worsening of their disease on imaging studies! These findings suggest that the levels of CTC were far more important at predicting survival compared to the actual visual changes noted on imaging tests. Further analysis established that CTC testing had superior reproducibility compared to imaging studies. There was a 15% disagreement in the interpretation of the imaging tests between the two radiologists, compared to less than 1% variation in the results of CTC testing. The authors of this study declared that *“this advantage in reproducibility implies that inaccurate disease status evaluations and inappropriate treatment decisions are less likely with the use of the CTC assay than with radiographic studies.”* They went on to enthusiastically conclude that “the assessment of CTCs has several advantages over serial radiographic evaluation. The CTC assay is more reproducible than radiographic evaluation, shows useful results at an earlier time point than do radiologic studies, and seems to be a more robust predictor of survival than is radiographic response.”

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