

Circulating Tumor Cell (CTC) Count

A USEFUL PROGNOSTIC MARKER FOR METASTATIC BREAST, COLORECTAL, AND PROSTATE CANCER

Test Highlights

- CellSearch™ system used for CTC count is an accurate and reproducible semi-automated method that is approved by the FDA for quantifying CTCs in whole blood.
- Elevated CTC count is associated with decreased progression-free survival (PFS) and decreased overall survival (OS) in patients treated for metastatic breast (MBC), colorectal (MCRC), or prostate cancer (MPC).
- CTC count may be used to evaluate response to therapy.

Clinical Background

- The American Cancer Society estimates that deaths each year from breast, colorectal, and prostate cancer are approximately 41,000, 55,000, and 27,000, respectively. The great majority of these deaths occur due to recurrent metastatic disease.
- Cancer metastasis is characterized by the migration of cells from the primary tumor into the peripheral circulation, where they spread to distant areas of the body and begin to grow. Malignant carcinomas are of epithelial origin, a cell type not normally seen in the blood.
- These circulating tumor cells (CTCs) can be separated from surrounding cells in the blood and then counted using the CellSearch system.
- A number of prospective multi-center studies using this technique for measuring CTCs have been published and indicate that the CTC count before and during treatment is an independent predictor of PFS and OS rates in patients with MBC, MCRC, or MPC.
- CTC count in MBC and MCRC patients correlates with imaging results.
- CTC count in MPC patients correlates with prostate-specific antigen (PSA) measurements.

Indications for Ordering

- CTC count represents the enumeration of CTCs of epithelial origin in whole blood of patients with MBC, MCRC, or MPC.
- Order this test prior to initiation of therapy to get CTC baseline, then for serial monitoring to assess prognosis and guide therapy.

Interpretation

- CTC count is reported as the number of CTCs/7.5 mL of blood.
- In patients with MBC, a CTC count of five or more per 7.5 mL of blood at any time during the course of the disease is associated with a poor prognosis and is predictive of shorter progression-free and overall survival.
- In patients with MCRC, a CTC count of three or more per 7.5 mL of blood at any time during the course of the disease is associated with a poor prognosis and is predictive of shorter progression-free and overall survival.
- In patients with MPC, a CTC count of five or more per 7.5 mL of blood at any time during the course of the disease is associated with a poor prognosis and is predictive of shorter progression-free and overall survival.

Limitations

- CTC count should be used in conjunction with all clinical information and diagnostic testing data (i.e., imaging, laboratory tests, physical examination and complete medical history) in accordance with appropriate patient-management procedures.
- CTC count is a prognostic marker and should not be used to demonstrate that any current line of therapy is more or less effective than another form of therapy or no therapy at all.
- CTC count is not as accurate as imaging results in assessing whether a patient has non-progressive or progressive disease.
- If the patient is on doxorubicin therapy, allow at least seven days following administration of a dose before blood draw. The results of this test should be interpreted with caution if samples are drawn within seven days of administration of doxorubicin therapy.
- CTCs that do not express epithelial cell adhesion molecule (EpCAM) will not be detected by this test.
- CTCs that express EpCAM but not cytokeratins 8, 18, and 19 (CK) will not be detected by this test.

Clinical Application of the CTC Count			
Serial Monitoring and Overall Patient Median Survival Times			
	MBC	MCRC	MPC
< cut-off at all time points	22.6 months	18.6 months	>26 months
≥ cut-off at all time points	4.1 months	3.9 months	6.8 months
≥ cut-off at baseline and < cut-off at final draw	19.8 months	11.7 months	21.3 months
< cut-off at early draw and ≥ cut-off at final draw	10.6 months	7.1 months	9.3 months

Methodology

- The CellSearch system includes the CellTracks® AutoPrep® system, a semi-automated cell-preparation instrument for CTC capture and staining, the CellSearch CTC kit, the CellTracks Analyzer II, a semi-automated fluorescent microscope, and a digital camera.
- The CTC kit includes a ferrofluid reagent consisting of magnetic nanoparticles coated with anti-EpCAM antibodies, which attach to CTCs expressing the EpCAM antigen and facilitate immunomagnetic separation from other cells in the blood.
- After immunomagnetic capture and washing with buffer, a permeabilizing buffer is added, along with phycoerythrin (PE)-labeled anti-CK and allophycocyanin (APC)-labeled anti-CD45 (leukocyte common antigen); nucleic-acid dye, 4',6-diamidino-2-phenylindole, and dihydrochloride (DAPI) are used to fluorescently label the cells.
- After incubation and another magnetic separation, excess fluorescent staining reagent is aspirated and the cells are resuspended in buffer.
- The stained immunomagnetically-labeled cells in buffer are transferred to the MagNest®, a device consisting of a fluid-holding cartridge and two magnets that orient the cells on the surface of the cartridge for scanning on the CellTracks analyzer. The entire surface of the cartridge is scanned using the four-color semi-automated fluorescent microscope. The digitally captured images are sorted by the software and presented to the operator for enumeration of CTC. CTCs are selected based on the following criteria: intact cell, CK-PE+, DAPI +, and APC-CD45 -.

References

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3. Cristofanilli M, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med* 2004;351:781-91.
4. Cohen SJ, et al. Isolation and characterization of circulating tumor cells in patients with metastatic colorectal cancer. *Clin Colorectal Cancer* 2006;6:125-32.
5. Meropol NJ, et al. Circulating tumor cells predict progression free survival and overall survival in patients with metastatic colorectal cancer. *Journal of Clinical Oncology* 2007;25, No.18S:4010.
6. Moreno JG, et al. Circulating tumor cells predict survival in patients with metastatic prostate cancer. *Urology* 2005;65:713-8.
7. Moreno JG, et al. Multicenter study evaluating circulating tumor cells as a surrogate for survival in men treated for castration refractory prostate cancer. *Journal of Clinical Oncology* 2007;25,18S:5016.

Test Information

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Circulating Tumor Cell Count (Cell Search™)

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.