

assessing the progression of cancer in cancer patients, for assessing efficacy of a drug during treatment. When originating from tumor cells, exosomes contain DNA sequences corresponding to oncogenes, including oncogenes that bear mutations responsible for the cancer. Nucleic acids originating from oncogenes, and which are found in exosomes, and which are being explored for their utility as biomarkers, include *KRAS*, *TP53*, *MET*, and *HER2* (167).

d. Circulating Tumor Cells

This mainly concerns cancerous cells released from solid tumors. A definition that distinguishes between primary tumor cells, CTCs, and disseminated tumor cells (DTCs), is provided by the following statement. The statement is that, “the existence of circulating tumor cells (CTC) and the settlement of these cells in secondary organs, such as liver, bone, and lungs, as disseminated metastatic tumor cells (DTC), is generally accepted. These cells are believed to be rare members among the cellular population of primary tumor cells” (168).

Thus, it is the case that CTCs represent a transition point between the primary tumor and a location of settlement. Toss et al. (169)

commented on bone marrow as a location of settlement, referring to the “notion that bone marrow may be a ‘perfect niche’ in which tumor cells ... survive,” where these settled cells are called DTCs.

For the analysis of CTCs, it is generally the case that a sample of peripheral blood is taken, leukocytes are removed, resulting in a population of cells expressing the epithelial cell protein, EpCAM. The cells are then tagged with fluorescent antibodies specific for cytokeratins expressed by epithelial cells (170).

In an example of a prognostic test based on CTCs, Wallwiener et al. (171) described the use of CTCs to monitor the progression of *metastatic breast cancer*. Using the cutoff point of five cells per 7.5 mL of blood, the authors found that a concentration of CTCs at levels of greater or equal to 5 cells/7.5 mL blood was associated with decreased survival to the breast cancer.

An advantage of CTCs, over DTCs, for use as a biomarker, is that CTCs are much easier to sample, especially where repeated sampling is desired. CTC counting has been characterized a “liquid biopsy,” that is a non-invasive test for predicting and monitoring response to treatment in various cancers

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¹⁷⁰Toss A, et al. CTC enumeration and characterization: moving towards personalized medicine. *Ann. Transl. Med.* 2014;2:108 (16 pp.).

¹⁷¹Wallwiener M, Riethdorf S, Hartkopf AD, et al. Serial enumeration of circulating tumor cells predicts treatment response and prognosis in metastatic breast cancer: a prospective study in 393 patients. *BMC Cancer* 2014;14:512 (12 pp.).