Commentary

Circulating tumor cells and cholangiocarcinoma

Amy Deipolyi[1], Rahmi Oklu[2,3]

[1]Division of Vascular & Interventional Radiology, Department of Radiology, New York University Medical Center, New York, NY, USA; [2]Division of Vascular & Interventional Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [3]Department of Medicine, Biomaterials Innovation Research Center, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, USA

Correspondence to: Rahmi Oklu, MD, PhD. Division of Vascular & Interventional Radiology, Massachusetts General Hospital, 55 Fruit Street, 290 Gray/Bigelow, Boston, MA 02114, USA. Email: rahmioklu@gmail.com.

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Circulating tumor cells (CTCs) are shed from a primary tumor and can lead to metastasis. Modern techniques to detect these cells in the peripheral blood of patients have been developed over the past two decades, with early reports showing increased numbers of CTCs in cancer patients compared to controls and higher CTC numbers associated with more progressive disease [e.g., (1)]. Since then, studies have reported that higher peripheral CTCs associate with reduced survival in cancers of the breast, colon, bladder, prostate, ovary, and lung, and in hepatocellular carcinoma (HCC) (2-7). CTC enumeration has therefore been suggested as a possible cancer-screening tool, or as an instrument of prognostication.

Extending findings from a pilot study of 13 cholangiocarcinoma (CCA) patients showing that 25% had detectable CTCs (8), Yang *et al.* studied 88 CCA patients prospectively (9). Of the 88 patients, 17% had two or more CTCs per 7.5 cc of peripheral blood. Increasing CTC numbers were associated with increased tumor burden and extent, and worsened survival. In models accounting for extrahepatic metastasis, age, and CA19-9 levels, CTC level remained an independent predictor of survival. In regard to sensitivity for metastatic disease, CTC cutoffs of 1, 2, and 5, yielded sensitivities of 53%, 37%, and 21%, respectively. Specificities were not reported. The authors conclude that CTCs may be a powerful tumor biomarker, and a prognostic tool for specific patient subsets that have yet to be defined.

The major challenge of this and similar work is the low overall sensitivity of CTC detection in cancer patients using methods that are commercially available. A number of techniques for enrichment and identification have been developed, with relative benefits and drawbacks (10). The most sensitive method to detect CTCs is the iChip platform, which uses inertial focusing and negative selection for the isolation of CTCs; however, this method is not yet commercially available (11). The technique used in Yang *et al.* is the Cell-Search System™, which involves an immuno-magnetic enrichment of CTCs with ferrofluid nanoparticles coated with antibodies to epithelial cell adhesion molecule (EpCAM), a transmembrane glycoprotein that mediates epithelial cell adhesion (12). The cells are then immunostained with markers to distinguish the epithelial cells from other cells such as leukocytes contaminating the specimen. Enriched and labeled cells are then counted by a semi-automated fluorescent microscope (10). The use of the Cell-Search System™ in CCA was predicated on the prior finding that almost all CCAs express EpCAM. However, EpCAM expression can be variable, which would decrease sensitivity for CTCs, particularly in HCC, urothelial cancer, clear cell renal carcinoma, squamous cell cancers, and certain breast cancers (13).

Nonetheless, only a minority of CCAs in Yang *et al.* were found to have detectable CTCs in peripheral blood. Perhaps other methods of detection could increase sensitivity and thus utility of the assay as a diagnostic tool. For example, in the setting of colon cancer, multimarker real time PCR assays outperform the Cell-Search System™ in detecting CTCs (14). Beyond discovering the most sensitive assay, the optimal threshold for determining a positive assay has yet to be defined. Whereas two CTCs per 7.5 cc peripheral blood has been used for colon cancer, and five CTCs has been used for prostate and breast cancer, it is yet to be established whether one, two, or five is the appropriate threshold for

CCA (15). As the sensitivity of CTC detection improves with newer devices, and the details of its interpretation worked out, CTC measurement will become more applicable in the clinical setting.

Given the low number of CCA patients in Yang *et al.* with detectable CTCs, the fact that a high CTC level independently predicted survival suggests that once these technical issues are worked out, CTC enumeration may be a powerful clinical tool. Though such an assay may not be applicable as a screening tool, it may be most useful for patients with more advanced disease helping to distinguish those who may still respond to treatment.

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Footnote

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