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Letter to the Editor

Reply to Rodolfo Montironi, Liang Cheng, Marina Scarpelli, Alessia Cimadamore, Francesco Montorsi, and Antonio Lopez-Beltran's Letter to the Editor re: Gillian Vandekerkhove, Werner J. Struss, Matti Annala, et al. Circulating Tumor DNA Abundance and Potential Utility in De Novo Metastatic Prostate Cancer. Eur Urol 2019;75:667–75: How Does Circulating DNA Reach the Blood Stream?

Montironi and colleagues present data to support an intriguing hypothesis on how tumor DNA from primary prostate cancer foci may reach the bloodstream. In our study, all patients had radiographic metastatic disease (predominantly to bone) at the time of blood draw [1]. Since these patients did not have prior local therapy, it is possible that some circulating tumor DNA (ctDNA) measured in peripheral blood comes from the "empty spaces" identified in whole-mount radical prostatectomy specimens by Montironi et al. However, across most cancers studied to date, patients with metastatic disease have higher ctDNA concentrations than those with localized disease. Indeed, in our patients with *de novo* metastatic prostate cancer, there was a positive relationship between clinical indicators of metastatic disease burden and plasma ctDNA abundance. This is consistent with observations in the metastatic castration-resistant setting, where ctDNA abundance is also strongly prognostic for overall survival [2,3]. In patients with high-volume metastatic disease, the vast majority of ctDNA is probably derived from metastatic sites, where tumor morphology and vascularity are different to the prostate gland itself. Nevertheless, in the setting of multiple synchronous tumors, the relative contribution of ctDNA from different sites around the body remains unexplored.

The vast majority of cell-free DNA comes from cellular apoptosis. This is evidenced by the periodic fragment size of cell-free DNA matching the apoptotic ladder. By definition, therefore, analysis of ctDNA informs on a dead tumor cell population. However, ctDNA release into the blood is closely related to a combination of tumor volume and proliferative capacity [4]. In normal tissue, debris from dying cells is collected by phagocytes and does not reach the bloodstream. This is supported by the fact that cell-free DNA in healthy individuals is derived from the hematopoietic lineage, rather than a combination of all human cell lineages [5]. Conversely, in bulky metastases with rapid tumor cell turnover, inefficient clearance of dead cells eventually leads to passive escape of DNA into blood. Importantly, high concordance for driver gene alterations between tumor tissue and ctDNA suggests that ctDNA is representative of live tumor cells at the time of collection [1,6]. Perhaps the best analogy outside of oncology is the high proportion of fetal cell-free DNA in the bloodstream of pregnant women: this cellular debris signifies a thriving and proliferating entity.

High-grade prostate tumors are also proliferative and invasive. However, in our experience most patients with localized disease have a plasma ctDNA fraction of $<1\%$. Detection and accurate characterization of ctDNA in this context require larger volumes of plasma and ultradeep next-generation sequencing. However, it is plausible that the mechanism proposed by Montironi and colleagues represents a major release method for ctDNA in patients without apparent macrometastatic dissemination.

Conflicts of interest: The authors have nothing to disclose.

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Alexander W. Wyatt[a,*]
Kim N. Chi[a,b]
Martin E. Gleave[a]

[a]*Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, Canada*
[b]*Department of Medical Oncology, BC Cancer, Vancouver, Canada*

*Corresponding author. Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, 2660 Oak Street, Vancouver, British Columbia V6H 3Z6, Canada. Tel. +1 604 8754818.
E-mail address: awyatt@prostatecentre.com (A.W. Wyatt).

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