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Detection of Tumor Cells in the Bone Offers Independent Prognostic Value in Bladder Cancer Patients: The Clinical and Basic Science Perspective

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The identification of novel molecular markers and/or the development of approaches to enhance our capacity to predict outcome beyond the standard measures of stage and grade lies at the heart of translational research. For certain bladder cancer patients, this is true because it is difficult to know if they will respond well to bladder-sparing regimens or develop recurrent and/or progressive disease. Therefore, molecular markers that enhance the ability of clinicians to determine outcome and help identify the best treatment are of paramount importance.

In addition to being translational in nature, such discoveries can also potentially serve as fertile intellectual territory for the basic scientist. This is because translational research serves as a forum for basic scientists (and clinician scientists who are engaged in basic research) to explore the molecular mechanisms that lie at the heart of cancer cell behavior. And just as basic science extends the frontier of our knowledge, basic insights revealed in the lab can potentially be used to enhance the way medicine is practiced in the clinic. One such case is the paper by Retz et al. [1], published in this issue of *European Urology*, showing the detection of cytokeratin 20 (CK20)–positive disseminated tumor cells (DTCs) in the bone marrow that act as an independent predictor of worse outcomes in bladder cancer patients undergoing radical cystectomy. CK20 is a member of the intermediate filament family of proteins that are expressed in several tissues. In the urinary bladder, CK20 expression is restricted to a specific cell population of superficial urothelium, referred to as *umbrella cells* [2].

Previously, breast and prostate cancer researchers have used the observation that epithelial-specific markers (eg, CK20) are not normally expressed in the bone marrow as the rationale for determining whether DTCs derived from primary tumors had colonized the bone microenvironment [3,4]. This involved collecting bone marrow aspirates of patients who were diagnosed with these malignancies prior to surgery. In addition, these groups asked if the presence of DTCs in bone marrow aspirates correlated with any particular primary tumor stage and/or if the presence of DTCs in the bone microenvironment had any correlation with clinical outcome.

Importantly, previous work has shown that the detection of DTCs in the bone marrow aspirates of prostate and breast cancer patients was not correlated with a specific tumor stage, suggesting that the metastatic cascade of tumor cell dissemination to distal tissues occurs much earlier than commonly thought. This theory of metastatic progression is referred to as the *parallel progression model* [5]. In addition, whereas a previous study showed that the presence of DTCs in the bone marrow aspirates of prostate cancer patients was a predictor of recurrence [3], no study of DTCs in the bone marrow of bladder cancer patients with long-term outcome had been performed until now. Outcome end points examined by Retz et al. [1] included 7-yr progression-free, tumor-specific, and overall survival. Interestingly, as was the case for detection of DTCs in prostate cancer bone marrow aspirates, the detection of CK20-positive DTCs in the bone marrow aspirates of bladder cancer patients was not significantly associated with any specific tumor stage. However, Retz et al showed that for all patients examined, progression-free, tumor-specific, and overall survival was significantly worse in patients who had CK20-positive bone marrow samples and was an independent predictor of worse

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outcomes when accounting for gender, age, stage, grade, adjuvant therapy, and lymph node status on multivariate analysis. The finding that CK20 status was a significant predictor in the 41 pN0 patients is particularly important because it indicates that the presence of CK20-positive bone marrow is an important prognostic indicator, even for those with no evidence of lymph node involvement. In summary, Retz et al show for the first time using long-term follow-up data that the detection of CK20-positive cells in the bone marrow aspirates of bladder cancer patients has prognostic significance, especially in pN0 patients.

To truly move these observations into the clinic, it will be necessary to expand on these initial observations in a larger patient cohort. It should also be noted that collecting bone marrow aspirates can be clinically difficult. Therefore, a larger multi-institutional study may enable researchers to compare CK20 status in bone marrow aspirates to CK20 status in patient blood samples. This would allow researchers to determine whether the detection of DTCs in the bone marrow is superior to the detection of circulating tumor cells (CTCs) in the vasculature. Should this work demonstrate the utility of such an assay as a predictor of outcome, significant work will be needed to develop standardized, reproducible, and robust quantitative assays for detecting DTCs and CTCs. This may enable researchers to reveal important quantitative insights into how the number of cells corresponds to clinical outcome. If larger studies indicate prognostic significance for the detection of DTCs in the bone marrow (or CTCs in the blood), hopefully this test can be standardized and will enable clinical labs to implement this approach in an inexpensive way.

These findings as well as those in the breast and prostate cancer fields regarding the detection of DTCs [4,6,7] in the bone marrow and CTCs in the blood [8] also act as a call for basic scientists to engage in studies designed to further understand the nature of metastatic cancer cells. Although the idea that cancer cells escape the primary tumor site prior to the detection of overt invasion is not new, this process is certainly difficult to study. Additionally, if tumor cells are capable of colonizing distal tissue early in tumor development, what is the signal that causes them to develop overt metastasis? Are they in dormant micrometastasis until they encounter a signal to thrive? Is this signal inherent in the cancer cells or is it a microenvironmental cue? If the cancer cells are dormant, how do we study cells that refuse to grow? Also, why are DTCs CK20 positive, when CK20 expression can also be lost in primary tumors? This could indicate that CK20 positive cells are selected to form micrometastases or, more likely, that if other markers were identified and utilized, we would detect other CK20-negative micrometastases in bone marrow aspirates. Furthermore, we are only in the beginning stages of defining the impact of metastatic cancer cells on the bone microenvironment. Although breast and prostate cancers have been known to display a homing phenotype to bone, the same has not been reported for bladder cancer, as the incidence of bone metastasis is comparatively low relative to other sites, such as the lung. Therefore, if the development of micrometastasis in bone occurs in bladder cancer patients, are DTCs detected in other soft tissues as well? Or do DTCs in the bone of bladder cancer patients have special clinical significance?

In conclusion, it is clear to see that the findings of Retz et al. [1] have potential for being clinically useful in the future, and the scientific community should eagerly await larger studies that follow up on these initial findings. Hopefully these findings, as well as those regarding DTCs in other cancers, will drive basic scientists and clinician scientists to engage in future studies as multidisciplinary teams dedicated to elucidating the underlying biology of DTCs in cancer. This would enable clinical and basic science research teams to work together synergistically to solve these very complex problems.

Conflicts of interest: The author has nothing to disclose.

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