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INVITED COMMENTARY

Prostate Cancer

New models for defining prostate cancer biology and patient prognosis

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Currently, the prognosis of patients with metastatic prostate cancer is most commonly defined by clinical factors including performance status, presence of visceral metastasis, lactate dehydrogenase level, opioid analgesic use, albumin level, presence of anemia, prostate-specific antigen level, and alkaline phosphatase level (*i.e.*, Halabi model).[1] This model is most commonly used in the current prospective clinical trials today. However, it is only an inference of the underlying biology and not a direct measurement of that biology.

PTEN is a tumor suppressor which negatively regulates the *PI3K-AKT-MTOR* oncogene pathway by directly inhibiting the activation at the *PI3K* node. This pathway regulates multiple genes involved in cellular growth, proliferation, and autophagy among other critical cellular mechanisms.[2] Alterations in this pathway, most commonly deletion of *PTEN* or activating point mutations to *PI3K* or *AKT*, are early truncal events identified in approximately 20% of patients with localized disease[3] and up to 50% of patients with metastatic disease.[4] It is one of the important drivers of prostate cancer biology.

In the publication accompanying this Commentary, Zhang *et al*.[5] evaluated 205 patient samples for PTEN loss, as measured by immunohistochemistry, and correlated loss with clinical outcomes. PTEN loss correlated with known poor prognostic factors such as high burden/volume of metastatic disease and high alkaline phosphatase and lactate dehydrogenase levels. The univariate model, incorporating the Halabi prognostic model, provides internal validation as these clinical factors were also prognostic for both progression-free survival and overall survival. In the univariate model, PTEN loss was significantly associated with both progression-free survival (hazard ratio: 2.04, $P < 0.001$) and overall survival (hazard ratio: 2.4, $P < 0.001$). PTEN loss remained significant in the multivariate model for both progression-free survival (hazard ratio: 1.67, 95% confidence interval: 1.14–2.43, $P = 0.008$) and overall survival (hazard ratio: 1.95, 95% confidence interval: 1.23–3.10, $P = 0.005$). Importantly, Gleason score was not associated with either progression-free survival or overall survival in this cohort, inconsistent with other studies. This is likely due to the infrequent number of patients in this study with a low or intermediate Gleason score.

In the multivariate analysis, many clinical factors remained significant, emphasizing that PTEN loss only partially defines the underlying biology. This is further explained by the multiple other canonical pathways or genomic alterations identified in the TCGA datasets such as *SPOP*, homologous recombination repair alterations, and ETS rearrangements among others. Future prognostic models will likely need to incorporate multiple genomic drivers of this disease and not *PTEN* status alone. Dr. Aparicio and her colleagues have shown that molecular alterations through genomic deletions or mutations to *TP53*, *PTEN*, and *Rb* defined a biologically aggressive prostate cancer phenotype. They call this entity "variant prostate cancer" to differentiate it from typical prostate adenocarcinoma due to the relative poor responsiveness to androgen axis therapy. These cancers are poorly responsive to hormone therapy yet appear to remain highly sensitive to chemotherapy approaches.[6,7] Their model incorporates multiple genomic alterations to more accurately define this population of patients with aggressive disease.

Another question is how this testing should be performed. In this study by Zhang *et al*.,[5] they analyzed tissue from prostate biopsies obtained at the time of diagnosis using immunohistochemistry, instead of tissue obtained at the time of metastasis. This explains the lower incidence of *PTEN* deletion found in this study (28.3%) compared with some other studies where the incidence has been shown to be higher (40%) in patients with metastatic disease.[8] The incidence of *PTEN* deletion is consistently lower in patients with localized disease at approximately 20%.[9] The authors used immunohistochemistry testing instead of genomic testing to assay for *PTEN* deletion which is a well-validated and a recommended approach.[10,11] A more recent approach is the use of liquid biopsies to perform genomic testing. This offers the benefit of testing multiple driver genes simultaneously and is safe to perform repeatedly. Liquid biopsy-based genomic testing is feasible and accurately identifies these patients.[12]

Predicting disease progression and prognosis plays an essential role in guiding patient goals, expectations, and treatment strategies. As the cost of genetic analysis decreases, it is becoming increasingly feasible for patients to undergo genetic and genomic screening to define and individualize the biology of each patient's cancer. Ideal future models will likely incorporate some of these clinical factors (for instance, cancer volume) in conjunction with direct measures of biology such as *PTEN* loss among other genomic alterations. In addition, since *PTEN* loss is an early truncal mutation, it likely can be used as a component in a complex model for all stages of disease from localized disease to treatment-refractory castration resistance.

Finally, there is another reason to do this type of testing for our patients – potentially new treatment options for this subset of patients. AKT inhibitors appear to be effective in prostate cancers with *PTEN* deletion. A recent study led by Dr. de Bono *et al.*[13] evaluated an AKT inhibitor, ipatasertib, in patients with mCRPC. In this clinical trial, 1101 patients were randomized to ipatasertib plus abiraterone or abiraterone plus placebo. *PTEN* deletion was a stratification factor, so not required for eligibility. Median radiographic progression-free survival improved in patients with PTEN loss by immunohistochemistry treated with the combination compared to abiraterone/placebo (18.5 months *vs* 16.5 months, hazard ratio: 0.77, 95% confidence interval: 0.61–0.98, $P = 0.0335$). Currently, other clinical trials are being conducted in the metastatic hormone-sensitive setting (NCT04493853, ClinicalTrials.gov).

The conclusion in the study by Zhang *et al.*[5] that PTEN loss is an important driver of prostate cancer and therefore has significant prognostic implications for patients with metastatic hormone-sensitive disease is consistent with other studies in both the localized and castration-resistant settings. This reaffirms the value of using this in prognostic models and potentially as a therapeutic target in the future.

COMPETING INTERESTS

Both authors declare no competing interests.

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