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LETTER TO EDITOR

Clinical impact of combined PTEN and ERG rearrangements in localized prostate cancer

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To the Editor,

Prostate cancer (PCa) is nowadays the second most common malignancy diagnosed among men and is responsible for one of the leading causes of cancer mortality. Clinically localized disease may present with a wide variety of clinical behavior including tumors of low clinical significance as well as highly aggressive ones. Among patients treated with either radical prostatectomy or radiotherapy there is a risk of *biochemical failure* (BF). As a result, it is of outmost interest to develop new markers predicting the risk of BF development. Several genes and molecular pathways are implicated in the disease development and progression including phosphatase and tensin homolog gene (PTEN) and ETS Related Gene (ERG).

PTEN is a tumor suppressor gene located in chromosome 10q23.3. It encodes the PTEN protein, a dual lipid phosphatase enzyme, which acts as a negative regulator of the PI3K-Akt survival pathway. PTEN protein dephosphorylates PIP3 converting it back to PIP2. As a result, the phosphorylation of Akt mediated by PIP2 conversion to PIP3 is inhibited and a G1 cell cycle arrest is induced. In addition, PTEN may promote oncogenesis in a PIP3 independent mechanism involving MAPK pathway crosstalk with PTEN pathway, cell migration, cell adhesion, tumor angiogenesis and DNA repair and tumor invasion. ERG is an oncogene member of the ETS family located in chromosome 21q22.2.

The connection between the ERG protein and prostate cancer is well documented. ERG protein is mostly involved in this process as a fusion protein with transmembrane protease serine 2 (TMPRSS2), a protein encoded by TMPRSS2 gene, located in chromosome 21q22.3 (1).

Although PTEN loss and ERG rearrangement are the most common genomic aberrations in prostate cancer, the relationship between them and how they interfere with cancer recurrence and progression is still unclear. Recently, a systematic review and metanalysis was published by Liu et al regarding the impact of PTEN loss and ERG rearrangement on recurrence after treatment with radical prostatectomy or brachytherapy. A total of 6744 patients from 17 papers were included in the metanalysis and primary endpoints assessed were biochemical *recurrence free (BRF) survival and recurrence free survival* (RFS). A subgroup analysis was performed according to the degree of PTEN deletion, ERG rearrangement and Gleason score. In terms of results, prostate cancer with PTEN deletion faced a higher risk for recurrence. BRF and RFS were lower in a statistically significant way in both groups with heterozygous or homozygous PTEN loss.

The effect was more profound in the homozygous deletion. On the other hand, no correlation was documented regarding the association of ERG rearrangement, regardless of PTEN deletion or not, and the risk for recurrence after radical prostatectomy or brachytherapy. Nevertheless, Gleason score was proved to be a significant factor predicting recurrence (2).

In terms of clinical impact in decision making, there are several clinical trials investigating the use of drugs targeting PTEN and ERG pathways. MAPK inhibitors are under investigation as there is a correlation between PTEN molecular pathway and MAPK signaling. PI3K inhibitor LY294002 and pan-AKT inhibitor AZD5363 deliver promising results in terms of slowing prostate cancer growth. In addition, multikinase inhibitors such as sorafenib, buparlisib and regorafenib also interfere with PI3K/AKT/mTOR pathway and present as possible treatment options. Moreover, cIAP-1 antagonist AT-IAP can sensitize PTEN deficient tumors to radiotherapy in vitro. Moreover, a recent phase II clinical trial of everolimus, an mTOR inhibitor, plus bicalutamide for castration-resistant prostate cancer presented valuable results with 75% of the patients treated with everolimus plus bicalutamide having a decrease in PSA of greater than or equal to 50% (1).

The prognostic value of PTEN loss and ERG rearrangement was also evaluated by *Bismar et al.* in a study including 463 patients where the PTEN and ERG status was correlated with clinical and pathological features such as Gleason score, patients' outcomes, and possible androgen deprivation therapy. ERG expression and PTEN loss was documented in

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28.2% and 38% of patients, respectively. It was quite interesting that among PTEN negative tumors, 21.8% presented as ERG positive. In cases where PTEN was intact patients presented with better cancer specific survival. On the other hand, patients with decreased PTEN intensity without ERG positivity showed the worst clinical outcome compared to those with no PTEN loss and no ERG expression, where they had best clinical outcome. Patients with ERG expression with or without PTEN loss showed intermediate risk in relation to lethal disease (3). The correlation between PTEN and ERG protein expression and prostate cancer is a field of investigation where many mechanisms and pathways are still being discovered in ongoing trials. There is a need of results from new, large clinical trials in order to establish the clinical utility of both PTEN and ERG status in the management of PCa patients.

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