**ORIGINAL ARTICLE**

**Oncologic results associated with combined PTEN loss and ERG expression in prostate cancer patients after radical prostatectomy**

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**Abstract**

**Introduction:** Prostate cancer is one of the leading causes of cancer mortality in Europe displaying a variety of clinical behavior from tumors of low clinical significance to highly aggressive tumors. There is an increasing interest in identifying molecular pathways and genes which can be used as prognostic factors. The purpose of this study is to evaluate PTEN loss and ERG expression on oncologic results in patients who underwent radical prostatectomy as treatment for localized prostate cancer.

**Methods:** We analyzed data from 68 patients who underwent radical prostatectomy for localized prostate cancer in our department the last year. In all patients we assessed PTEN and TMPRSS - 2 ERG expression by immunohistochemistry methods. Patients were divided into four groups according to PTEN and TMPRSS - 2 combined expression and oncologic results were compared accordingly.

**Results:** This study support data showing that PTEN loss is an unfavourable prognostic marker. Furthermore, the worst oncologic results following radical prostatectomy were present in the group of patients who had PTEN deletion without expression of TMPRSS - 2 ERG fusion protein. Loss of PTEN expression combined with non expression of TMPRSS - 2 ERG fusion was associated with higher rates of positive surgical margins (17.6%), higher rates of Gleason Score 8 or 9 (8.8%) and more frequent rates of seminal vesicles invasion (7.4%).

**Key words**

PTEN; TMPRSS2 - ERG; prostate cancer; radical prostatectomy

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ly deleted tumor suppressor gene in prostate cancer. Binding of growth factors to the receptor tyrosine kinase activates the receptor complex, which in turn recruits and activates PI3K. Activated PI3K converts PIP2 to PIP3 which subsequently mediates the phosphorylation of Akt through PDK1. As a result, phosphorylated Akt targets mTOR which is involved in cell growth, proliferation and survival. Total absence of PTEN expression is associated with high Gleason score and advanced pathological stage.

ERG gene is an oncogene meaning that it encodes a protein typically mutated in cancer. ERG can fuse with TMPRSS - 2 to form an oncogenic fusion gene which is very often encountered in prostate cancer patients. This fusion is estimated to be present in about 50% of prostate cancer cases and is related in vivo with tumor progression.

**Material and methods**

We analyzed data from 68 patients who underwent radical prostatectomy for localized prostate cancer in our department the last year. In all patients we assessed PTEN and TMPRSS - 2 ERG expression by immunohistochemistry methods involving antibodies against ERG (EP111, Dako) and PTEN (6H2.1, Dako) in paraffin embedded samples (Figure 1 - 2).

**Results**

PTEN loss was present in 51 patients (75%) and TMPRSS - 2 ERG rearrangement was discovered in 17 patients (25%) (Figure 1 - 2). Oncologic results were evaluated by postoperative Gleason score, positive surgical margins and TNM status. As a result, 25 patients (36.8%) presented with positive surgical margins, 10 patients (14.7%) had seminal vesicles invasion and 13 (19.1%) patients had Gleason Score 8 or 9. All patients were divided into four groups according to PTEN and TMPRSS - 2 combined expression and oncologic results were compared accordingly. As a result, loss of PTEN expression combined with non expression of TMPRSS - 2 ERG fusion was associated with higher rates of positive surgical margins (17.6%), higher rates of Gleason Score 8 or 9 (8.8%) and more frequent rates of seminal vesicles invasion (7.4%) (Table 1). As far as it concerns the presence of Gleason Score 8 or 9, no statistical difference was noted between Group B and Group D.

**Discussion**

The search for accurate prognostic biomarkers in prostate cancer is critical for evolution of accurate management of prostate cancer patients. This study evaluates the combined expression of two genomic biomarkers (PTEN, TMPRSS - 2 ERG fusion) on oncologic results in patients underwent radical prostatectomy as treatment for localized prostate cancer.

The tumor suppressor gene PTEN is one of the most frequently mutated genes linked to a variety of human cancers including prostate cancer. Nowadays, in vitro and in vivo studies support data showing that PTEN interacts with the androgen receptor (AR) in various
stages of prostate cancer. More specifically, the interaction between PTEN and AR inhibits the AR nuclear translocation and promotes the AR protein degradation that results in the suppression of AR transactivation and induction of apoptosis. Moreover, the loss of PTEN expression in prostate LNCaP cells leads to constitutive activation of Akt which is an important cell surviving factor. As the PI3K/Akt and the androgen/AR signaling pathways represent two major survival pathways in the LNCaP prostate cancer cells and PTEN could repress both pathways it is proposed that inhibition of these two pathways by PTEN might contribute to PTEN - induced cell apoptosis in the LNCaP prostate cancer cells. On the other hand, there are data supporting the theory that PTEN functions as a transcriptional inhibitor of AR by preventing Akt activation, and that a downstream effect of the protein kinase Akt mediates this interaction. Unchecked Akt activation, which is frequently observed in advanced prostate cancer may be associated with uncontrolled AR signaling, which may explain why androgen - independent prostate cancer cells are insensitive to hormonal manipulation, but still require AR for their survival and proliferation. Although clinical significance of PTEN loss still needs further clarification, loss of PTEN expression is thought to be a negative prognostic indicator linked to high Gleason score and advanced stage of prostate cancer.

As far as it concerns TMPRSS2 - ERG gene fusion, it is also a frequent genomic alteration as PTEN loss in prostate cancer cells with significant clinical importance. TMPRSS2 - ERG fusion is associated with a greater likelihood of lethal prostate cancer, moderate to poorly differentiated tumors and higher stage disease with lymph node metastasis.

Most studies examine individual effects of each genomic biomarker on oncologic results. Theoretically, the most favourable group in terms of prognosis should include patients in which PTEN tumor suppressor gene is not deleted and TMPRSS - 2 ERG oncoprotein is not expressed. In our study, patients with unfavourable oncologic results after radical prostatectomy presented with PTEN loss and non expression of TMPRSS - ERG protein. Our results support the candidacy of PTEN as a tumor suppressor gene in prostate cancer progression. It is obvious that PTEN loss is an important negative prognostic factor. Although recent studies proposed that the synergic co - operation between PTEN deletion and ERG rearrangement could be a significant driver for prostate cancer development and progression no such results were present in our study. A possible explanation may be that prostate cancer progression is initially driven by PTEN loss which may facilitate ERG rearrangement in the future. Also, recent studies suggest that ERG fusion is not required for PTEN loss to determine aggressive tumor behaviour, because PTEN deletion in both ERG fusion positive and fusion negative cancers was independently linked to poor prognosis, while the presence of ERG fusion was unrelated to patient prognosis. The importance of identifying such genomic biomarkers is supported by recent developments of

### Table 1

<table>
<thead>
<tr>
<th>Oncologic results</th>
<th>GROUP A ERG+/PTEN -</th>
<th>GROUP B ERG-/PTEN +</th>
<th>GROUP C ERG+/PTEN +</th>
<th>GROUP D ERG-/PTEN -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive surgical margins (25 patients, 36.8%)</td>
<td>3 patients 4.4%</td>
<td>6 patients 8.8%</td>
<td>4 patients 6%</td>
<td>12 patients 17.6% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Seminal vesicles invasion (10 patients, 14.7%)</td>
<td>0%</td>
<td>2 patients 2.9%</td>
<td>3 patients 4.4%</td>
<td>5 patients 7.4% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Gleason Score 8&amp;9 (13 patients, 19.1%)</td>
<td>0%</td>
<td>6 patients 8.8%</td>
<td>1 patient 1.5%</td>
<td>6 patients 8.8% (p &lt; 0.05)</td>
</tr>
</tbody>
</table>
specific kinase inhibitors targeting the mTOR pathway in prostate cancer patients with PTEN deletion\textsuperscript{17}.

**Conclusion**

Although recent extensive research has led to a more detailed understanding of the molecular pathways in prostate cancer progression, more study is needed in order to evaluate the most important genomic biomarkers related to tumor development and progression. This study supports data showing that PTEN loss is an unfavourable prognostic marker. Furthermore, the worst oncologic results following radical prostatectomy were present in the group of patients who had PTEN deletion without expression of TMPRSS - 2 ERG fusion protein. More extensive studies are needed including more patients in order to determine which patient group has favourable prognosis according to PTEN loss and TMPRSS - 2 ERG expression.\textsuperscript{17}

**Σκοπός:** Ο καρκίνος προστάτη αποτελεί μία από τις βασικότερες αιτίες θανάτου από καρκίνο στην Ευρώπη. Παρουσιάζεται με εύρος που εκτείνεται από όγκους χαμηλής κλινικής σημασίας έως πολύ επιθετικούς όγκους. Τα τελευταία χρόνια υπάρχει αυξανόμενο ενδιαφέρον για την ανεύρεση μοριακών μηχανισμών που μπορεί να χρησιμοποιηθούν και ως προγνωστικοί παράγοντες. Σκοπός αυτής της μελέτης είναι η επίδραση της συνδυασμένης απώλειας του PTEN και έκφρασης της ERG στα οικολογικά αποτελέσματα ασθενών με καρκίνο προστάτη που υποβλήθηκαν σε ριζική προστατεκτομή.

**Μέθοδος:** Αναλύθηκαν δεδομένα 68 ασθενών που υποβλήθηκαν σε ριζική προστατεκτομή στο τμήμα μας το τελευταίο έτος. Σε όλους τους ασθενείς αξιολογήθηκε η έκφραση του PTEN και της TMPRSS2 - ERG πρωτεινής με ανοσοϊστοχημεία.

**Αποτελέσματα:** Η μελέτη υποστηρίζει τα δεδομένα της βιβλιογραφίας που δείχνουν ότι η απώλεια του PTEN είναι ένας επιβαρυντικός προγνωστικός παράγοντας. Επιπλέον, τα πιο επιβαρυντικά οικολογικά αποτελέσματα βρέθηκαν στην ομάδα που παρουσίαζε απώλεια του PTEN χωρίς όμως παράλληλη έκφραση της TMPRSS2 - 2 ERG πρωτεινής καθώς οι ασθενείς αυτής της ομάδας παρουσίαζαν υψηλότερες ποσοστά θετικών χειρουργικών ορίων (17.6%), διήθηση ατακτών κύστεων (7.4%) καθώς και Gleason Score 8 ή 9 (8.8%).
Oncologic results associated with combined PTEN loss and ERG expression in prostate cancer patients after radical prostatectomy p. 52 - 56

References