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ORIGINAL PAPER

Clinical impact of ERG and PTEN status in prostate cancer patients underwent radical prostatectomy

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Summary *Objectives: Phosphate and tensin homolog gene (PTEN) acts as a regulator of PI3-K-Akt molecular pathway. ETS Related gene (ERG), an oncogene located in chromosome 21q22.2, is involved in prostate cancer (PCa) by serine 2 (TMPRSS2), a protein encoded by TMPRSS2 gene. The aim of this study is to evaluate the clinical impact of PTEN loss and ERG rearrangement in terms of oncologic results in patients diagnosed with localized PCa who underwent radical prostatectomy.*

Materials and methods: Prospective data were collected from a total of 74 patients who underwent open radical retropubic prostatectomy for localized PCa and immunohistochemical study was performed in tissue samples. The primary antibodies for anti-ERG antibody as well as anti-PTEN antibody were obtained from DAKO. ERG was considered positive if at least 20% of the evaluated cells were stained at least with medium intensity. PTEN protein loss was considered when the intensity of cytoplasmic and nuclear staining was mild or entirely negative across > 10% of tumor cells.

Results: Homogenous loss of PTEN was associated with higher clinical International Society of Urological Pathology (ISUP) grade (p = 0.018) while no statistical significant association was present regarding the presence of ERG rearrangement with either ISUPc or ISUPp. After a median follow up of 34 months, 24 patients developed biochemical recurrence. No statistical significant correlation of ERG status with biochemical recurrence was noted while PTEN was associated with biochemical recurrence development in a statistical significant way. Lastly the combination of PTEN loss with ERG rearrangement presence was detected more often in higher ISUPc and ISUPp as well as biochemical recurrence development, although in a non statistical significant way.

Conclusions: Homogenous and heterogenous PTEN loss was associated with biochemical recurrence. No association of ERG and biochemical recurrence was noted. The combination of PTEN loss and ERG rearrangement presented a trend for higher ISUPc and ISUPp as well as biochemical recurrence but not in a statistical significant way.

KEY WORDS: *ERG; PTEN; Prostate cancer; Radical prostatectomy.*

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INTRODUCTION

Prostate cancer (PCa) represents a major health problem as it is the second most commonly diagnosed malignancy among males leading to severe morbidity and mortality (1). PCa presents a wide variety of clinical behavior ranging from tumors of low metastatic potential to highly aggressive tumors characterized by a high risk of biochemical failure and metastasis development after initial treatment (2). As several molecular pathways and oncogenes are involved in PCa progression to lethal disease, understanding the genetic and molecular differences separating indolent from highly aggressive tumors is the cornerstone of risk stratification and selection of best treatment available.

The PI3-K-Akt molecular pathway, found to be upregulated in 30-50% of PCa patients, regulates a variety of cellular function including cell survival and proliferation, cell growth and differentiation and cell cycle progression and metabolism (3). The *phosphate and tensin homolog gene* (PTEN), a tumor suppressor gene located on chromosome 10q23.3, is quite frequently mutated in PCa patients and acts as a regulator of PI3-K-Akt molecular pathway (4). ERG oncogene (ETS Related gene) is a member of the ETS gene family located in chromosome 21q22.2 (5). In 50% of PCa patients ERG is involved as a fusion protein with transmembrane protease, serine 2 (TMPRSS2), a protein encoded by TMPRSS2 gene located in 21q22.3 (6). Although ETS fusion is encountered early in the carcinogenesis process, the presence of the fusion protein is also associated with poorly differentiated tumors, higher stage disease as well as lymph node involvement (7). As far as it concerns the clinical impact of PTEN loss combined with the presence of ETS fusion protein, both preclinical and clinical studies suggest that the co-existence of these aberrations may be indicative of poor prognosis (8).

The aim of this study is to evaluate the clinical impact of PTEN loss and ERG rearrangement in terms of oncologic results in patients diagnosed with localized PCa who underwent radical prostatectomy.

MATERIALS AND METHODS

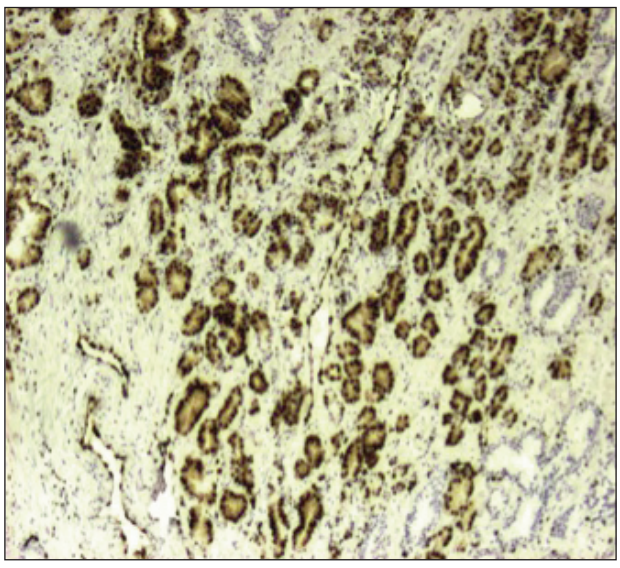
Data were collected in a prospective way from a total of 74 patients who underwent open radical retropubic

No conflict of interest declared.

prostatectomy for localized PCa during the years 2017 and 2018. Demographic information, PSA levels at diagnosis and clinical TNM stage were recorded. All patients underwent bone scan and CT scan prior to surgery for staging purpose. Patients with PSA levels above 20 ng/dl were excluded from the study. Histopathological examination of radical prostatectomy specimens defined the pathological stage, histopathological type as well as the Gleason score. Patients were followed up by PSA testing every three months until biochemical recurrence defined as PSA levels above 0.2 ng/dl.

Immunohistochemical study was performed in paraffin-embedded formalin-fixed tissue samples. Sections of 4mm were mounted on TOMO slides and fixated in oven at 70-80°C, de-waxed in xylene and then underwent through decreasing concentrations of alcohol. For anti-ERG antibody, the primary antibody was obtained from DAKO (*FLEX Monoclonal Rabbit Rabbit Anti-Human ERG, Clone EP111, Ready-to-Use*). After heat-induced epitope retrieval and a PH9 buffer, the sections were incubated for 1h with the antibody and counterstained in hematoxylin. For anti-PTEN antibody, the primary antibody was obtained from DAKO [Monoclonal Mouse Anti-Human PTEN (Concenctrate) Clone 6H2.1]. After heat-induced epitope retrieval and PH9 buffer, the sections were incubated for 1h in 1:100 of the primary antibody, followed by 15min in Linker. Counterstain was performed with hematoxylin. ERG was considered positive if at least 20% of the evaluated cells (neoplastic or with HGPIN) were stained at least with medium intensity (Figure 1). Endothelial cells were used as positive control. A tissue sample was considered to have PTEN protein loss if the intensity of cytoplasmic and nuclear staining was mild or entirely negative across > 10% of tumor cells, compared with surrounding benign glands and/or stroma, used as positive controls for PTEN protein expression. If the neoplastic cells showed PTEN loss in 10-90% of neoplastic cells, it was considered heterogeneous PTEN protein loss. If neoplastic cells showed PTEN protein loss in > 90%, it was considered homogeneous PTEN loss.

Figure 1.
Positive ERG staining using anti-human ERG antibody.



Regarding statistical methodology, continuous variables were expressed using medians, minimum-maximum values and interquartile range, while categorical variables using numbers and proportions. Fisher's exact test or Chi square test and Kruskal-Wallis test were used to analyze data, since after testing for distributions non-normality was detected. When a statistical significance was noted, pairwise comparisons were used to detect which exact groups differ. Pairwise comparisons were performed whenever a statistical significance was detected, using the Dunn's procedure. Statistical significance was set at p = 0.05. All analyses were done with IBM SPSS Statistics 25.0 software (*SPSS Inc., Chicago, IL.*).

Results

Median age was 70 years and median PSA was 7.3 ng/dl. Demographics as well as clinical and pathological ISUP grade and TNM stage are presented in Table 1.

PTEN status was defined as homologous loss in 15 patients, heterologous loss in 43 patients and as intact in 16 patients. ERG rearrangement was present in 29 patients and absent in 45.

In terms of correlation of PTEN status with ISUP grade, homogenous loss was associated with higher clinical ISUP grade (p = 0.018) while the medians of intact-homogeneous groups differed significantly for median ISUP pathology grade (p = 0.022) (Table 2).

On the other hand, no statistical significant association

Table 1.
Patients' demographics.

Number of patients	74
Age (median)	70
PSA	7.3 ng/dl
Clinical ISUP (number of patients)	
1	23
2	17
3	20
4	7
5	7
Pathology ISUP (number of patients)	
1	10
2	25
3	24
4	7
5	8
Pathology TNM	
pT2	50
pT3a	14
pT3b	10

Table 2.
PTEN status correlation with ISUPc and ISUPp.

	Median ISUPc	Median ISUPp
Homogeneous loss	3	3
Heterogeneous loss	2	3
Intact	1	2
p-value	0.018 *	0.022 **

* Using Kruskall-Wallis H test, the medians of intact-homogeneous groups differed significantly for median ISUPc grade.
** Using Kruskall-Wallis H test, the medians of intact-homogeneous groups differed significantly for median ISUPp grade.

Table 3.
ERG status and correlation with ISUPc and ISUPp.

	Median ISUPc	Median ISUPp
ERG (+)	2	3
ERG (-)	2	3
p-value	0.836	0.993

Table 4.
Biochemical recurrence and ERG status (chi-square test).

	No biochemical recurrence (%)	Biochemical recurrence (%)	p-value
Negative ERG	29 (64.4)	16 (35.6)	0.475
Positive ERG	21 (72.4)	8 (27.6)	

Table 5.
Biochemical recurrence and PTEN status (chi-square test).

	No biochemical recurrence (%)	Biochemical recurrence (%)	p-value
Heterogeneous loss	31 (72.1)	12(27.9)	0.031
Homogeneous loss	6 (40)	9 (60)	
Intact	13 (81.3)	3 (18.7)	

was present regarding the presence of ERG rearrangement with either ISUPc or ISUPp (Table3).
After a median follow up of 34 months, 24 patients developed biochemical recurrence defined as PSA levels above 0.2 ng/dl. No statistical significant correlation of ERG status with biochemical recurrence was noted (Table 4). On the other hand, both homogenous and heterogenous loss was associated with biochemical recurrence development in a statistically significant way (Table 5). As far as it concerns the combination of PTEN loss with ERG rearrangement presence, a trend in higher ISUPc and ISUPp as well as biochemical recurrence development was detected, although in a non-statistical significant way. Among patients who presented with combined PTEN homogenous loss and ERG rearrangement, 56% presented with biochemical recurrence during follow up. The combination of PTEN homogenous loss combined with no ERG rearrangement also presented high rates of biochemical failure (66%). Nevertheless, this group consisted only of 6 patients, thus no strong evidence could be extracted regarding this combination.

Discussion

It is nowadays well established that PCa is a disease presented with a wide clinical heterogeneity. Spectrum includes from indolent tumors of low clinical significance to highly aggressive tumors of high probability of biochemical recurrence after local treatment as well as severe metastatic potential. Currently, risk stratification for biochemical recurrence development after radical prostatectomy for patients with localized disease stratifies patients into three groups based on PSA, Gleason score and TNM status (9). To further stratify patients according to molecular and genetic profile, it is of great interest to develop novel markers based in the genomic instability characterized by activation of oncogenes or deactivation of tumor suppressor genes.
PTEN is a tumor suppressor gene located in chromosome 12q23.3 acting as a regulator of the PI3-K-Akt molecular pathway (4). The PI3-K-Akt pathway, frequently upregulated in PCa patients, is an important intracellular molecular pathway regulating crucial cellular functions including cell proliferation, growth, differentiation, cell cycle progression, metabolism and survival (3). Several growth factors including *epidermal growth factor* (EGF), *platelet derived growth factor* (PDGF) and *insulin like growth factor* (IGF) initiate the activation of the PI3-K-Akt pathway by activating tyrosine kinase receptors promoting the phosphorylation of PI3K at the cell membrane level. Phosphorylated PI3K becomes active and promotes the conversion of PIP2 to PIP3. This event leads to the phosphorylation of Akt mediated by PDK1 (10). Akt plays an important role in carcinogenesis and tumor progression mainly by interfering with antiapoptotic pathways (11). Moreover, it may influence the activity of tumor suppressor gene p53 (12). Akt also interacts with the androgen receptor promoting nuclear translocation in an androgen independent manner (13). Activated Akt has also a profound role in carcinogenesis by promoting cell growth and protein synthesis through the regulation of the mam*malian target of rapamycin* (mTOR) pathway (14). PTEN suppressor gene protein product is a dual lipid phosphatase which acts as a negative regulator of the PI3-K-Akt pathway. PTEN protein removes the 3-phosphatase from PIP3 converting it back to PIP2 thus inhibiting the phosphorylation of Akt (4, 10). In addition, genomic stability is also influenced by PTEN protein through involvement with the MAPK signaling network which affects both directly and indirectly the androgen receptor activity (14).
Since PTEN is the most commonly tumor suppressor gene mutated in PCA, PTEN loss may act as a prognostic marker associated with poor oncological outcomes and may facilitate the selection of patients who are more likely to benefit from intensive definite treatment modalities (15). PTEN mutations are more frequently encountered in metastasis providing further evidence that PTEN loss is associated with the disease progression (16). More specifically, PTEN deletion is associated with higher disease stage among patients with Gleason score 7 (17). A meta-analysis involving 26 published studies with a total of 8097 patients presented that intact PTEN status results in less aggressive disease and lower Gleason score (18). Results from a multicenter analysis support that PTEN deletion is strongly associated with seminal vesicle involvement as well as extracapsular extension (19). Furthermore, homologous, and heterologous PTEN loss is associated with greater risk of biochemical recurrence compared with no PTEN loss (20, 21). In a meta-analysis including 2,154 cases with positive expression of PTEN and 1.006 PTEN deletion cases, PTEN positive expression was associated with prolonged biochemical free survival (22). Nevertheless, patients with homologous PTEN loss present worst prognosis in terms of biochemical free survival (23). *Lotan et al.*, presented data supporting that only homologous PTEN loss is associated with worst bio-

chemical free survival, while heterogenous loss has the same impact as PTEN intact status (24). As far as it concerns lymph node involvement, it is more frequently encountered in patients with PTEN deletion (25).
ETS Related gene (ERG) is an oncogene member of the ETS gene family located in chromosome 21q22.5. It encodes ERG protein which is involved in PCa carcinogenesis and progression as a fusion protein with transmembrane protease, serine 2 (TMPRSS2), a protein encoded by TMPRSS2 gene located in 21q22.3 (5, 6). TMPRSS2:ERG fusion is the most common ETS family rearrangement and is detected in 50% of PCa patients (26). Such rearrangement leads to neoplastic phenotype by overexpressing transcription factors which are important from the first step of carcinogenesis (27).
ERG rearrangement is encountered rarely in indolent PCa tumors and it is usually associated with more advanced stage with either extracapsular extension or seminal vesicles involvement (28, 29). Furthermore, it presents an independent prognostic value regarding both biochemical and clinical recurrence, especially among grade group 4 or 5 patients (30). Among patients with localized PCa treated with radical prostatectomy, TMPRSS2-ERG fusion was associated with higher tumor stage but not with other oncological parameters (31). On the other hand, *Lee et al.* demonstrated that positive ERG status is frequently present among patients with perineural invasion or positive apical margins (32). Quite interesting is the fact that ERG status among PCa patients is characterized by racial disparities. Highest frequencies of ERG rearrangements are encountered among Caucasian descents, lower frequencies among African Americans and even lower prevalence among Asian men. In Asian cohorts, ERG positive status was more frequent in low Gleason score and low stage patients in contrast with western cohorts (33). As TMPRSS2-ERG fusion is not a frequent genomic alteration among Asian PCa patients it has limited significance in clinical practices in Asian populations (34). In a meta-analysis including 6744 patients, *Liu et al.* conclude that ERG status is not correlated with biochemical free survival or recurrence free survival (35). In non-surgical cohorts, ERG expression is associated with advanced stage, higher probability of metastasis as well as increased mortality (36).
As far as it concerns immunohistochemistry as a method of PTEN and ERG status evaluation, the technique presents 100% sensitivity and 97.8% specificity for detecting PTEN genomic alterations (37). Although most studies use FISH in order to detect PTEN alterations, immunohistochemistry using commercially available antibodies is a validated method with similar results as high concordance is present between the two methods (38, 39). Characterization of ERG status by immunohistochemistry in prostate tissue has also an excellent correlation with FISH and is validated method to be used in clinical practice (40).
ERG fusion protein is often accompanied by PTEN loss, a condition which further up regulates the Akt pathway leading to more aggressive cancer progression (41). Early in the carcinogenesis process, PTEN loss and subsequent low PTEN protein results in genomic instability. Such instability may provoke ERG fusion and thus a synergistic action in Akt pathway leading to poor prognosis (10, 41). Regarding the relationship between PTEN and ERG status in terms of oncological results, *Brady et al.* presented that combined loss of PTEN with negative ERG expression leads to a trend over immediate recurrence after surgery but not in a statistically significant way (42). On the other hand, *Mehra et al.* concluded that patients who exhibited ERG rearrangement and loss of PTEN had no significant difference in time to recurrence compared to patients with wild-type ERG and loss of PTEN (21).
A proposed method for risk stratification in a non-surgical cohort including patients treated with androgen deprivation therapy suggests that worst clinical outcome is among patients with decreased PTEN intensity without ERG positivity. Patients with positive ERG expression presented intermediate risk for lethal disease regardless PTEN status (43). In an analysis of 80 PCa patients no patient with low grade disease bared concurrent TMPRSS2-ERG fusion and PTEN loss (44). In a large radical prostatectomy cohort including 815 patients, loss of PTEN in ERG negative patients was predictive of secondary therapies as well as shorter disease specific survival (45). It is quite clear that although great interest exists in determining the role of combined PTEN status with ERG fusion no solid conclusions can be made as data remain conflicting (46, 47).
To our knowledge this is the first study evaluating the role of individual PTEN and ERG status and their possible combination regarding oncological results in men who underwent radical prostatectomy. Disadvantages of the present study include the relatively low sample which underpowered statistical analysis and the fact that PTEN and ERG status was examined only by immunohistochemistry and not by FISH.

Conclusions

Homogenous and heterogenous PTEN loss was associated with biochemical recurrence in PCa patients treated with radical prostatectomy. No association of ERG status and biochemical recurrence was noted. The combination of PTEN loss and ERG rearrangement presented a trend for higher ISUPc and ISUPp as well as biochemical recurrence but not in a statistically significant way.

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