Original Article

Expression and Prognostic Role of Erythroblast Transformation Specific-related Gene (ERG) Oncoprotein in Prostatic Cancer

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Objective: To determine the prevalence and prognostic value of ERG in prostatic cancer. The association of ERG status and other clinic-pathologic features were also studied.

Materials and Methods: Tissue paraffin blocks of patients who had diagnosis of prostatic acinar adenocarcinoma during 2006 to 2013 at Faculty of Medicine Vajira Hospital were identified. The original H&E stained slides were reviewed to select 2 areas with the most prominent Gleason pattern for tissue sampling. The selected tissue samples were embedded in tissue microarray (TMA) blocks and processed for ERG staining. Intensity and area of positive ERG stain were evaluated independently by two pathologists. Clinico-pathological data collected were age, pre-operative prostate-specific antigen (PSA), tumor stage, PSA biochemical-relapse, and pathological information of peri-neural or lymphovascular invasion, surgical margin, the International Society of Urological Pathology (ISUP) grade group, and Gleason score were collected and analyzed.

Results: Among 107 samples, positive ERG staining was found in 31.8% (34 cases). Features which were significantly associated with ERG positive comparing to those in ERG negative were: younger age, 67.7±8.5 years vs. 72.6±8.6 years (p = 0.008); lower Gleason score (6 and 7), 79.4% (27 cases) vs. 20.6% (7 cases) (p = 0.010) and lower ISUP grade group (group 1, 2 and 3), 82.4% (28 cases) vs. 17.6% (6 cases) (p = 0.004), respectively. No significant different association between ERG status and other clinic-pathologic features including survivals. The 5-year overall survival and 5-year disease-free survival (95% confidence intervals) of the patients with ERG positive and negative were: 84.4% (70.1 to 98.7%) vs. 77.1% (66.1 to 88.1%) (p = 0.399) and 77.4% (60.9 to 93.9%) vs. 78.2% (67.6 to 88.8%) (p = 0.571), respectively.

***Conclusion*:** The prevalence of ERG-positive in prostate cancer patients was 31.8%. The patients with ERG positive were younger, more of low Gleason score and low ISUP grade group. No significant association between ERG status and other clinic-pathologic parameters as well as survivals were found.

Keywords: Prostatic cancer, ERG, Immunohistochemistry

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Prostate cancer is the second most common cancer in men after lung cancer. The global incidence in 2012 reported 1,112,000 new cases of cancer with 307,000 deaths[1]. Prostate cancer was more commonly found in developed than in developing countries[1]. In Asia, 122,000 new cases (10 patients per 100,000 population) of prostate cancer were reported; this accounted for 14% of the global incidence. The combined number of deaths were highest in Japan (32%) followed by China (28%) and Australia (15%)[2]. In addition, the incidence of prostate cancer in Asian countries was found to be on the rise[2-8]. In Thailand, there were 2,134 new cases reported in 2008 an increase on average of 3% per year between 1983 to 2009, with a 17% increase rates of death per year between 1994 to 2006[2].

Prostate cancer usually originates at peripheral zone of the prostate, and rarely that it would advance into the transitional zone. Thus, signs and symptoms of urinary tract obstruction are generally not observed. Digital rectal examination, serum prostate-specific antigen (PSA), and biopsy are the main diagnostic methods. Radiological examination is generally performed to assess the extent of disease prior to treatments. Prostate cancer is characterized by its histopathological origins as glandular neoplasms or tumors of other urinary tract epithelium e.g. urothelial, squamous, and basal cell. The most commonly histopathology of prostate cancer found in more than 90% is acinar type adenocarcinoma[9].

At present, there are many available treatments for prostate cancer including active surveillance, radical

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prostatectomy, irradiation, androgen deprivation therapy, chemotherapy and targeted therapy. Treatment plans in each patient usually depend upon pre-operative PSA levels, histologic grade (Gleason score) and TNM stage of tumor[9,10].

In general, the patients with prostate cancer are divided into 3 major groups. The first group are patients with clinical localized disease, whereby carcinoma cells are not detected in other organs. In this group, patients are divided into 4 subgroups, depending on the risk of recurrence and survival. These risk levels are: very low-, low-, intermediate- and high-risk. The second group is locally advanced disease group or those with cancer spreading to nearby organs whereas the third group, disseminated disease, has cancer spread to other organs[9,10].

Prognosis of patients with prostate cancer is determined according to various factors described by the World Health Organization (2016)[11]. These factors include pre-operative PSA, histologic grade (Gleason score), and TNM stage which indicate the extent of lesions. These factors are usually assessed for treatment planning. However, the treatment outcomes in each individual patient of the same risk group may vary. Recurrence rates may range from 20% to 60% in intermediate- and high-risk groups after surgery or radiation[12,13].

Another important prognostic indicator is genetic factor. Various forms of gene mutations in prostate cancer have been identified. The most common genetic aberration found is transmembrane protease, serine 2-erythroblast specific transformation (ETS) and related gene fusion (TMPRSS2-ERG fusion). TMPRSS2 is a gene at the chromosomal position of 21q22.3 which encodes transmembrane protease serine 2 enzyme. Cells that express such genes respond well to androgen hormone. ERG is a gene at the chromosomal position of 21q22.2 which acts as oncogene that produces ERG oncoprotein. The significant roles of this gene are; controlling cell proliferation, differentiation, apoptosis and angiogenesis[14,15]. TMPRSS2-ERG fusion genes complex results in androgen hormonal response and unregulated cell fission[16-20].

The prevalence of such gene among populations vary depending on their geographic or ethnic origins. According to studies in Western countries, TMPRSS2-ERG fusion was found in 50 to 70% of prostate cancer patients[21,22]. On the other hand, it was found in only 39% in Malaysia, 23% in the Philippines, and 16% in Japan[23-25].

ERG oncoprotein can be detected by immunohistochemistry (IHC) which has higher sensitivity (96 to 100%) and specificity (85 to 99%) comparing to other standard methods of fluorescent in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR)[26-31].

Although the prognostic role of TMPRSS2-ERG fusion complex has been studied, the results were inconsistent. In most studies, TMPRSS2-ERG fusion was found to be a poor prognostic determinant, associated with advanced stage cancer, high Gleason score, connective tissue changes indicating aggressiveness of the disease, higher recurrence rates, short duration of PSA progression-free, and survival[23,32-34]. However, other studies found that that TMPRSS2-ERG fusion was unrelated to Gleason score, pathological stage, or survival[35,36].

Due to the discrepancies in rates of TMPRSS2-ERG fusion in different countries, data from each country is important. This research aimed to investigate TMPRSS2-ERG fusion complex in prostate cancer patients in Thailand. Furthermore, with the inconsistent findings of its prognostic role from previous studies, the present study also evaluated the relationship between the expression of ERG oncoprotein and other clinic-pathologic prognosis factors and survivals. This information would serve as database for future applications of targeted therapy especially for Thai patients with prostate cancer.

Materials and Methods

Study population

The patients who were diagnosed as prostatic cancer by core needle biopsy (CNB) or transurethral resection of the prostate (TURP) during January 2006 to December 2013 at Faculty of Medicine Vajira Hospital were identified. Inclusion criteria were prostatic cancer of acinar adenocarcinoma. Other subtypes of prostatic cancer, metastatic cancer from other site, absence of paraffin block and absence of pre-operative PSA were excluded from the study.

Pathological analysis

The original H&E stained slides of the patients were reviewed to select 2 areas with the most prominent Gleason pattern for tissue sampling. The selected tissue samples were retrieved from the paraffin blocks by manual technique and embedded in tissue microarray (TMA) blocks. The slides of 4 µm sectioning were immunohistochemical stained for ERG staining by Leica Bond-maX autostainer (Leica Microsystems, Bannockburn, IL).

In brief, the slides were incubated for 60 minutes at 60°C and treated with Bond Dewax Solution (Leica Microsystems). Epitope retrieval was performed by incubating the slides in Bond Epitope Retrieval Solution 2 (Leica Microsystems) for 20 minutes at 100°C. Immunohistochemical analysis was performed using the Bond Polymer Refine Detection Kit (Leica Microsystems), a 3-step indirect immunoperoxidase technique. Primary antibody (ERG mouse monoclonal antibody, Biocare Medical, clone 9FY at 1: 75 dilution) was applied for 45 minutes at room temperature followed by 3 consecutive rinses with Bond Wash Solution (Leica Microsystems). Peroxidase block (3% hydrogen peroxide) was then applied for 5 minutes and rinsed 3 times with Bond Wash Solution. Post primary polymer (Leica Microsystems) was applied for 15 minutes before rinsing 3 times with Bond Wash Solution. Polymer Poly-HRP IgG (Leica Microsystems) was applied for 8 minutes and rinsed 3 times with Bond Wash Solution and one with Deionized water before the diaminobenzidine chromogen was applied for 4 minutes followed by 3 deionized water rinses. Slides were counterstained with hematoxylin for 5 minutes.

All original H&E stained slides were reviewed independently by two pathologists (CC, NP) to confirm a diagnosis of prostatic acinar adenocarcinoma, Gleason score, ISUP grade group, tumor volume, neural invasion, lymphovascular invasion, and surgical margin status of radical prostatectomy specimen. ERG stain was evaluated as positive or negative result. In positive case, intensity of the ERG stain was assessed as 1+, 2+ and 3+ as mild, moderate and marked intensity. Volume of positive area was also assessed. The clinical and pathological information were blinded in all processes.

Data collection

Clinical data of age, pre-operative PSA, tumor stage, mean tumor area assessed from original H&E stained slides, PSA biochemical relapse, and pathological information of peri-neural invasion, lymphovascular invasion, surgical margin in case of radical prostatectomy, the International Society of Urological Pathology (ISUP) grade group, and Gleason score were collected. The clinical and pathological information were blinded in all processes.

Gleason scoring system and ISUP grade grouping were re-evaluated according to 2016 World Health Organization. Gleason score was categorized as low when the scores were 6 or 7 and high if the scores were 8, 9 or 10. Whereas the ISUP grade was defined as low ISUP grade group including group 1, 2 and 3 or high ISUP grade including group 4 and 5. Overall survival (OS) was obtained from the date of diagnosis to the date of death or to the end of the study whereas progression-free survival (PFS) was obtained from the date of diagnosis to the date of progression or recurrence including PSA biochemical relapse, or date of death.

Statistical analysis

Patient characteristics were presented as percentage, mean $\pm$ standard deviation (SD) and median with interquartile range. Chi-square test, Fisher's exact test, or Mann-whitney U test was used to test the association between ERG status and other clinic-pathologic features as appropriate. Kaplan-Meier along with the log-rank tests were used to test the association between ERG status and 5-year PFS and 5-year OS. The p-value <0.05 was considered as statistical significant.

Results

A total of 107 samples were available and included for analysis. The mean age of the patient was 71.1$\pm$8.8 years. Thirty-three patients had undergone radical prostatectomy; 11 of their specimens had positive surgical margin.

The median pre-operative PSA was 16.8 ng/mL (IQR, 8.2 to 75.7 ng/mL). Majority of the tumors (66 cases or 61.7%) had Gleason score 6 to 7, and was defined as ISUP Grade group 1 to 3. The mean tumor volume was 33% (IQR, 20 to 66.5%). Slightly more than half had early stage 1 to 2 (55 cases or 51.4%). Neural invasion was identified in approximately 1/3 (36 cases or 33.6%) whereas lymphovascular invasion was rarely found (6 cases or 5.6%).

Information of PSA biochemical relapse was available for 102 patients. ERG status revealed positive results for 31.8% (34 cases) (Figure 1). Most cases were scored as mild (score as 1+, Figure 1B) and moderate (score as 2+, Figure 1C) intensity (17/34 and 16/34 cases respectively). Only one sample was scored as strong intensity (score as 3+, Figure 1D). Characteristic features of the study population were shown in Table 1.

The association of ERG status and several parameters were investigated. ERG positive group was associated with younger patient. Mean patient age was lower in ERG positive group (67.7$\pm$8.5) when compared to ERG negative group (72.6$\pm$8.6) (p = 0.008). The authors found that ERG positive group was correlated with low Gleason score 79.4% (27 cases) vs. 20.6% (7 cases) (p = 0.01) and low ISUP grade group 82.4% (28 cases) vs. 17.6% (6 cases) (p = 0.004). Other parameters displayed no significant difference between ERG positive and negative groups. Details are shown in Table 2.

Five patients were lost to follow-up after a diagnosis. After a median follow-up of 59.1 months (3 to 129 months) among other 102 patients, 6 had disease progression and 18 patients had recurrence. Overall, 18 patients were dead. The 5-year PFS and 5-year OS were 78.0% (95% confidence interval [CI], 69.2 to 86.8%) and 79.3% (95% CI, 70.5 to 88.1%).

The authors investigated ERG status in relation to 5-year PFS and 5-year OS. The 5-year PFS and 5-year OS of the patients with ERG positive expression were not significantly different from those with ERG negative expression: 77.4% (95% CI, 60.9 to 93.9%) vs. 78.2% (95% CI, 67.6 to 88.8%) (p = 0.571) and 84.4% (95% CI, 70.1 to 98.7%) vs. 77.1% (95% CI, 66.1 to 88.1%) (p = 0.399) respectively (Table 3) (Figure 2).

Discussion

Since the discovery of TMPRSS2-ERG fusion, several studies were conducted to examine its prevalence and prognostic value in patients with prostatic adenocarcinoma. Previous studies among Western patients revealed high incidence of up to 50 to 70% of TMPRSS2-ERG fusion in prostatic adenocarcinoma[21,22]. The incidence was much lower in studies among Asian patients: 39% in Malaysia, 23% in the Philippines and 16% in Japan[23-25]. The present study shows 31.8% of ERG positive rate which was much lower than those from the Western countries but was in the range as demonstrated from studies in Asia. This parity may be the results from different genetic background of the patients in each study. This ethnic influence was also observed in the different incidence of prostate cancer. Few studies reported lower genetic risk of prostate cancer in Asian compared to Western men[37,38]. The incidence was 37.2 prostate cancer per 100,000 populations in Asian American and 69.0 cases per 100,000 populations in White American[37,38].

Aside from the ethnic background, another possible

influencing factor on the prevalence of TMPRSS2-ERG fusion is androgenic activity. High testosterone concentration facilitates TMPRSS2-ERG fusion in vitro by induce proximity of 2 genomic loci[39,40]. High ERG expression in African-American men may be explained by high free circulating testosterone with higher expression of androgen receptor in their prostatic tissue of either benign and malignant[25,41]. Nevertheless, the white Caucasian with lower androgen activity than African American were also found to have higher ERG expression[37,38] indicating multifactorial including other unknown factors which may influence the ERG expression.

The prognostic value of the TMPRSS2-ERG fusion in prostatic adenocarcinoma was inconsistent in several studies. Some showed significant association between TMPRSS2-ERG fusion and worse prognostic parameters, such as high Gleason score, high recurrent rate, advance tumor stage and low PSA progression-free survival[23,32-34]. However, other studies did not find such association[35,36]. The present study found significant association of ERG positive status with younger patient (p = 0.008), low Gleason score (p = 0.01) and low ISUP grade group (p = 0.004). This was in contrast with previous studies which reported association of ERG positive status with high Gleason score[23,34].

Possible reason for inconsistent findings of ERG prognostic value in several studies could be different methods used in detecting ERG rearrangement (immunohistochemistry versus FISH). In addition, the definition criteria of ERG positive status by either immunohistochemical technique or FISH were also different in each report[23-25]. Another reason could be different study population. The older study population is usually patient with advance disease. This study reveals significant association of ERG expression to worse prognostic parameter. The population of other recent study is patient from PSA screening program which usually be localized disease. This group shows no association with prognostic parameters[16,21].

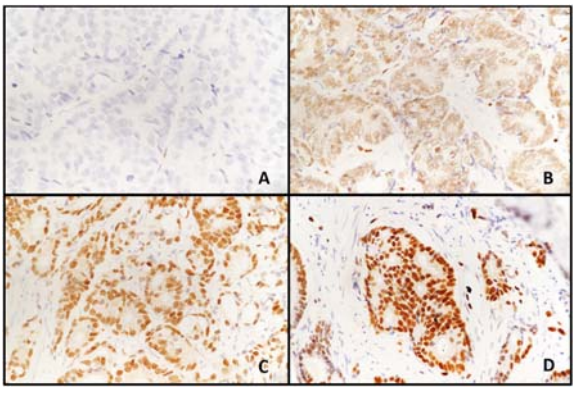

Figure 1. ERG stain assessment: Negative (A), Mild intensity (B), Moderate intensity (C), Marked intensity (D).

Conclusion

The immunohistochemical study showed 31.8% of prostatic acinar adenocarcinoma had ERG positive. This ERG positive rate was relatively lower than those observed in studies from Western population but comparable to studies from Asia. The ERG positive rate was significantly higher in younger patients, tumors with a low Gleason score and low ISUP grade group. The present study could not demonstrate any survival differences between the prostatic cancer patients with positive or negative ERG status.

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Table 1. Demographics of the study population investigated for ERG expression (n = 107)

Parameters	
Age (years)	71.10±8.83
Preoperative PSA (ng/mL)	16.86 (8.22 to 75.74)
Gleason score	
6	19 (17.8%)
7	47 (43.9%)
8	11 (10.3%)
9	28 (26.2%)
10	2 (1.8%)
ISUP grade group	
1	19 (17.8%)
2	43 (40.2%)
3	4 (3.7%)
4	11 (10.3%)
5	30 (28.0%)
Tumor area (%)	33.0 (20.0 to 66.5)
Stage	
1	20 (18.7%)
2	35 (32.7%)
3	24 (22.4%)
4	28 (26.2%)
Surgical margin	
Negative	22 (20.6%)
Positive	11 (10.3%)
Non prostatectomy samples	74 (69.2%)
Peri-neural invasion	
Negative	71 (66.4%)
Positive	36 (33.6%)
Lymphovascular invasion	
Negative	101 (94.4%)
Positive	6 (5.6%)
PSA biochemical relapse	
Negative	88 (82.2%)
Positive	14 (13.1%)
Loss to follow-up	5 (4.7%)
ERG	
Negative	73 (68.2%)
Positive	34 (31.8%)
Intensity 1+	17 (50.0%)
Intensity 2+	16 (47.1%)
Intensity 3+	1 (2.9%)

Data presented as n (%), mean ± SD, or median (interquartile range)

Table 2. Distribution of ERG negative and positive according to clinical-pathological features (n=107)

Variables	ERG		*p*-value*
	Negative (n = 73)	Positive (n = 34)	
Age (years)	72.6±8.60	67.8±8.52	0.008
Preoperative PSA (ng/mL)	20.6 (9.9 to 95.9)	11.4 (7.6 to 40.1)	0.143
Gleason score			
<8	39 (53.4%)	27 (79.4%)	0.010
≥8	34 (46.6%)	7 (20.6%)	
ISUP Grade group			
<4	39 (53.4%)	28 (82.4%)	0.004
≥4	34 (46.6%)	6 (17.6%)	
Tumor area (%)	25.0 (20.0 to 68.8)	36.5 (20.0 to 60.0)	0.229
Stage			
<3	35 (47.9%)	20 (58.8%)	0.259
≥3	38 (52.1%)	14 (41.2%)	
Surgical margin			
Negative	13 (17.8%)	9 (26.5%)	0.277
Positive	6 (8.2%)	5 (14.7%)	
Non prostatectomy samples	54 (74.0%)	20 (58.8%)	
Peri-neural invasion			
Negative	51 (69.9%)	20 (58.8%)	0.260
Positive	22 (30.1%)	14 (41.2%)	
Lymphovascular invasion			
Negative	69 (94.5%)	32 (94.1%)	1.000
Positive	4 (5.5%)	2 (5.9%)	
PSA biochemical relapse			
Negative	57 (78.1%)	31 (91.2%)	0.180
Positive	11 (15.1%)	3 (8.8%)	
Loss to follow-up	5 (6.8%)	0 (0.0%)	

Data are presented as n (%), mean±SD, or median (interquartile range)
*: comparison between ERG negative and positive group; t-test for age, Mann-Whitney U test for preoperative PSA and tumor area, Chi-square test for Gleason score, ISUP grade group, stage, surgical margin and peri-neural invasion, and Fisher's exact test for lymphovascular invasion and PSA biochemical relapse

Table 3. Association between ERG status and Clinical outcome

Survival (%)	All patients	ERG		*p*-value*
		Negative	Positive	
5 years Disease-free survival rate	78.0%	78.2%	77.4%	0.571
(95% confidence interval)	(69.2 to 86.8%)	(67.6 to 88.8%)	(60.9 to 93.9%)	
5 years Overall survival rate	79.3%	77.1%	84.4%	0.399
(95% confidence interval)	(70.5 to 88.1%)	(66.1 to 88.1%)	(70.1 to 98.7%)	

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What is already known on this topic?

TMPRSS2-ERG fusion is the most common genetic aberration of prostatic cancer. The prevalence reported in previous studies depending partly on the ethnicity: higher in Western compared to Asian countries. Many studies revealed inconsistent result of the prognostic value of ERG status. Some displayed its association with worse prognostic parameters and survivals but the others did not show the association. No information of the prevalence and prognostic value of ERG expression in Thai population had been reported.

What this study adds?

The prevalence of ERG expression in Thai prostatic cancer patients was approximately 32%. The ERG positive expression was associated with younger age with better prognostic features of low Gleason score and low ISUP grade group. However, there was no association of ERG expression

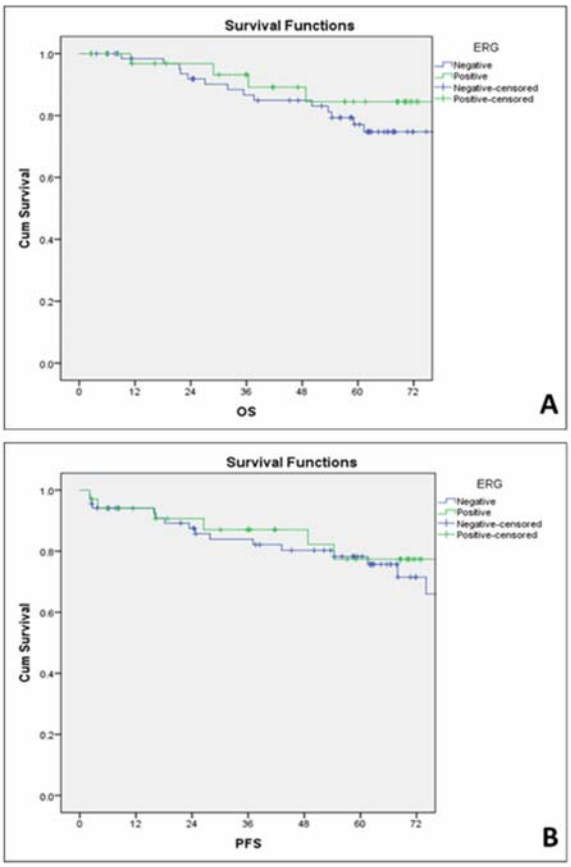

Figure 2. Overall survival (A) and progression-free survival (B) of the patients according to the ERG status.

and survival.

Potential conflicts of interests

The authors declare no conflict of interest.

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