A Combination Of Ki67 Expression And Gleason Score For Prostatic Adenocarcinoma Offers Better Prognostic Information Than Either Alone

B Rugwizangoga, E Vuhahula, J Kitinya

Citation

Abstract
Aims
Prostate cancer (PCa) is a common cause of morbidity and mortality in men worldwide. Many cases remain indolent while others are aggressive. Gleason score (GS) is a recognized prognosticator, but in some cases it does not predict the disease progression accurately. Development of PCa progression markers is anxiously awaited, to complement the GS system. This study aimed at determining whether the combination of Ki67 index and GS can offer better PCa prognosis information than either alone.

Methods and Results
The study included 214 archival cases of PCa diagnosed in a tertiary hospital in Dar es Salaam, Tanzania, from 2005 to 2006. The mean age was 70.5 (42-96) years; mean PSA was 79.578 (2.32-500.00) ng/mL; 68.0% had loco-regional advanced disease, whereas 26.1% had distant metastases; high GS predominated. Ki67 index consisted of a ratio of MIB-1-positive cells in hotspots of at least 500 cells. Median Ki67 index was 10.39 (0.00-50.94) %. Retrospective follow-up (ranges 17 days to 60 months) was possible to only 48 cases; mean survival was 24.5 months. GS correlated with PSA (P=0.001), tumour extent (P=0.009), stage (P=0.009) and survival (P=0.029). Ki67 index correlated with GS (P=0.001), tumour extent (P=0.032), progression (P=0.020) and survival (P=0.021). GS rather than Ki67 index predicted the stage; both GS and Ki67 index similarly predicted survival, but Ki67 index detected progressive cases missed by GS system.

Conclusion
A combination of GS and Ki67 index offers better PCa prognostic information than either alone. Multicentre prospective studies are recommended to confirm these findings.

INTRODUCTION
PCa develops from prostate gland secretory cells and often progresses slowly; it may remain localised, but can grow into a large aggressive tumour.1 The key to early diagnosis is regular physical examination and serum PSA test.2 Treatment is based on hormonal manipulation.

In terms of prevalence of cancer in men, PCa is the second worldwide, the first in developed countries and sixth in developing countries; it is the sixth cause of cancer death in men likewise worldwide, in developed and in developing countries.3 Globally, Black men are more affected (228.7 per 100,000 in USA)4 than Whites (141.0 per 100,000 in USA)4 than Asians (3.9 per 100,000 in India);5 geographical variations also exist.

The incidence rates per 100,000 are lower in Africa than in American Blacks, and vary from 19.3 in West Africa,6 to 23 in East Africa,7 to 40.5 in Southern Africa.6 In Tanzania, about 1,248 cases are diagnosed yearly,7 though annual estimates are 25,063 cases.8

PCa continuum is a concept describing the natural progression of PCa, from localized to locally advanced to advanced (metastases) and hormone-refractory PCa.9 Most PCa cases are diagnosed on haematoxylin and eosin (H&E)-
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stained sections, few need immunohistochemistry\textsuperscript{10,11} to confirms absence of basal cells by lack of low-molecular weight cytokeratin (34\textsubscript{E}12, CK\textsubscript{5/6}) or negative p63,\textsubscript{12,13,14,15} in combination with secretory cell positivity to the product of \textsuperscript{1}3\textsubscript{methylacyl-CoA-racemase (AMACR) gene.\textsuperscript{14}}

PCa pathogenesis depends on dihydrotestosterone–androgen receptor complex (DHT–AR) which regulates gene expression in cancer cells\textsuperscript{16} Therapeutic options include surgery, hormonotherapy, chemotherapy and radiotherapy, the aim being androgen blockade.

PCa case-fatality rate is about 16\%; some men die with but not from PCa,\textsuperscript{17} while others remain indolent. An overall survival benefit was reported,\textsuperscript{18} but the stress caused by aggressive, sometimes unnecessary, treatment cannot be ignored.\textsuperscript{9,16} The main challenge in PCa as far as the management is concerned is to discriminate cases that will likelihood remain indolent versus cases that will progress to fatal outcome, for appropriate courses of treatment.

GS is a recognized PCa prognostic factor; others are tumour proliferation markers, including Ki67,\textsuperscript{19} and a member of E twenty-six (ETS) family of transcription factors called Prostate-derived ETS factor (PDEF);\textsuperscript{20} others are metabolic markers adiponectin and leptin.\textsuperscript{17}

Ki67 antigen is a non-histone nucleoprotein selectively expressed by actively cycling cells demonstrable in paraffin-embedded histological sections using MIB-1 antibody.\textsuperscript{21,22}

In European series, Ki67 index was shown to correlate with PCa stage, GS and prognosis,\textsuperscript{19} but Ki67 index was not compared with GS regarding the prediction of PCa progression. In some cases, GS may fail to predict PCa progression. A combination of these two factors may be a better predictor of PCa biological behaviour than either alone. In this study, we wanted to find out if GS plus Ki67 index were better at predicting PCa prognosis than either alone.

**MATERIALS AND METHODS**

Population

The study was conducted at Muhimbili National Hospital (MNH), the national referral and teaching hospital for Muhimbili University of Health and Allied Sciences (MUHAS). Study population included all cases of PCa diagnosed at MNH from January 1st 2005 to December 31st, 2006 (Figure 1).

**Figure 1**

Methodology algorithm. About 83.60\% of the recruited cases were retained in the study. TURP: Transurethral resection of the prostate.

Recruitment of cases was retrospective, collecting all archival data. Cases for which PCa was not confirmed, those without tissue blocks and/or clinical data, were excluded. A pilot study of 20 randomly selected case files was conducted to determine adequacy of clinical information was found to be adequate in 12 cases; this was considered satisfactory for the study.

Laboratory methods

Archival paraffin wax-embedded tissue blocks were cut to obtain 4-\textmu\text{m}-thick sections which were routinely stained with H&E and coverslipped using distyrene plasticiser xylene (DPX). GS was obtained using standard Gleason grading system.\textsuperscript{10} Tumour extent consisted of average of ‘core/section’ length involved by the tumour for each case.\textsuperscript{23}
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The investigator and two senior pathologists individually assigned GS and tumour extent on tissue for each case, using light microscope. In case of discrepancy, consensus was obtained.

Immunohistochemistry (IHC) procedures consisted of passing 4μm-thick section-bearing IHC slides through the heat antigen retrieval using citrate buffer at pH 6.0 and 0.01 M concentration, MIB-1 (Dako Denmark A/S Produktionssvej 42 DK-2600 Glostrup, Denmark) standard immunoperoxidase technique and diaminobenzidine (DAB) as chromogen, then cover-slipping, was done. Negative controls were achieved by omission of primary antibody; positive controls were known cases of diffuse large B cell lymphoma. In hotspots, percentage of positive cells among at least 500 cells at 400X (10X ocular and 40X objective) was determined using a 10 x 10 grid (0.0625 mm²) in the eyepiece. Criteria for MIB-1 positivity were strong and complete brown-yellowish nuclear coloration.

Statistical methods

Data were collected in sheets; analysis was done through Statistical Package of Social Sciences (SPSS) 16.0 for Windows, and Win Pepi version 11.1 used in analysis of incidence rates through Poisson distribution. Minimal number of cases needed for statistical analysis was four, determined through the Survey Systems Software (15 Lone Oak, Suite 2 Petalum CA94952, USA). PCa progression was determined by comparing the stage at diagnosis with stage at last follow-up for stages IIA, IIB, and III; for stage IV, progression was determined by occurrence of new metastasis or complication or death attributable to PCa.

Stratified analysis was not performed because of the paucity of cases in strata. Two-sided P value <0.05 was considered confirming statistically significant variable associations. For easy correlations, GS were grouped in low and high risk groups.24 Ki67 index low and high risk groups were determined by the median Ki67 index value.

Limitations of the study

Patient files were available in only 75 cases; 48 of them (64.00%) had follow-up after PCa diagnosis. After compilation of clinical data from files and request forms, 8 cases out of 256 were excluded due to lack of clinical data (Figure 1). Paraffin-embedded tissue blocks were missing in 29 cases which were excluded from the study. Financial and time constraints prevented a multicentre study.

Ethical considerations

Ethical clearance was obtained from MUHAS Ethical Clearance Committee. Permission to use archival data was obtained from MNH management. All patients’ information was treated with strict confidentiality.

RESULTS

The mean age was 70.46 (range 42-96) years (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
<th>Std. Deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>206</td>
<td>79.46</td>
<td>79</td>
<td>78</td>
<td>9.78</td>
<td>42</td>
<td>95</td>
</tr>
<tr>
<td>Pre-treatment PSA</td>
<td>140</td>
<td>79.78</td>
<td>160</td>
<td>100</td>
<td>62.07</td>
<td>3.52</td>
<td>500</td>
</tr>
<tr>
<td>Tumour extent (%)</td>
<td>214</td>
<td>67.88</td>
<td>70</td>
<td>89</td>
<td>18.98</td>
<td>29</td>
<td>99.5</td>
</tr>
<tr>
<td>Ki67 index (%)</td>
<td>103</td>
<td>12.91</td>
<td>10.59</td>
<td>0</td>
<td>10.38</td>
<td>0</td>
<td>50.94</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>48</td>
<td>16.89</td>
<td>9.425</td>
<td>2</td>
<td>18.37</td>
<td>0.1</td>
<td>60</td>
</tr>
<tr>
<td>Survival duration</td>
<td>15</td>
<td>24.50</td>
<td>21.75</td>
<td>69</td>
<td>22.54</td>
<td>0.56</td>
<td>69</td>
</tr>
</tbody>
</table>

Africans represented 94.4%; the race was not specified in 12 (5.6%) cases. The residence was specified in 92 cases and was essentially from Dar es Salaam city (46) and bordering Regions (21). The mean pre-treatment serum PSA was 79.578 (range 2.32-500.00) ng/mL (Table 1). 188 cases (87.9%) were core biopsies, 24 cases (12.1%) transurethral resection of prostate (TURP) specimens, 2 cases (0.9%) were metastatic bone biopsies.

All cases were acinar prostatic adenocarcinoma. GS 2-4 were found in 5 (2.4%) cases; GS 5-6 in 53 (24.7%) cases, GS 7 predominated [82 (38.3%) cases] and GS 8-10 in 74 (34.6%) cases. The mean tumour extent was 67.88 (range 20-99.5) % (Table 1). The mean Ki67 index in 103 MIB-1-stained PCa cases was 12.00 (0.0-50.94) %, median was 10.39% (Table 1). Figure 2 illustrates the MIB-1 stained sections.
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Figure 2
Photomicrographs of immunoperoxidase MIB-1 stained sections. A-C: Prostatic adenocarcinoma, with respective Ki67 indexes: A, 50.9% (Gleason 5+4=9); B, 45% (Gleason 4+4=8); C, 10.9% (Gleason 3+4=7). D, 0.9%, benign prostatic hyperplasia. All are at high power (x400).

153 cases (70.09%) could be staged based on the provided clinical, radiological, PSA and GS findings. Advanced PCa disease (stage III and IV) was encountered in 68%.

Documented follow-up after diagnosis was present in 48 cases. 33 of them (68.7%) were incompletely followed-up; 2 (4.2%) were alive with the disease at 60 months. 13 (27.1%) died within 60 months after diagnosis, including one who died at 60 months from time of diagnosis; 12 out of 13 (92.3%) died of PCa disease; one case died of diabetes mellitus 49 months after diagnosis. 32 out of 48 cases (87.5%) had advanced PCa (stages III and IV) at last follow-up. The mean follow-up duration was 31.2 (range 0.56 to 60) months (Table 1). The mean survival of the 15 fully followed-up patients was 24.50 (0.56 to 60) months (Table 1). Among the 153 cases with known stages, 40 (26.14%) had distant metastases; 38 out of 40 (95%) metastatic PCa involved bones, respectively spine in 32 cases, iliac bone in 5 cases and 1 case in each of humerus, 1 liver and 1 distant lymph node metastases.

Survival decreased with stage (Figure 3, Log rank P=0.018; 95% CI = 13.09-35.91 months).

The mean survival in months was 48.67 for stage IIA, 21.08 for stage IIB, 40.87 for stage III (outlier), and 10.93 for stage IV. Tumour extent increased with GS (P= 0.000; 95% CI is 66.26-69.49%) and Ki67 index (Chi-square P=0.032). Ki67 index increased with GS (P=0.000, Table 2) and decreased with age (Chi-square P=0.006).

Table 2
Correlation of Gleason score and Ki67 index Ki67 index increased with the Gleason score; P value indicates the statistically significant association between Ki67 indices and the Gleason scores grouped into low and high risk prognostic groups.

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Mean</th>
<th>N</th>
<th>Standard deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score 2-7</td>
<td>9.0949</td>
<td>63</td>
<td>7.6023</td>
<td>0.00</td>
<td>45.91</td>
</tr>
<tr>
<td>Gleason score 8-10</td>
<td>16.5887</td>
<td>40</td>
<td>12.43429</td>
<td>0.00</td>
<td>59.94</td>
</tr>
<tr>
<td>Total</td>
<td>12.0051</td>
<td>103</td>
<td>10.37869</td>
<td>0.00</td>
<td>59.94</td>
</tr>
</tbody>
</table>

P=0.066

Three alternatives of GS grouping were used to compare GS with survival, namely considering GS 7 as low, intermediate or high grade (Table 3).
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Table 3
Correlation of survival duration to the Gleason score There is a statistically significant association between Gleason score prognostic groups and survival if Gleason score 7 is considered as being of low risk prognosis (P=0.029), rather than intermediate (P=0.101) or high risk prognosis (P=0.483).

<table>
<thead>
<tr>
<th>Gleason score grouping method</th>
<th>Prognostic groups</th>
<th>Mean survival (months)</th>
<th>95% CI (months)</th>
<th>Log Rank (Mantel-Cox) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score 7 considered high grade</td>
<td>Gleason score 2-6</td>
<td>36.75 (n=4)</td>
<td>6.04 to 51.45</td>
<td>0.483</td>
</tr>
<tr>
<td></td>
<td>Gleason score 7-10</td>
<td>22.96 (n=81)</td>
<td>9.22 to 50.69</td>
<td></td>
</tr>
<tr>
<td>Gleason score 7 considered intermediate grade</td>
<td>Gleason score 2-6</td>
<td>28.75 (n=4)</td>
<td>6.04 to 51.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gleason score 7</td>
<td>24.65 (n=3)</td>
<td>7.67 to 41.00</td>
<td>0.101</td>
</tr>
<tr>
<td></td>
<td>Gleason score 8-10</td>
<td>12.36 (n=6)</td>
<td>5.29 to 21.51</td>
<td></td>
</tr>
<tr>
<td>Gleason score 7 considered low grade</td>
<td>Gleason score 2-7</td>
<td>31.86 (n=9)</td>
<td>14.51 to 48.21</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>Gleason score 8-10</td>
<td>13.94 (n=6)</td>
<td>5.59 to 21.51</td>
<td></td>
</tr>
</tbody>
</table>

Overall | | 24.50 | 15.09 to 35.91 |

GS and survival inversely correlated if GS 7 was considered as low grade (Table 3, Figure 4, P=0.029).

Figure 4
Correlation of the survival of patients to the Gleason score The mean survival for patients with Gleason scores 2-7 was 31.86 months; it was 13.46 months for patients with Gleason scores 8-10; the 95% confidence interval= (11.96-31.63) months.

The mean survival for the low risk group Ki67< median (10.39%) was 44.00 months versus 14.75 months for the high risk group.

GS rather than Ki67 index correlated with pre-treatment serum PSA levels (P=0.000 and P=0.825, respectively). 5 patients whose PSA levels were normal had high grade tumours, high Ki67 index (6.9% to 18.7%), high tumour extent and progressive disease; 2 of those 5 patients died within 1 month and 22 months of diagnosis respectively. This shows that GS and Ki67 index depict aggressive PCa than does PSA test. GS rather than Ki67 index, significantly predicted the stage (P=0.007 and P=0.573, respectively).

There was progression to higher stage in most cases: 3 out of 5 (60%) for stage IIA, 8 out of 11 (72.7%) for stage IIB, 8 out of 14 (57.1 %) for stage III, while 6 out of 18 cases (33.3%) of stage IV acquired new metastasis, complication or death attributable to PCa disease (Table 4); 23 cases had no evidence of progression.
Table 4
Gleason score and Ki67 index compared on basis of disease progression There is a statistically significant association between Ki67 index and PCa progression (P=0.020), but not between Gleason score and PCa progression (P=0.073). However, the difference between Ki67 index and Gleason score in predicting the PCa progression was not statistically significant (P=0.715). Note: SE = standard error for rate ratio; N=48.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Gleason score</th>
<th>Ki67 index</th>
<th>Comparison of Gleason score and Ki67</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate per 1,000 person months</td>
<td>Attributable fraction</td>
<td>Rate per 1,000 person months</td>
</tr>
<tr>
<td>Low</td>
<td>24.97%</td>
<td>19.6%</td>
<td>21.944</td>
</tr>
<tr>
<td>High</td>
<td>61.69%</td>
<td>59.5%</td>
<td>66.762</td>
</tr>
<tr>
<td>Overall</td>
<td>39.845</td>
<td>-</td>
<td>35.571</td>
</tr>
<tr>
<td>Fisher’s Exact test</td>
<td>P value = 0.073</td>
<td>95% CI is 0.921 to 6.885%</td>
<td>P value = 0.020</td>
</tr>
</tbody>
</table>

Ki67 index rather than GS correlated with disease progression (Fisher’s P = 0.020, 95% CI is 1.163-6.885%, and P = 0.073, 95% CI is 0.921-6.030%, respectively). When compared to Gleason score, Ki67 index would help to predict an additional progressive PCa case for 18 cases followed-up for 1 year.

Each of Ki67 index and GS correlated with survival, as seen above, and both tests were equivalent in predicting the patient’s survival (Table 5).

Table 5
Comparison of Gleason score and Ki67 index in predicting the survival There is a statistically significant association between Gleason score and survival (P=0.029) and between Ki67 index and survival (P=0.021), and there is no statistically significant difference between Ki67 index and Gleason score in predicting the patient’s survival (P=0.483). Note: SE = standard error for mean; n= number

<table>
<thead>
<tr>
<th>Survival group</th>
<th>Gleason score (Table 2, Figure 4)</th>
<th>Ki67 index (Figure 5)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (months)</td>
<td>SE</td>
<td>n</td>
</tr>
<tr>
<td>Low risk group</td>
<td>31.80</td>
<td>8.489</td>
<td>9</td>
</tr>
<tr>
<td>High risk group</td>
<td>54.60</td>
<td>4.110</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>40.50</td>
<td>5.836</td>
<td>15</td>
</tr>
<tr>
<td>P value</td>
<td>Log Rank: P=0.029</td>
<td>Log Rank: P=0.021</td>
<td>chi square P = 0.483</td>
</tr>
<tr>
<td>95% CI</td>
<td>13.89 to 35.51</td>
<td>13.89 to 35.91</td>
<td>-21.646 to 42.246</td>
</tr>
</tbody>
</table>

DISCUSSION
Introduction
Prostate cancer constitutes a life-threatening illness in men worldwide. There is a challenge of determining, at time of diagnosis, which case will remain indolent or be aggressive.

Proliferation markers may augment the role played by GS in predicting PCa prognosis.19 This study tested the usefulness of combining Ki67 index and GS to predict PCa prognosis.

PCa was found in 34.73% of all prostate specimens; this is a quite high proportion. Most PCa cases in Tanzania and East Africa in general are treated by bilateral subcapsular orchidectomy (BSO).25 The cost of the hormonal therapy (complete androgen blockade) remains a challenge to Tanzanians. PCa prevention is based on establishment of PSA baseline, then follow-up with sequential PSA tests, every three or six months.26,27

Distribution and correlations of variables
The mean age in this study (70.46 years) was similar to that found in Uganda (70 years)28 and previous Tanzanian study (68.12 years).29 Andropause (age related reduction in testosterone levels in males) is a recognized risk factor of PCa, affecting 1 in 200 aging men;30 the increase of PCa with age has been confirmed.24,30,31,32,33 Race was specified in 94.4% of cases who were all Africans. No specified Asian case was found though Tanzania has many Asians; PCa incidence is known to be low in Asians.4 The mean pre-treatment serum PSA (79.578 ng/mL) was higher than in a USA study (26.8 ng/mL),34 reflecting delay in medical care, and presumably the black race.23 PSA level directly correlated with GS, similar to other studies.10,25,29,35

All PCa cases studied were acinar adenocarcinoma; a finding similar to that of the previous study at MNH (99.1%).29 GS 7 was predominant (38.3%); GS 8-10 cases represented 34.6%. Preponderance of GS 7 was previously confirmed to be around 43%.36,37 In the original GS system, GS 6 predominated (39.05%).38 The overtime increase in proportion of GS 7 and above has been documented.36,39,40

Advanced PCa (stages III and IV) was diagnosed in 68.0% of patients. In 1974, Gleason found advanced PCa (stages III and IV) in 85.5%.39 In a recent USA study, stage IV was found in 0.3%, stage III in 27.9% of prostatectomy specimens.41 This indicates an increase in early medical care-seeking behaviour in USA, thanks to PSA screening.40 In this study, 40 out of 153 (26.14%) documented cases had PCa distant metastases; 95% of metastases involved bones, essentially spine. The rate of PCA metastases in literature is around 35%.31 The predilection of PCa for bone metastases is well known and was confirmed in this study.31,42
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The mean survival was 24.50 months. Survival was associated with stage, GS and Ki67 index. Other studies have confirmed the association between survival and Ki67 index, stage and GS.10,24,25,38,39,40,41

The median Ki67 index in this study (10.39%) was similar to that of a Danish study (10.30%).19 Ki67 index decreased with age and increased with GS; this supports the assumption that a low grade and therefore, slowly progressive malignancy will be symptomatic over time at advanced age, as compared to a high grade, aggressive malignancy which will be rapidly symptomatic and therefore diagnosed at relatively younger age. Similarly, the Danish series showed Ki67 index to correlate with grade.19 There is however, no definitive cut-off point of Ki67 index value determining a low/high risk groups of patients.24

Comparison of Gleason score and Ki67 expression

GS rather than Ki67 index correlated with pre-treatment PSA levels. Moreover, GS rather than Ki67 index predicted the tumour stage. Conversely, Ki67 index rather than GS predicted PCA progression; when compared to GS, Ki67 index would help to predict PCa progression in 1 additional case for 18 cases followed up for 1 year. However, Buhmeida et al. found GS to be an independent progression-associated indicator in all regardless of prostate disease stage, while Ki67 index was progression-associated prognosticator only in organ-confined PCa.33 The incomplete follow-up in this Tanzanian series may be the cause of discrepancy, therefore a multicentre and prospective study is recommended.

In this study, GS and Ki67 index were equivalent tests in predicting survival although Buhmeida et al. found GS to be an independent survival-associated indicator in all PCA regardless of stage, while Ki67 index was survival-associated prognosticator only in organ-confined PCa.33

CONCLUSION

This study showed that GS and Ki67 index synergistically offer better prognostic information than either alone, in management of PCa. The contribution of Ki67 index in predicting PCa behaviour is promising, and needs confirmation through multiregression analysis in larger multicentre studies on PCa prognosticators. The Government and stakeholders in health system should scientifically address the issues related to PCa epidemiology, integrated and multidisciplinary preventive and therapeutic programmes.

References

20. Findlay VJ, Turner DP, Yordy JS et al. Prostate-Derived ETS Factor Regulates Epithelial-to-Mesenchymal Transition through Both SLUG-Dependent and Independent
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