Decreased ATM Protein Expression Is Substantiated with PTEN Loss in Defining Aggressive Phenotype of Prostate Cancer Associated with Lethal Disease

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Nallasivam Palanisamy

See next page for additional authors

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Simon R. Walker\textsuperscript{a}, Ramy Abdelsalam\textsuperscript{a}, Sunita Ghosh\textsuperscript{b}, Julie Livingstone\textsuperscript{c}, Nallasivam Palanisamy\textsuperscript{d}, Paul C. Boutros\textsuperscript{c}, Steven M. Yip\textsuperscript{e}, Susan P. Lees-Miller\textsuperscript{f,g}, Tarek A. Bismar\textsuperscript{a,f,g,*}

\textsuperscript{a}Department of Pathology and Laboratory Medicine, University of Calgary Cumming School of Medicine and Alberta Precision Laboratories, Calgary, AB, Canada; \textsuperscript{b}Department of Medical Oncology, Faculty of Medicine and Dentistry, University of Alberta, and Alberta Health Services-Cancer Control, Edmonton, AB, Canada; \textsuperscript{c}Departments of Human Genetics and Urology, University of California, Los Angeles, CA, USA; \textsuperscript{d}Department of Urology, Vattikuti Urology Institute, Henry Ford Health System Detroit, MI, USA; \textsuperscript{e}Tom Baker Cancer Centre, Calgary, AB, Canada; \textsuperscript{f}Departments of Oncology, Biochemistry and Molecular Biology, University of Calgary Cumming School of Medicine, Calgary, AB, Canada; \textsuperscript{g}Arnie Charbonneau Cancer Institute, Calgary, AB, Canada

Abstract

\textbf{Background:} Ataxia Telangiectasia Mutated (ATM) serine/threonine protein kinase is a known tumor suppressor, involved in DNA damage repair. It has prognostic and predictive therapeutic implications and is associated with aggressive prostate cancer (PCa).

\textbf{Objective:} To investigate the prognostic value of ATM protein expression in PCa patients and assessed the combined value of ATM, ERG, and PTEN status.

\textbf{Design, setting, and participants:} This study consisted of 303 patients with incidental, locally advanced, and castrate-resistant PCa by transurethral resection of the prostate (TURP).

\textbf{Outcome measurements and statistical analysis:} TURP samples from 303 PCa patients were assessed by immunohistochemistry (IHC for ATM, ERG, and PTEN). Individual and combined marker status were correlated with International Society of Urological Pathology Gleason grade group, overall survival (OS), and PCa-specific mortality (PCSM).

\textbf{Results and limitations:} Decreased ATM expression (negative/weak intensity) occurred in 164/303 (54.1\%) patients, and was associated with shorter OS and higher PCSM ($p = 0.015$ and $p = 0.001$, respectively). Negative/weak ATM expression was significantly associated with PCSM with a hazard ratio of 2.09 (95\% confidence interval 1.34–3.27, $p = 0.001$). Assessment of Combined ATM/PTEN expression showed improved prognostic power to predict OS and PCSM, independent of Gleason grade groups.

* Corresponding author. Departments of Pathology & Laboratory Medicine and Oncology, Rockyview General Hospital, Calgary, Alberta T2V 1P9, Canada. Tel. +1 (403) 943-8430; Fax: +1 (403) 943-3333. E-mail address: tabismar@ucalgary.ca (T.A. Bismar).
Conclusions: Decreased ATM protein expression is associated with poor outcomes in advanced PCa patients. Patients with combined low ATM/PTEN negative expression are at the highest risk for reduced OS and PCSM. Assessing the combined status of ATM/PTEN by IHC in PCa patients may aid in risk stratification relative to OS and PCSM. Moreover, since ATM plays an integral role in DNA damage response pathways, future studies will enhance our understanding of how outcomes of patients with altered ATM and PTEN expression can be improved further with poly-ADP ribose polymerase inhibitors (PARPi), combinations of PARPi and androgen receptor–targeted therapies, as well as platinum-based chemotherapies.

Patient summary: Lower ATM intensity is associated with increased cancer-specific mortality in prostate cancer patients. Patients with lower ATM and PTEN negative expression showed decreased overall survival and increased cancer mortality compared with controls.

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1. Introduction

Prostate cancer (PCa) is among the top cancers facing men in the western world. Despite our enhanced understanding of DNA damage repair (DDR) alterations in PCa, there continues to be a great need for biomarkers that are more effective at predicting outcomes and treatment responses, particularly in advanced disease. However, there is great heterogeneity in the DDR group, where data are largely driven by BRCA2 alterations, as exemplified by the gene-by-gene subgroup analysis of the PROFOUND clinical trial [1]. To date, there is a need to develop biomarkers that could more easily be implemented clinically to predict which patients are likely to benefit from targeted therapy (eg, poly-ADP ribose polymerase inhibitors [PARPi]) or platinum-based chemotherapy, while assisting in stratification of patients into different prognostic groups.

Germline and somatic mutations in the DNA repair and DDR pathways have gained increasing attention in PCa [2–7]. Recent data suggest that 23% of metastatic castrate-resistant patients will harbor germline or somatic DDR variants, with germline variants occurring in approximately 12% of patients with metastatic castrate-resistant prostate cancer (mCRPC) [8,9]. The most commonly mutated DDR gene in PCa is BRCA2 [8]. The Ataxia Telangiectasia Mutated serine/threonine kinase (ATM) gene, which is located on 11q22.3, is required for DDR pathway signaling, and mutations in this gene are present in roughly 6% of mCRPC patients [2,10]. However, loss of ATM protein expression as detected by immunohistochemistry (IHC) far exceeds the above rate of ATM mutations in lung adenocarcinoma [11]. This may be due to epigenetic changes such as methylation of the ATM gene [12]. All these data, along with our recent report documenting that ATM-deficient cancer cell lines are sensitive to the combination of PARPi plus an ATR inhibitor but not to either agent alone [2,4–7], indicate that an assessment of patients’ tumor samples for decreased activity by IHC may allow for better identification of patients who could benefit from combination targeted therapies.

Patients with mCRPC harboring ATM, BRCA2, or BRCA1 mutations have experienced overall survival (OS) and radiographic progression-free survival (rPFS) benefit when treated with PARP inhibition (olaparib), in contrast to patients with physician’s choice androgen receptor (AR)-targeted therapy [1]. In an exploratory gene-by-gene subgroup analysis, patients with ATM alterations seemed to derive a somewhat lower rPFS benefit than previously expected [1]. It is necessary to clearly define the specific clinical outcomes associated with altered ATM protein expression in PCa.

ERG expression reflective of TIMPSS2-ERG gene rearrangements is known to play a significant role in PCa subtyping, being detected in close to 50% of cases. PTEN deletions are also known to be a significant player in PCa progression, and its incidence is increased with higher grade group (GG) and stage, and in castration-resistant disease.

Given the importance of ERG and PTEN genomic alteration as a significant player in PCa subtyping and prognosis, we aimed to incorporate the prognostic value and association of ATM status combined with ERG and PTEN status. In this study, we investigated the prognostic value of ATM protein expression in a cohort of PCa patients treated mainly by androgen deprivation therapy (ADT) and assessed the combined value of ATM, ERG, and PTEN IHC status in relation to lethal disease and OS [13,14].

2. Patients and methods

2.1. Study population and tissue microarray construction

The study cohort consisted of men diagnosed with PCa by transurethral resection of the prostate (TURP) between 2005 and 2013 (n = 303). Patients within this cohort were either not treated actively or treated by luteinizing hormone-releasing hormone (LHRH) agonist, and spanned from incidental, locally advanced disease to metastatic castrate-resistant disease. Treatments were implemented after TURP (advanced group) or prior to TURP samples in patients who had a previous diagnosis of PCa to relieve symptomatic obstruction of locally advanced disease while on LHRH (castrate-resistant prostate cancer [CRPC] group). The incidental group was defined as the group of patients with no prior hormonal
therapy with Gleason GG of \(\leq 3\). Those with Gleason GG \(\geq 4\) without prior hormonal therapy were considered the advanced group. Clinical follow-up information was recorded and approved by the University of Calgary and Cumming School of Medicine ethics review board from the Alberta Tumour Registry for dates of therapy, survival, and cause-specific survival. The cohort’s samples were assembled onto two tissue microarrays (TMAs) with an average of two cores per patient using a manual tissue arrayer (Beecher Instruments, Silver Spring, MD, USA). Adjacent benign prostate tissue samples were also available for analysis. However, benign samples analysis was limited in number as the TMA was constructed mainly from tumor areas (\(n = 135\)). The proportions of benign tissues analyzed were 46 (55.4%) in the incidental, 21 (25.3%) in the advanced, and 12 (14.4%) in the castrate-resistant group.

2.2. ATM, ERG, and PTEN expression by IHC

ATM IHC was performed on a Dako Omnis autostainer. Briefly, 4 \(\mu\)m formalin-fixed paraffin-embedded sections were pretreated with citrate pH 9.0 epitope retrieval buffer. We used a rabbit monoclonal to recombinant ATM (Y170 from Abcam #32420). The antibody was used diluted to 1/400 using Dako antibody diluent and incubated for 30 min, followed by 30 min secondary incubation. The FLEX DAB+ Substrate Chromogen system was used as a postincubation detection reagent. ATM HC expression was assessed using a four-tiered system (0, negative; 1, weak; 2, moderate; and 3, high intensity) relative to internal control of stromal and basal cells. ERG and PTEN IHC was assessed as negative versus positive and stained as previously described [14,15].

2.3. Pathological analysis

Histological diagnoses of individual TMA cores were confirmed by the study pathologists (S.W., R.S., and T.A.B.) on the initial slides. Gleason scoring was assessed according to the 2014 World Health Organization/International Society of Urological Pathology GGs. In each patient, the predominant two patterns of PCa were sampled and included on the TMAs for analysis. Figures 1 and 2 show examples of ATM intensity in various Gleason GGs.

2.4. Statistical analysis

SPSS version 25 was used to conduct all statistical analysis (IBM SPSS Statistics for Windows, version 25.0, released 2017; IBM Corp., Armonk, NY, USA). Frequency and proportions were reported for categorical data. Mean and standard deviations were reported for normally distributed continuous data; median and range were reported for non-normally distributed continuous data. Chi-square tests were used to compare two categorical variables, and Fisher’s exact test was used where the cell frequencies were <5. OS was defined as the time from the date of diagnosis of PCa as detected on TURP specimen to the date of death; patients alive at the end of the study period were censored. Prostate cancer–specific mortality (PCSM) was defined as death due to PCa; patients who died due to other reason or who were alive at the end of the study period were censored. OS, PCSM, and recurrence-free survival (RFS) were analyzed using the Kaplan-Meier method. Median time and the 95% confidence interval (CI) were reported. Log rank tests were used to compare two or more survival curves. Cox proportional hazards models were used to determine the factors associated with OS, PCSM, and RFS; the hazard ratio (HR) and the corresponding 95% CI were reported. Adjusted Cox model was fitted as well. A \(p\) value of <0.05 was used for statistical significance, and two-sided tests were used.

3. Results

3.1. ATM protein expression across various PCa stages and in relation to Gleason GGs and other genomic aberrations

A total of 303 cancer samples were analyzed with 135 adjacent benign samples. Decreased ATM intensity in
PCa was noted in 164/303 (54.1%) patients. Table 1 lists the distribution of the subgroups included, and their median follow-up and OS/cause-specific survival. Table 2 lists patients’ demographics and biomarker distributions within the cohort studied. ATM intensity was comparable between PCa diagnosis and benign prostate tissue (mean = 1.06, standard deviation [SD] = 0.903 vs mean = 1.07, SD = ±0.903; p = 0.9608). ATM intensity was also significantly lower in CRPC and advanced PCa than in incidental disease (1.15 ± 0.87 and 1.13 ± 0.88 vs 1.59 ± 0.90, p < 0.0001; Fig. 1F).

Decreased ATM was also associated with advanced Gleason grade grouping, with 87/125 (57.2%) patients with GG5 showing decreased ATM expression versus 38/97 (25%) of GG1 (p < 0.0001). Although, no significant association was observed between ATM intensity and that of PTEN or ERG. 20.1% (61/303) patients showed decreased ATM intensity and loss of PTEN expression. On the contrary, 38.6% (117/303) patients in this cohort showed combined ERG negative and decreased ATM intensity.

3.2. Association of ATM with patients’ clinical outcome

Decreased ATM intensity (negative/weak; suggested to be referenced as high risk) was associated with poor OS and cancer-specific mortality (HR: 1.45; CI: 1.08–1.96, p = 0.015, and HR: 2.09; CI: 1.34–3.27, p = 0.001, respectively; Fig. 3A and B), in contrast to patients with normal ATM intensity (moderate/high; suggested to be referenced as low risk). The median OS for low-risk ATM was 59.4 (54.3–64.6) mo and that for high-risk ATM was 38.7 (31.0–46.4) mo. The median PCSM values for low- and high-risk ATM were, respectively, 85.3 and 64.0 mo (43.9–84.1; p = 0.014 and 0.001, respectively). However, the associations reported between ATM expression and OS or PCSM was not significant after adjusting for Gleason score.

Since PTEN and ERG are known to be significantly associated with disease progression and patient prognosis, we opted to investigate whether combining ATM intensity with PTEN or ERG intensity would provide added prognostic value. In this cohort, patients’ tumors with low ATM
intensity and PTEN negative staining or negative ERG expression were associated with significantly lower OS and higher cancer-specific mortality, compared with patients with other combinations of ATM and PTEN. The prognostic value of combined ATM/PTEN or ATM/ERG status was higher than that of ATM, PTEN, or ERG alone. Patients with decreased ATM expression and PTEN negative expression showed the highest association with lethal disease (Table 3). However, after adjusting for Gleason GG, the combined ATM/PTEN signature was the only combination significant to PCSM and OS (HR: 2.58, CI: 1.23–5.39, p = 0.012, and HR: 1.81, CI: 1.13–2.9, p = 0.0145, respectively; Fig. 4A and B, and Table 4). Again, there was significant disadvantage for OS and PCSM between the low- and high-risk groups for combined PTEN/ATM status. For PTEN loss and high-risk ATM, median OS was 20.6 (14.4–26.8) mo, in contrast to the PTEN intact and low-risk ATM median OS of 65.2 (57.5–72.8) mo (p < 0.0001). For PCSM, PTEN loss and high-risk ATM mean PCSM was 36.4 (23.2–49.6) mo versus PTEN intact and low-risk ATM mean PCSM of 85.3 (58.7–111.8) mo (p < 0.0001). To gain additional insight into the prognostication of ATM/PTEN status, we investigated the prognostic value of combined PTEN/ATM status and ERG/ATM adjusting for metastatic disease at presentation. As shown in Table 5, the most powerful combination for OS and PCSM was PTEN negative/ATM high risk (ie, negative to weak intensity) with HRs of 2.47 (95% CI: 1.60–3.83, p < 0.001) and 3.92 (95% CI: 2.02–7.62, p < 0.0001), respectively. The combination of ERG, PTEN, and ATM for OS demonstrated an HR of 1.47 (0.95–2.27, p = 0.081). When adjusting this HR for Gleason score, the HR is 0.96 (0.60–1.54, p = 0.871). For PCSM, the combination of ERG, PTEN, and ATM gave HRs of 2.09 (1.34–3.27, p = 0.001), and an HR of 0.91 (0.48–1.73, p = 0.768) was obtained when adjusting HR for Gleason score.

### Discussion

In this study, we document significant prognostic value for ATM protein expression in patients with advanced PCa. Patients with decreased ATM expression were more likely to exhibit lethal outcome with HRs of about 1.5 times. Incorporation of the status of PTEN into ATM showed even higher association with lethal disease, with almost three-fold that of the control group, and even after adjusting for Gleason GG, this was still significant at about 1.5 times the risk for lethal disease. Incorporation of validated
biomarkers into clinical practice would be of great importance in improving our predictability of disease progression. This would allow for better targeted therapy validation for those at the highest risk of disease progression. Furthermore, as more men with low- and intermediate-grade PCa elect to enroll into active surveillance programs versus active therapy, such biomarkers that are easily implemented clinically at a fractional cost of those for complex genomic signatures may prove to be easier to be incorporated into clinical practice [16]. Therefore, considerable research is conducted to improve clinical insights and assist in the development of precision therapies for advanced PCa [16,17]. Several reports showed a significant correlation between ERG rearrangements and PTEN deletions in PCa [14,17,18]. ERG and PTEN genomic aberrations have been shown to be prevalent (up to 40% and 50%, respectively) in PCa, and both aberrations have been suggested to inform about distinct molecular subtypes of PCa in addition to other key genomic markers such as SPOP and SPINK1 genomic aberrations [19,20].

A major benefit of our study is that we carried out a detailed investigation about the prognostic value of assessing ATM protein expression in a large cohort of men with PCa. Additionally, we associated ATM expression with PTEN and ERG expression, and confirmed added prognostic value for assessing ATM and PTEN intensity in men with PCa in relation to cause-specific mortality and OS. Establishment of conditions for IHC of ATM protein expression in PCa patients as described here may also be beneficial in selection of patients who might benefit from treatment with a PARPi combined with an ATR inhibitor, as shown in our in vitro studies [2,4]; however, the effects of loss of ERG and/or PTEN on sensitivity of ATM-deficient PCa cells to PARPi and ATR inhibitors remains to be determined.

Table 3 – Univariate analysis for overall survival and cancer-specific mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall survival</th>
<th>Prostate cancer–specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>ATM score 2/3</td>
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<td>score 0/1</td>
<td>1.45 (1.08–1.96)</td>
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<td>PTEN and ATM combined (PTEN positive and ATM score 2/3)</td>
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<td>PTEN negative and ATM score 0/1</td>
<td>2.88 (1.89–4.40)</td>
<td>&lt;0.0001</td>
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<td>PTEN negative and ATM score 2/3</td>
<td>2.13 (1.31–3.47)</td>
<td>0.002</td>
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<tr>
<td>PTEN positive and ATM score 0/1</td>
<td>1.33 (0.88–2.02)</td>
<td>0.177</td>
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<tr>
<td>PTEN positive and ATM score 2/3</td>
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<td></td>
</tr>
<tr>
<td>EG and ATM combined (ERG negative and ATM score 2/3)</td>
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<td></td>
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<tr>
<td>EG positive and ATM score 0/1</td>
<td>2.18 (1.37–3.48)</td>
<td>0.001</td>
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<td>EG positive and ATM score 2/3</td>
<td>1.79 (1.09–2.94)</td>
<td>0.022</td>
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<td>EG negative and ATM score 0/1</td>
<td>1.51 (1.03–2.21)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio.

* ATM scores: 0, negative; 1, weak; 2, moderate; and 3, high. PTEN/ERG positive refers to any intensity.

Fig. 3 – Kaplan-Meier curves for ATM expression relative to (A) overall survival and (B) prostate cancer–specific mortality. ATM intensity: negative/weak versus moderate/high.
Fig. 4 – Kaplan-Meier curves for combined ATM and PTEN expression relative to (A) overall survival and (A) prostate cancer–specific mortality. ATM negative/weak versus moderate/high, and PTEN negative versus PTEN expression.

Table 4 – Multivariate analysis and HRs of the different biomarker combinations for overall survival and prostate cancer–specific mortality in the TURP cohort (multivariate analysis for overall and cause-specific survival a)

<table>
<thead>
<tr>
<th>Variables b)</th>
<th>Overall survival</th>
<th>Prostate cancer–specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
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<td>PTEN and ATM combined (PTEN positive and ATM score 2/3)</td>
<td></td>
<td></td>
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<td>PTEN negative and ATM score 0/1</td>
<td>1.81 (1.13–2.9)</td>
<td>0.0146</td>
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<td>PTEN negative and ATM score 2/3</td>
<td>1.66 (0.99–2.78)</td>
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<td>PTEN positive and ATM score 0/1</td>
<td>1.18 (0.76–1.83)</td>
<td>0.454</td>
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<td>ERG and ATM combined (ERG negative and ATM score 2/3)</td>
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<td>ERG positive and ATM score 0/1</td>
<td>1.35 (0.81–2.25)</td>
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<td>ERG positive and ATM score 2/3</td>
<td>1.44 (0.85–2.43)</td>
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<td>ERG negative and ATM score 0/1</td>
<td>1.28 (0.85–1.92)</td>
<td>0.239</td>
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</table>

CI = confidence interval; HR = hazard ratio; TURP = transurethral resection of the prostate.

a Adjusted for Gleason score.

b ATM scores: 0, negative; 1, weak; 2, moderate; and 3, high. PTEN/ERG positive refers to any intensity.

Table 5 – Multivariate analysis and HRs of the different biomarker combinations for overall survival and cancer-specific mortality in the TURP cohort (adjusted for metastatic disease at the time of presentation)

<table>
<thead>
<tr>
<th>Variables a)</th>
<th>Overall survival</th>
<th>Prostate cancer–specific mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>PTEN and ATM combined (PTEN positive and ATM score 2/3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN negative and ATM score 0/1</td>
<td>2.47 (1.60–3.83)</td>
<td>&lt;0.0001</td>
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<tr>
<td>PTEN negative and ATM score 2/3</td>
<td>1.85 (1.13–3.02)</td>
<td>0.015</td>
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<td>PTEN positive and ATM score 0/1</td>
<td>1.28 (0.84–1.94)</td>
<td>0.251</td>
</tr>
<tr>
<td>ERG and ATM combined (ERG negative and ATM score 2/3)</td>
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<td></td>
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<tr>
<td>ERG positive and ATM score 0/1</td>
<td>1.87 (1.16–3.01)</td>
<td>0.010</td>
</tr>
<tr>
<td>ERG positive and ATM score 2/3</td>
<td>1.48 (0.89–2.45)</td>
<td>0.131</td>
</tr>
<tr>
<td>ERG negative and ATM score 0/1</td>
<td>1.39 (0.94–2.03)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; TURP = transurethral resection of the prostate.

a ATM scores: 0, negative; 1, weak; 2, moderate; and 3, high-intensity staining. PTEN/ERG positive refers to any intensity.
In the current study, assessment of the combination of ATM/PTEN status showed significant differences in OS and PCSM between high- and low-risk groups as pertaining to PTEN/ATM intensities. Patients with tumors showing both low ATM expression and loss of PTEN expression (high-risk group) demonstrated significantly poorer OS and PCSM of close to 3.3 and 4.07 yr, respectively, compared with patients in the low-risk group for PTEN/ATM. The latter data support potentially incorporating the combined status of ATM/PTEN to assist in better stratifying PCa patients and identify those at a higher risk for lethal outcome and potential benefit from ADT. Additionally, since an exploratory gene level subgroup analysis of the OS PROFOUND data suggests that patients with ATM alterations, in contrast to other homologous recombination repair alterations, may derive less benefit with olaparib PARPi, this may be a more elegant predictive biomarker to determine which patients with ATM alterations may benefit from PARPi and show OS and PCSM survival advantage [1]. Future studies will enhance our understanding of how outcomes of patients with altered ATM and PTEN expression can be enhanced further with PARPi, combinations of PARPi and AR-targeted therapies, as well as platinum-based chemotherapies [21,22].

Our study had several limitations. Unfortunately, we had incomplete data for Gleason scoring, survival/death, and ATM IHC status. Our study was a retrospective study and lacked an independent cohort of validation. Furthermore, we did not have access to TNM staging information for our cohort.

5. Conclusions

In conclusion, we document significant prognostic value for assessing protein expression of ATM in combination with PTEN in patients with PCa managed by ADT. High-risk patients (ie, those with decreased ATM protein expression and negative PTEN intensity) are at the highest risk for lethal PCa and poor OS of close to 4 and 3 yr, respectively. Assessment of combined ATM/PTEN protein intensity may aid in selecting patients who could benefit from more targeted therapy.

Author contributions: Tarek A. Bismar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bismar.
Acquisition of data: Walker, Livingstone.
Analysis and interpretation of data: Ghosh, Livingstone.
Drafting of the manuscript: Walker, Bismar.
Critical revision of the manuscript for important intellectual content: Bismar, Boutros, Livingston.
Statistical analysis: Ghosh.
Obtaining funding: Bismar.
Administrative, technical, or material support: Palanisamy.
Supervision: Bismar.
Other: None.

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Ethics statement: The study was approved by the U Calgary Cumming School of Medicine ethics review board and in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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