Prognostic value of PTEN in de novo diagnosed metastatic prostate cancer

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The purpose of our study is to investigate the prognostic value of phosphatase and tensin homolog on chromosome 10 (PTEN) expression in patients with de novo metastatic castration naive prostate cancer (mCNPC). A total of 205 patients with mCNPC at Fudan University Shanghai Cancer Center (Shanghai, China) were retrospectively examined. Immunohistochemical staining of PTEN was performed on prostate biopsy samples of these patients. Associations among clinicopathological features, patient survival and PTEN protein expression were analyzed. PTEN loss occurred in 58 of 205 (28.3\%) patients. Loss of PTEN was significantly correlated with high metastatic volume (\(P = 0.017\)). No association between PTEN expression and Gleason score was observed. Patients with PTEN loss had significantly shorter progression-free survival (PFS, \(P < 0.001\)) and overall survival (OS, \(P < 0.001\)) compared with patients with intact PTEN expression. Multivariate analysis showed that elevated alkaline phosphatase, high metastatic volume and PTEN loss were independent poor prognostic factors for PFS. The Eastern Cooperative Oncology Group performance status (ECOG PS) \(\geq 2\) and PTEN loss were independent poor prognostic factors for OS. The adjusted hazard ratio of PTEN loss for PFS and OS was 1.67 (95\% confidence interval [CI]: 1.14–2.43, \(P = 0.008\)) and 1.95 (95\% CI: 1.23–3.10, \(P = 0.005\)), respectively.

PTEN loss was also found to be associated with poor prognosis of patients with castration-resistant prostate cancer (CRPC).\textsuperscript{10} However, the expression status and prognostic value of PTEN in castration naïve prostate cancer (CNPC) has not been examined. The status of PTEN, which is suppressor of the serine/threonine kinase (AKT) signal, predicts the efficacy of the AKT inhibitor in CRPC.\textsuperscript{11} Thus, elucidating the significance of PTEN in CNPC may help stratify different risk groups of CNPC and the trial design of drugs targeting PTEN-phosphatidylinositol 3-kinase (PI3K)-AKT axis.

Therefore, in this study, we evaluated the expression status and prognostic value of PTEN in de novo metastatic CNPC.

INTRODUCTION

Prostate cancer is the second-most common cancer in men worldwide and accounts for 358,000 cancer-related deaths each year.\textsuperscript{1} Although early detection of prostate cancer by prostate-specific antigen (PSA) screening has significantly improved patient prognosis, patients who are diagnosed with metastatic disease at their first visit have a poor 5-year survival rate of less than 30\%.\textsuperscript{2,4} For patients with de novo diagnosed metastatic prostate cancer, the extent of metastasis is considered to be the most important prognostic factor. Metastatic burden, defined by the ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study, was widely adopted for subgroup analysis in recent clinical trials.\textsuperscript{2,4,5} However, the extent of metastasis may just represent the current state of the disease and it cannot reflect the rate of progression from low metastatic burden to high metastatic burden. The intrinsic genetic alteration is the driving force that determines the malignancy of tumor and could be more closely correlated with patient prognosis and treatment strategy.

Loss of phosphatase and tensin homolog on chromosome 10 (PTEN) is frequently observed in prostate cancer.\textsuperscript{6} Previous studies have demonstrated a correlation of PTEN loss with recurrence and metastases after radical prostatectomy of localized prostate cancer.\textsuperscript{7–9} PTEN loss was also found to be associated with poor prognosis of patients with castration-resistant prostate cancer (CRPC).\textsuperscript{10} However, the expression status and prognostic value of PTEN in castration naïve prostate cancer (CNPC) has not been examined. The status of PTEN, which is suppressor of the serine/threonine kinase (AKT) signal, predicts the efficacy of the AKT inhibitor in CRPC.\textsuperscript{11} Thus, elucidating the significance of PTEN in CNPC may help stratify different risk groups of CNPC and the trial design of drugs targeting PTEN-phosphatidylinositol 3-kinase (PI3K)-AKT axis.

Therefore, in this study, we evaluated the expression status and prognostic value of PTEN in de novo metastatic CNPC.

PATIENTS AND METHODS

Patients

A total of 205 de novo metastatic CNPC patients diagnosed with metastatic prostate cancer by prostate biopsy in Fudan University Shanghai Cancer Center (FUSCC; Shanghai, China) from June 2012 to December 2014 were retrospectively examined in this study. All patients signed informed consent form, approved by the ethic committee of Fudan University Shanghai Cancer Center, for research use of their pathologic sample and clinical information (approval No. 050432-4-1911D). Diagnoses of prostate cancer were based on transrectal ultrasound-guided 12- to 18-core biopsy of the prostate. Metastatic sites were defined by pelvic
magnetic resonance imaging (MRI), thoracic and abdominal computed tomography (CT) scan, and skeletal scintigraphy. Additional MRI was performed for patients with unequivocal skeletal findings to affirm the diagnosis of bone lesions. Patients were classified into high-volume and low-volume disease according to the CHAARTED study. High metastatic volume disease was defined as the existence of visceral metastasis or ≥4 bone lesions, with at least one outside the vertebral column or pelvis. Patients received traditional androgen deprivation therapy (ADT) using goserelin (3.6 mg administered subcutaneously each month; AstraZeneca, London, UK) plus bicalutamide (50 mg orally each day; AstraZeneca) until the development of CRPC. CRPC was defined as documented biochemical progression (three consecutive increases in PSA concentrations 1 week apart, resulting in two 50% increases over the nadir, and PSA >2 ng ml\(^{-1}\) or radiological progression (the appearance of new lesions: ≥2 bone lesions on bone scan or soft tissue lesion progression as defined by the Response Evaluation Criteria in Solid Tumours\(^\text{a,11}\)) and testosterone <50 ng dl\(^{-1}\) or 1.7 nmol l\(^{-1}\). At the end of the study, 136 patients progressed to CRPC. Among these patients, 49 (36.0%) and 42 (30.9%) were treated with abiraterone and docetaxel, respectively, as the first-line therapy. The remaining 45 (33.1%) patients who progressed to CRPC received flutamide, estramustine, or estrogen as the first-line therapy because of economic considerations. During the study, only abiraterone and docetaxel were approved by the China Food and Drug Administration for the treatment of CRPC in China. Therefore, after failure of the first-line therapy, only 16 (11.8%) patients received life-prolonging agents (6 received abiraterone and 10 received docetaxel) for subsequent therapy.

**Construction of the microarray**

Formalin-fixed paraffin-embedded tissues of prostate needle biopsies were obtained from the tissue bank of FUSCC. The diagnosis and Gleason score of each sample were reconfirmed by an experienced pathologist. Two areas with the highest Gleason score of each tissue sample were included in microarrays.

**Immunohistochemistry (IHC)**

IHC staining of PTEN was performed as described in a previous study.\(^7\) Briefly, slides were heated at 60°C for 2 h and then deparaffinized with a gradient ethanol series. Antigen retrieval was performed by incubating samples in boiled citrate buffer (pH 6.0) for 30 min. Rabbit anti-human PTEN antibody (9188, Cell Signaling Technology, Beverly, MA, USA) was applied to samples at a dilution of 1:200, and slides were incubated overnight at 4°C, followed by incubation with horseradish peroxidase-labeled secondary antibody (PV-9000, ZSGB-BIO, Beijing, China). The sections were stained with 3,3′-diaminobenzidine reagent and counterstained with hematoxylin (ZSGB-BIO).

The evaluation of IHC results was conducted by two pathologists. Intact PTEN expression was defined as positive PTEN staining in the cytoplasm and nucleus of more than 90% of tumor cells. Heterologous PTEN loss was defined as negative PTEN cytoplasmic and nuclear staining in >10% and <100% of tumor cells, and PTEN homologous loss was defined as PTEN loss in 100% of tumor cells.\(^2,14\) Both PTEN heterologous and homologous loss were considered as PTEN loss for statistical analysis. Representative IHC results are presented in Figure 1a.

**Statistical analyses**

Patient characteristics are summarized using descriptive methods. Continuous variables are presented as median and range. Categorical variables are summarized as number and frequency. Parametric (t test) and nonparametric (Chi-square test or Mann–Whitney U test) tests were applied for comparisons between two groups. Survival curves for progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier survival analysis. PFS was defined as the time from commencing ADT to the date of progression to CRPC. Univariate and multivariate Cox analyses were conducted to evaluate each factor’s impact on survival. All P values were determined two-sided. P < 0.05 was considered statistically significant. Statistical analyses were performed using R software (R Development Core Team [2018]; R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

**Association of patient characteristics with PTEN expression**

This study included 205 patients diagnosed with de novo metastatic CNPC. The median patient age was 68 years and the median PSA at diagnosis was 172 ng ml\(^{-1}\), ranging from 10 ng ml\(^{-1}\) to 7100 ng ml\(^{-1}\). Biopsy results showed that 137 (66.8%) of these patients presented Gleason score ≥9 disease. The majority of these patients (89.8%) were M1b stage, and visceral metastases were observed in eight patients. On the basis of the CHAARTED standards, 80 and 125 patients were classified into low metastatic volume and high metastatic volume groups, respectively.\(^7\) After a median follow-up of 39 months, 136 patients developed CRPC and 84 had died at the end of the study. Among the 84 patients, 80 died of prostate cancer or treatment-related events (Table 1).

**Table 1: Patient summary of Fudan University Shanghai Cancer Center mPCa cohort**

| Characteristic                  | All patients (n=205) |
|--------------------------------|----------------------|
| Age (year), median (range)     | 68 (38–86)           |
| PSA (ng ml\(^{-1}\)), median (range) | 172.0 (10.0–7100.0) |
| Hemoglobin (g l\(^{-1}\)), median (range) | 134.0 (79.0–164.0) |
| Albumin (g l\(^{-1}\)), median (range) | 43.1 (26.8–71.4)    |
| LDH (U l\(^{-1}\)), median (range) | 171.0 (103.0–891.0) |
| ALP (U l\(^{-1}\)), median (range) | 122.3 (21.0–3000.0) |
| ECOG PS, n (%)                 |                     |
| <2                             | 170 (82.9)           |
| ≥2                             | 35 (17.1)            |
| Gleason score, n (%)           | 12 (5.9)             |
| ≥7                             | 56 (27.3)            |
| ≥9                             | 137 (66.8)           |
| Metastatic site, n (%)         |                      |
| Lymph node                     | 41 (20.0)            |
| Bone                           | 191 (93.2)           |
| Viscera                        | 8 (3.9)              |
| M stage, n (%)                 | 13 (6.3)             |
| M1a                            | 184 (89.8)           |
| M1b                            | 8 (3.9)              |
| Metastatic volume, n (%)       | 80 (39.0)            |
| Low                            | 125 (61.0)           |
| High                           | 109 (53.2)           |
| Perineural invasion, n (%)     | Present              |
| Absent                         | 96 (46.8)            |
| Present                        | 58 (28.3)            |
| PTEN expression, n (%)         | 147 (71.7)           |

\(^{FUSCC: Fudan University Shanghai Cancer Center; PSA: prostate-specific antigen; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; ECOG PS: Eastern Cooperative Oncology Group performance status; PTEN: phosphatase and tensin homolog on chromosome 10; mPCa: metastatic prostate cancer}\)
PTEN loss was observed in 58 (28.3%) patients, including 54 with homologous PTEN loss and 4 with heterologous PTEN loss. PTEN expression was not associated with baseline PSA level \((P = 0.723)\) or Gleason score \((P = 0.289)\). More patients with PTEN loss presented high metastatic volume disease compared with patients with intact PTEN \((P = 0.017)\; \text{Table 2}\).

**Univariate and multivariate analysis of PTEN expression in predicting PFS and OS**

Kaplan–Meier survival curves showed that patients with PTEN loss had significantly shorter PFS (median PFS: 43.8 months vs 80.2 months, \(P < 0.001\)) and OS (median OS: 11.9 months vs 30.6 months, \(P < 0.001\)) than those with intact PTEN expression (Figure 1b and 1c). Univariate analysis showed that reduced hemoglobin and albumin, elevated lactic dehydrogenase (LDH) and alkaline phosphatase (ALP), Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, and high metastatic volume were associated with shorter PFS as well as PTEN loss (Table 3). In a multivariate Cox model, elevated LDH, metastatic volume, and PTEN expression were significantly associated with PFS. The adjusted hazard ratio (HR) was 1.67 (1.14–2.43, \(P = 0.008\)) for PTEN loss in predicting PFS. Factors associated with OS in univariate analysis included blood hemoglobin and albumin concentration, ECOG PS, metastatic volume, and PTEN expression (Table 3). Multivariate analysis showed that only ECOG PS and PTEN expression were significant prognostic factors in predicting OS. The adjusted HR for PTEN loss in predicting OS was 1.95 (1.23–3.10, \(P = 0.005\)).

**The prognostic value of PTEN in patients according to metastatic volume**

Metastatic volume is a well-recognized prognostic factor in metastatic prostate cancer. The absence of PTEN protein mutations and/or deletions in localized CNPC, metastatic CNPC, and metastatic CPRC was significant in patients with low metastatic volume \((P < 0.001)\) and OS (median OS: 11.9 months vs 30.6 months, \(P < 0.001\)) than those with intact PTEN expression (Figure 1b and 1c). Univariate analysis showed that reduced hemoglobin and albumin, elevated lactic dehydrogenase (LDH) and alkaline phosphatase (ALP), Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, and high metastatic volume were associated with shorter PFS as well as PTEN loss (Table 3). In a multivariate Cox model, elevated LDH, metastatic volume, and PTEN expression were significantly associated with PFS. The adjusted hazard ratio (HR) was 1.67 (1.14–2.43, \(P = 0.008\)) for PTEN loss in predicting PFS. Factors associated with OS in univariate analysis included blood hemoglobin and albumin concentration, ECOG PS, metastatic volume, and PTEN expression (Table 3). Multivariate analysis showed that only ECOG PS and PTEN expression were significant prognostic factors in predicting OS. The adjusted HR for PTEN loss in predicting OS was 1.95 (1.23–3.10, \(P = 0.005\)).

**DISCUSSION**

To the best of our knowledge, this is the first study investigating the prognostic value of PTEN protein expression in de novo metastatic CNPC. PTEN loss was present in 28.3% of the 205 patients with de novo metastatic CNPC in the current study group. Survival analysis revealed that PTEN loss was an independent predictor for poor prognosis. Further analysis suggested that PTEN expression status combined with the level of metastatic volume provided better risk classification compared with metastatic volume alone for patients with metastatic CNPC.

PTEN loss is a typical alteration that frequently occurs in prostate cancer. The frequency of PTEN loss increases during the development of prostate cancer.\(^{15}\) Fluorescence in situ hybridization revealed homogenous PTEN deletion in 15%–20% localized prostate cancer cases and in more than 50% metastatic CRPC cases.\(^{16}\) In recent years, detecting PTEN protein loss by IHC has been more widely adopted to evaluate PTEN status in cancers. Lotan et al.\(^7\) demonstrated that IHC could detect 75%–86% of cases with PTEN gene loss. PTEN protein loss was also found to be associated with the development of CRPC. In this study, we found that PTEN protein loss occurred at an incidence higher than localized prostate cancer and lower than metastatic CRPC reported by previous studies.\(^3,10\) Similarly, a recent study used massively parallel targeted sequencing to detect 16%, 28%, and 67% PTEN mutations and/or deletions in localized CNPC, metastatic CNPC, and metastatic CRPC, respectively.\(^17\)

The prognostic value of PTEN expression has been widely studied in localized prostate cancer. The absence of PTEN protein
Table 2: Association of PTEN expression status with patients’ characteristics

| Patient characteristic | PTEN expression | P      |
|------------------------|----------------|--------|
|                        | Loss (total=58) | Intact (total=147) |
| Age (year), median     | 68             | 68     | 0.699 |
| Baseline PSA (ng ml⁻¹), n (%) | 28 (48.3) | 75 (51.0) | 0.723 |
| ≤172                   | 30 (51.7)      | 72 (49.0) |        |
| >172                   | 45 (77.6)      | 122 (83.0) | 0.370 |
| Hemoglobin (g l⁻¹), n (%) | 13 (22.4) | 25 (17.0) |        |
| Normal (≥120)          | 43 (74.1)      | 82 (55.8) | 0.017 |
| Decreased (<120)       | 11 (19.0)      | 10 (6.8) |        |
| Albumin (g l⁻¹), n (%) | 82 (55.8)      | 125 (85.0) | 0.202 |
| Normal (≥40)           | 47 (81.0)      | 137 (93.2) | 0.010 |
| Decreased (<40)        | 11 (19.0)      | 10 (6.8) |        |
| LDH (U l⁻¹), n (%)     | 47 (81.0)      | 137 (93.2) | 0.026 |
| Normal (≤250)          | 11 (19.0)      | 10 (6.8) |        |
| Elevated (>250)        | 32 (55.2)      | 105 (71.4) |        |
| ECOG performance status, n (%) | 2 (25.9) | 65 (44.2) |        |
| Gleason score, n (%)   | 5 (8.6)        | 7 (4.8) | 0.289 |
| <7                     | 53 (91.4)      | 140 (95.2) |        |
| ≥8                     | 32 (55.2)      | 105 (71.4) |        |
| Metastatic volume, n (%) | 43 (74.1) | 82 (55.8) |        |
| High                   | 82 (55.8)      |        |        |

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expressed was associated with increased tumor grade and stage, earlier biochemical recurrence, and metastases after radical prostatectomy.17–19 However, few studies have focused on the clinical significance of PTEN status in metastatic disease. Ferraldeschi et al.10 demonstrated that PTEN loss was associated with shorter OS in metastatic CRPC patients treated with abiraterone. Another study recently reported that genetic alteration of TP53, PTEN, and R181 was associated with poor OS of both metastatic CNPC and metastatic CRPC. However, these data need to be interpreted carefully because PTEN status was not analyzed separately, and because the study had a small sample size of only 43 metastatic CNPC patients.17 Our work investigated the relationship between PTEN expression, clinicopathological features, and outcome in 205 metastatic CNPC patients. PTEN loss was associated with higher metastatic volume; however, a correlation between PTEN loss and Gleason score, which was reported in localized prostate cancer, was not observed in our cohort. This may be because only 5.9% of the metastatic CNPC patients in our study showed Gleason score ≤7 tumors. The low numbers of patients with low Gleason score may also be the reason why Gleason score did not present prognostic value in survival analysis. We further demonstrated that PTEN protein loss was an independent predictor for PFS and OS.

Recent clinical trials have identified new treatment strategies for CNPC. Agents such as abiraterone and docetaxel that are used for CRPC were found to improve disease control and survival for patients with CNPC.24 Local therapy such as radiotherapy for primary cancer may also benefit patients with low metastatic volume.18,19 Risk stratification of metastatic patients was critical for treatment selection. Subgroup analysis in these studies revealed that patients with low metastatic volume benefited from radiotherapy, whereas patients with high metastatic volume benefited more from aggressive medical treatment using the emerging drugs.26 For these reasons, we investigated if the addition of PTEN expression could optimize risk stratification classified by metastatic volume. We found that PTEN loss identified a group of patients with poor prognosis among those with low volume metastatic disease. The PFS of this group of patients was comparable to patients with high volume disease, indicating that PTEN is superior to metastatic volume in predicting patient outcome. These results indicate that PTEN status should be considered for risk stratification in future clinical trials.

PTEN exerts its antitumor function mainly through suppressing the activation of PI3K-AKT pathway, and aberrant PI3K-AKT signaling is well-recognized mechanism drive uncontrolled proliferation of tumor cells. Small molecular inhibitors targeting PI3K and AKT are being investigated in clinical trials.11,12 Preliminary results have suggested that the combination of AKT inhibitor and abiraterone leads to longer survival than abiraterone alone in metastatic CRPC patients with PTEN loss but not in patients with intact PTEN expression.11 Thus, PTEN loss is a strong indicator for the efficacy of treatment targeting the PI3K-AKT pathway. Recent studies revealed that PTEN loss and activation of the PI3K-AKT pathway can also facilitate disease progression to CRPC.12,13 Although PTEN loss was more frequently observed in patients with metastatic CRPC, one study reported good concordance between samples collected in matched CNPC and CRPC tissues.14 Together with our findings, these data support the idea that PTEN loss is a driving force rather than a consequence of CRPC. Early intervention targeting the PI3K-AKT pathway in metastatic CNPC patients with PTEN loss may thus impede the development of CRPC and prolong survival.

Previous studies have demonstrated that tumor suppressor genes, such as PTEN, TP53, and R181 genes, are often altered simultaneously in prostate cancer.17,24,25 Whether other gene alterations, rather than PTEN alteration itself, are causative factors for the poor patient prognosis is still unknown. As the treatment of CNPC has evolved rapidly in recent years, genome sequencing studies are expected to provide insights into genomic correlations with patient survival and treatment efficacy.

In conclusion, our results from a de novo metastatic CNPC cohort that received standard treatment demonstrated that PTEN loss predicts poor prognosis for patients with CNPC independent of metastatic volume. PTEN expression evaluated by immunohistochemistry can be used for better risk stratification and subgroup analysis in clinical trials.

CONCLUSION

PTEN protein loss is an independent predictor for shorter PFS and OS in patients with de novo metastatic CNPC.

AUTHOR CONTRIBUTIONS

BD and DWY contributed to conceptualization and project administration. JYZ, YYK, and QFW performed data curation. JYZ, YYK, and ZL conducted formal analysis. NL and YJY provided technical support. JYZ and YYK wrote the original article. BD and DWY reviewed and edited the original article. BD contributed to funding acquisition. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.
### Table 3: Univariate and multivariate analysis of each factor's value in predicting PFS and OS

| Factors                     | Univariate PFS (HR [95% CI] P) | Multivariate PFS (HR [95% CI] P) | Univariate OS (HR [95% CI] P) | Multivariate OS (HR [95% CI] P) |
|-----------------------------|--------------------------------|----------------------------------|-----------------------------|----------------------------------|
| Age (year)                  |                                |                                  |                             |                                  |
| ≤68 (Ref)                   | 1                              |                                  | 1                           |                                  |
| >68                         | 0.94 (0.67–1.32) 0.727          |                                  | 1.29 (0.84–1.99) 0.245       |                                  |
| Baseline PSA (ng ml⁻¹)      |                                |                                  |                             |                                  |
| ≤172 (Ref)                  | 1                              |                                  | 1                           |                                  |
| >172                        | 1.25 (0.89–1.76) 0.192          |                                  | 1.35 (0.88–2.09) 0.170       |                                  |
| Hemoglobin (g l⁻¹)          |                                |                                  |                             |                                  |
| ≥120 (Ref)                  | 1                              |                                  | 1                           |                                  |
| <120                        | 1.73 (1.15–2.60) 0.009          |                                  | 1.67 (1.01–2.74) 0.044       |                                  |
| Albumin (g l⁻¹)             |                                |                                  |                             |                                  |
| >40 (Ref)                   | 1                              |                                  | 1                           |                                  |
| <40                         | 1.74 (1.16–2.60) 0.007          |                                  | 2.00 (1.23–3.24) 0.005       |                                  |
| LDH (U l⁻¹)                 |                                |                                  |                             |                                  |
| ≤250 (Ref)                  | 1                              |                                  | 1                           |                                  |
| >250                        | 2.24 (1.33–3.79) 0.003          |                                  | 1.79 (1.01–3.19) 0.046       |                                  |
| ALP (U l⁻¹)                 |                                |                                  |                             |                                  |
| ≤160 (Ref)                  | 1                              |                                  | 1                           |                                  |
| >160                        | 1.62 (1.14–2.29) 0.007          |                                  | 0.94 (0.62–1.42) 0.762       |                                  |
| ECOG PS                     |                                |                                  |                             |                                  |
| <2 (Ref)                    | 1                              |                                  | 1                           |                                  |
| ≥2                          | 1.75 (1.16–2.65) 0.008          |                                  | 1.41 (0.92–2.17) 0.120       |                                  |
| Gleason score               |                                |                                  |                             |                                  |
| <8 (Ref)                    | 1                              |                                  | 1                           |                                  |
| ≥8                          | 1.15 (0.54–2.46) 0.721          |                                  | 0.84 (0.36–1.95) 0.692       |                                  |
| Metastatic volume           |                                |                                  |                             |                                  |
| Low (Ref)                   | 1                              |                                  | 1                           |                                  |
| High                        | 2.02 (1.39–2.92) <0.001         |                                  | 1.61 (1.06–2.46) 0.025       |                                  |
| PTEN expression             |                                |                                  |                             |                                  |
| Intact (Ref)                | 1                              |                                  | 1                           |                                  |
| Loss                        | 2.04 (1.42–2.93) <0.001         |                                  | 1.67 (1.14–2.43) 0.008       |                                  |

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