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ORIGINAL ARTICLE

Prostate Cancer

Clinical and oncologic findings of extraprostatic extension on needle biopsy in *de novo* metastatic prostate cancer

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This study aimed to explore the clinical and oncologic findings in patients with *de novo* metastatic prostate cancer (mPCa) and extraprostatic extension (EPE) on biopsy. We retrospectively evaluated data on 630 patients with *de novo* mPCa between January 2009 and December 2017 in the West China Hospital (Chengdu, China), including evaluating the relationships between EPE and other variables and the association of EPE with survival outcomes by the Chi-square test, Kaplan–Meier curves, and the Cox proportional-hazards model. EPE was found in 70/630 patients, making a prevalence of 11.1%. The presence of EPE on biopsy was associated with higher Gleason scores and higher incidence of neuroendocrine differentiation (NED), intraductal carcinoma of the prostate (IDC-P), and perineural invasion (PNI). Compared with those without EPE, patients with EPE had shorter castration-resistant prostate cancer-free survival (CFS; median: 14.1 *vs* 17.1 months, $P = 0.015$) and overall survival (OS; median: 43.7 *vs* 68.3 months, $P = 0.032$). According to multivariate analysis, EPE was not an independent predictor for survival. Subgroup analyses demonstrated that patients with favorable characteristics, including negative NED or IDC-P status, Eastern Cooperative Oncology Group (ECOG) score <2, and prostate-specific antigen (PSA) <50 ng ml^{-1}, had worse prognoses if EPE was detected. In patients with PSA <50 ng ml^{-1}, EPE was a negative independent predictor for OS (hazard ratio [HR]: 4.239, 95% confidence interval [CI]: 1.218–14.756, $P = 0.023$). EPE was strongly associated with other aggressive clinicopathological features and poorer CFS and OS. These data suggest that EPE may be an indicator of poor prognosis, particularly in patients, otherwise considered likely to have favorable survival outcomes.

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Keywords: extraprostatic extension; metastatic prostate cancer; prevalence; prognosis

INTRODUCTION

Since the development of prostate-specific antigen (PSA) screening, prostate cancer (PCa) has become the most commonly diagnosed solid malignancy in men.[1] Clinically, it presents as a spectrum from indolent biological behavior to metastatic progression.[2]

Extraprostatic extension (EPE) is defined as the presence of prostatic tumor tissue beyond the normal boundaries of the prostate gland. It often presents as a mixture of carcinoma and periprostatic adipose tissue or as a tissue that extends beyond the prostate gland boundaries.[3] It is well established that the presence of EPE in a radical prostatectomy (RP) specimen plays a vital role in pathological staging and risk stratification.[3,4] EPE in an RP specimen is an adverse prognostic factor and an indicator for adjuvant radiation therapy.[5] EPE can also be detected by prostate biopsy. However, because it is relatively rarely detected, there is limited information on the clinical significance of biopsy-detected EPE in patients with PCa.[6,7] In addition, neither the detection rate of EPE in metastatic PCa (mPCa) nor its clinical outcomes have yet been reported.

The aim of this study was to investigate the prevalence of EPE in needle biopsy specimens and its clinical significance in patients with *de novo* mPCa.

PATIENTS AND METHODS

Patients

Between January 2009 and December 2017, 1742 patients were diagnosed as having PCa by ultrasound-guided random transperineal prostate biopsy in the West China Hospital (Chengdu, China). Among them, 117 patients (6.7%) were found to have EPE in biopsy specimens. Of the 1742 patients with PCa, 630 (36.2%) patients with initial diagnoses of mPCa were included in this retrospective study. All study patients had bone metastases and 3.5% (22/630) of them also had visceral metastases. Metastases were identified by bone scan, positron emission tomography (PET), computed tomography (CT), or magnetic resonance imaging (MRI). All patients were treated with maximal androgen blockade (MAB), including nonsteroidal antiandrogens plus either orchiectomy or medical castration, before

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progression to metastatic castration-resistant PCa (mCRPC) or death. After progression to mCRPC, patients were sequentially treated with docetaxel or abiraterone acetate. The median follow-up was 32.5 months. Data collection and analysis were authorized by the Ethics Committee of the West China Hospital, Sichuan University. Informed consent was obtained from all included patients.

The diagnosis was determined by the ultrasound-guided transperineal needle prostate biopsy in all patients. Two urological pathologists independently evaluated the samples histopathologically. EPE was defined as the presence of tumor cells within or adjacent to periprostatic adipose tissue on either side of the prostate gland.[3] Baseline patient characteristics and clinicopathologic data were collected via a PCa database in our center. These included age, Eastern Cooperative Oncology Group (ECOG) score, total Gleason score, neuroendocrine differentiation (NED, defined as scattered neuroendocrine cells identified by immunohistochemical positivity for synaptophysin or chromogranin comprising more than 5% of all tumor cells) status, intraductal carcinoma of the prostate (IDC-P) status, perineural invasion (PNI) status, type of castration, and baseline serum PSA, alkaline phosphatase (ALP), and hemoglobin (HGB) concentrations. Patients were also classified into high-, intermediate-, and low-risk groups according to Glass risk stratification.[8]

Outcomes

The primary endpoints were detection rate of EPE on prostate biopsy and overall survival (OS), which was defined as the time between initial diagnosis of mPCa and death from any cause. The secondary endpoint was CRPC-free survival (CFS), defined as the time between initial diagnosis of mPCa and progression to mCRPC. The diagnosis of CRPC was based on the 2017 European Association of Urology (EAU) guidelines.[9]

Statistical analyses

Continuous variables are presented as median and interquartile range (IQR) and categorical variables as frequencies and percentages. The detection rate of EPE on needle core biopsy was calculated as the number of patients with EPE according to pathology reports divided by the total number of patients with pathologically diagnosed PCa. The Chi-square test was used to compare baseline characteristics between patients with and without EPE. Survival curves were generated by the Kaplan–Meier method and compared by log-rank test. Univariate and multivariate analyses were conducted using the Cox proportional-hazards model. Subgroup analyses were conducted to evaluate whether the presence of EPE affected the prognosis in subgroups with different baseline factors; the results are presented as forest plots. A two-sided $P < 0.05$ was considered to denote statistical significance. SPSS version 25.0 (SPSS, Chicago, IL, USA) was used for statistical analyses.

RESULTS

Baseline characteristics and detection rate of EPE

The baseline characteristics of the 630 patients with mPCa are summarized in **Table 1**. mCRPC was identified in 66.0% (416/630) of them, and 30.2% (190/630) of patients had died by the time of cutoff. The median OS and CFS for the entire cohort were 65.7 (95% confidence interval [CI]: 59.7–71.7) months and 16.5 (95% CI: 15.0–18.0) months, respectively.

Random transperineal biopsies were positive for EPE in 11.1% (70/630) of the patients. Compared with patients without EPE, those with EPE had more aggressive clinicopathological factors, including higher total Gleason scores 9–10 (87.1% *vs* 43.7%, $P < 0.001$); higher incidence of NED (30.0% *vs* 12.7%, $P < 0.001$), IDC-P (45.7% *vs* 26.3%, $P = 0.001$), and PNI (62.9% *vs* 20.9%, $P < 0.001$); and lower baseline HGB concentrations (27.1% *vs* 16.3%, $P = 0.024$).

The clinical significance of EPE regarding CFS and OS in patients with mPCa

At the last follow-up, mCRPC and death had occurred in 72.9% (51/70) and 38.6% (27/70) of patients with EPE, respectively, and 65.2% (365/560) and 29.1% (163/560) of patients without EPE, respectively. **Figure 1** shows OS and CFS curves stratified according to the EPE status. Compared with those without EPE, patients with EPE had significantly shorter OS (median: 43.7 *vs* 68.3 months, $P = 0.032$) and CFS (median: 14.1 *vs* 17.1 months, $P = 0.015$).

According to univariate analysis, the presence of EPE on needle biopsy was significantly associated with poorer OS (hazard ratio [HR]: 1.619, 95% CI: 1.036–2.529, $P = 0.034$) and CFS (HR: 1.437, 95% CI: 1.070–1.931, $P = 0.016$) in patients with mPCa. However, after adjustment for other prognostic factors, EPE was no longer an independent predictive factor according to multivariate analysis (**Table 2**).

Subgroup analysis of the impact of EPE on CFS and OS in patients with mPCa

All patients were stratified into various subgroups according to baseline characteristics. The impact of EPE on OS and CFS in various subgroups is shown by forest plots (**Figure 2**). Notably, EPE was found to be a risk factor for CFS and OS, especially in patients with relatively favorable baseline characteristics such as negative NED status, negative IDC-P status, and low ECOG scores and baseline PSA concentrations. As shown in **Figure 3a** and **3b**, when patients were assigned to low-/intermediate- and high-risk groups using the Glass model, EPE was found to be significantly associated with shorter OS (median: 63.8 *vs* 71.4 months, $P = 0.021$) in the low-/intermediate-risk group but not in the high-risk group (median: 37.0 *vs* 48.8 months, $P = 0.672$).

As shown in **Figure 3c** and **3d**, further analysis revealed that, in patients with PSA <50 ng ml^{-1}, EPE was significantly associated with much shorter OS (median: 21.6 *vs* 70.1 months, $P < 0.001$) and CFS (median: 8.5 *vs* 20.7 months, $P = 0.001$). Multivariate analysis indicated that EPE was independently associated with poorer OS (HR: 4.239, 95% CI: 1.218–14.756, $P = 0.023$) in this subset of patients. In contrast, in other subgroups in which EPE showed statistically prognostic value in the forest plot, it was not confirmed to be a predictor by multivariate analyses (data not shown).

DISCUSSION

To the best of our knowledge, this is the first study to report detection of EPE on needle biopsy and investigation of the clinical significance of EPE in patients with *de novo* mPCa. The prevalence of EPE on prostate biopsy in this cohort of mPCa patients was as high as 11.1%.

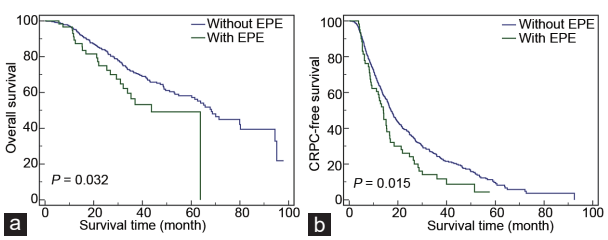

Figure 1: Kaplan–Meier curves of (**a**) overall survival and (**b**) CRPC-free survival for the whole mPCa cohort with and without EPE. EPE: extraprostatic extension; CRPC: castration-resistant prostate cancer; mPCa: metastatic prostate cancer.

Table 1: Baseline characteristics of patients with and without extraprostatic extension

Baseline characteristics	*Without EPE (n=560)*	*With EPE (n=70)*	*P*
Age (year), median (IQR)	71.0 (66.0, 76.0)	71.0 (64.0, 75.0)	
<70, *n* (%)	215 (38.4)	30 (42.9)	0.47
≥70, *n* (%)	345 (61.6)	40 (57.1)	
Total Gleason score, *n* (%)			
≤7	75 (13.4)	3 (4.3)	<0.001
8	240 (42.9)	6 (8.6)	
9–10	245 (43.7)	61 (87.1)	
NED, *n* (%)			
Negative	489 (87.3)	49 (70.0)	<0.001
Positive	71 (12.7)	21 (30.0)	
IDC-P, *n* (%)			
Negative	413 (73.7)	38 (54.3)	0.001
Positive	147 (26.3)	32 (45.7)	
PNI, *n* (%)			
Negative	443 (79.1)	26 (37.1)	<0.001
Positive	117 (20.9)	44 (62.9)	
ECOG score, *n* (%)			
<2	459 (82.0)	60 (85.7)	0.437
≥2	101 (18.0)	10 (14.3)	
Type of castration, *n* (%)			
Medical castration	253 (45.2)	25 (35.7)	0.133
Surgical castration	307 (54.8)	45 (64.3)	
Baseline PSA (ng ml^{-1}), median (IQR)	101.0 (42.9, 101.0)	101.0 (92.3, 101.0)	
<50, *n* (%)	130 (23.2)	13 (18.6)	0.382
≥50, *n* (%)	430 (76.8)	57 (81.4)	
Baseline ALP (IU l^{-1}), median (IQR)	107.0 (74.0, 213.0)	128.0 (65.0, 285.0)	
≤160, *n* (%)	242 (43.2)	25 (35.7)	0.231
>160, *n* (%)	318 (56.8)	45 (64.3)	
Baseline HGB (g l^{-1}), median (IQR)	132.0 (120.0, 143.0)	125.0 (105.0, 137.0)	
<120, *n* (%)	91 (16.3)	19 (27.1)	0.024
≥120, *n* (%)	469 (83.7)	51 (72.9)	
Glass risk stratification, *n* (%)			
Low	65 (11.6)	2 (2.9)	0.059
Intermediate	411 (73.4)	59 (84.3)	
High	84 (15.0)	9 (12.8)	

P values were calculated through Chi-square test for categorical variables. ALP: alkaline phosphatase; ECOG: Eastern Cooperative Oncology Group; EPE: extraprostatic extension; HGB: hemoglobin; IDC-P: intraductal carcinoma of the prostate; IQR: interquartile range; NED: neuroendocrine differentiation; PNI: perineural invasion; PSA: prostate-specific antigen

Table 2: Univariate and multivariate analyses of castration-resistant prostate cancer-free survival and overall survival for patients with metastatic prostate cancer

	Univariate analysis of CFS		*Multivariate analysis of CFS*		*Univariate analysis of OS*		*Multivariate analysis of OS*	
	HR (95% CI)	*P*	*HR (95% CI)*	*P*	*HR (95% CI)*	*P*	*HR (95% CI)*	*P*
EPE (positive *vs* negative)	1.437 (1.070–1.931)	0.016	1.062 (0.773–1.459)	0.712	1.619 (1.036–2.529)	0.034	1.185 (0.739–1.901)	0.48
PNI (positive *vs* negative)	1.293 (1.042–1.604)	0.02	0.884 (0.695–1.124)	0.316	1.275 (0.909–1.789)	0.16	NI	
IDC-P (positive *vs* negative)	1.833 (1.477–2.273)	<0.001	1.418 (1.120–1.796)	0.004	2.041 (1.457–2.860)	<0.001	1.505 (1.030–2.199)	0.035
Total Gleason score (8 *vs* ≤7)	1.623 (1.140–2.309)	0.007	1.411 (0.981–2.028)	0.063	1.749 (0.959–3.191)	0.068	1.592 (0.861–2.943)	0.138
Total Gleason score, (9–10) *vs* ≤7	2.353 (1.667–3.322)	<0.001	1.885 (1.313–2.706)	0.001	2.854 (1.588–5.128)	<0.001	2.166 (1.184–3.964)	0.012
Age (≥70 years *vs* <70 years)	0.722 (0.590–0.884)	0.002	0.866 (0.704–1.065)	0.174	0.662 (0.482–0.91)	0.011	0.829 (0.597–1.151)	0.262
ALP (>160 IU l^{-1} *vs* ≤160 IU l^{-1})	2.888 (2.332–3.577)	<0.001	2.469 (1.970–3.095)	<0.001	2.337 (1.678–3.253)	<0.001	1.881 (1.330–2.661)	<0.001
NED (positive *vs* negative)	1.355 (1.049–1.75)	0.02	1.214 (0.931–1.582)	0.153	1.473 (0.994–2.185)	0.054	NI	
ECOG (≥2 *vs* <2)	1.508 (1.189–1.914)	0.001	1.296 (1.016–1.652)	0.037	2.205 (1.571–3.096)	<0.001	1.938 (1.372–2.738)	<0.001
HGB (≥120 g l^{-1} *vs* <120 g l^{-1})	0.602 (0.471–0.771)	<0.001	0.753 (0.583–0.973)	0.031	0.533 (0.364–0.781)	0.001	0.655 (0.440–0.974)	0.036
PSA (≥50 ng ml^{-1} *vs* <50 ng ml^{-1})	1.354 (1.066–1.720)	0.013	1.177 (0.922–1.502)	0.192	1.166 (0.804–1.691)	0.419	NI	

ALP: alkaline phosphatase; CI: confidence interval; CFS: castration-resistant prostate cancer-free survival; ECOG: Eastern Cooperative Oncology Group; EPE: extraprostatic extension; HGB: hemoglobin; HR: hazard ratio; IDC-P: intraductal carcinoma of the prostate; NED: neuroendocrine differentiation; NI: not included; OS: overall survival; PNI: perineural invasion; PSA: prostate-specific antigen

We found that the presence of EPE on biopsy in patients with mPCa was associated with other adverse features, including high Gleason score, low baseline HGB concentration, and the presence of NED, IDC-P, and PNI. Patients with EPE had significantly shorter CFS and OS than

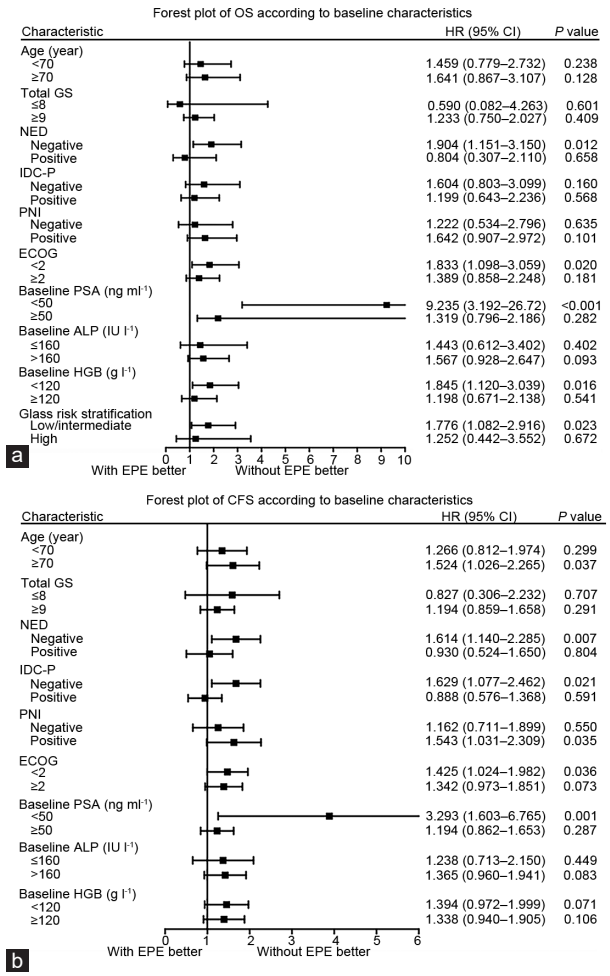

Figure 2: Forest plots showing the prognostic significance of EPE in predicting (**a**) overall survival and (**b**) CRPC-free survival for patients with different baseline characteristics. ALP: alkaline phosphatase; CFS: CRPC-free survival; CI: confidence interval; CRPC: castration-resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; EPE: extraprostatic extension; GS: Gleason score; HGB: hemoglobin; HR: hazard ratio; IDC-P: intraductal carcinoma of the prostate; NED: neuroendocrine differentiation; OS: overall survival; PNI: perineural invasion; PSA: prostate-specific antigen.

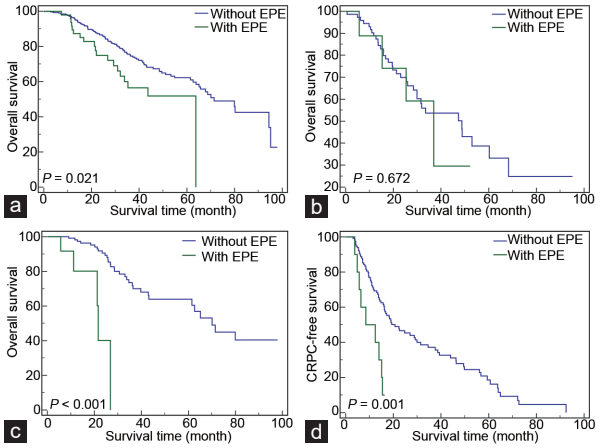

Figure 3: Kaplan–Meier curves of overall survival for patients who were stratified into (**a**) Glass low-/intermediate-risk group and (**b**) Glass high-risk group with and without EPE. Kaplan–Meier curves of (**c**) overall survival and (**d**) CRPC-free survival for patients who had a PSA value of <50 ng ml^{-1} with and without EPE. EPE: extraprostatic extension; PSA: prostate-specific antigen; CRPC: castration-resistant prostate cancer.

those without EPE. However, EPE was not an independent prognostic factor for CFS or OS for the entire cohort. Notably, in patients with a baseline PSA <50 ng ml^{-1}, EPE was associated with both poorer CFS and OS in univariate analyses and independently related to shorter OS in multivariate analysis.

To date, only two studies have reported the outcomes of patients with EPE on needle biopsy.[6,7] Miller *et al*.[7] from John Hopkins University (JHU) reviewed 51 891 cases of prostatic adenocarcinoma from 1997 to 2009 and reported a prevalence of positive EPE on needle biopsy of 0.19%. Fleshner *et al*.[6] analyzed 19 950 biopsies performed between 2004 and 2015 at the Memorial Sloan Kettering Cancer Center and reported detection of EPE in 0.6% of patients. In the present study, we detected EPE in 6.7% of the entire database of patients with PCa (n = 1742), which is a higher percentage than in the two previous studies mentioned above. The high percentage of patients with mPCa (36.2%, 630/1742) in our entire cohort may be in part responsible for this discrepancy. We detected EPE in 11.1% of patients with mPCa in this study. Given that it has been speculated that invasion through the prostatic capsule plays a role in metastasis of PCa,[10] it is not surprising that the proportion of patients with EPE was high in our study cohort. In addition, ethnic differences may have contributed to the discrepancy in rates of EPE. The patients in the studies by Miller *et al*.[7] and Fleshner *et al*.[6] were mainly from the USA, whereas all patients in our study were Asians.

PNI is characterized by neoplastic invasion of nerves within the perineural space[11] and is reportedly to be one of the major routes of extension of carcinoma to periprostatic soft tissue through the prostatic capsule.[12,13] The usefulness of PNI detected on needle biopsy as a predictor of EPE is still controversial. Similar to the results of the present study, a recent systematic review and meta-analysis of ten studies found a strong association between PNI and EPE on univariate analysis.[14] However, Egan and Bostwick[15] have reported that PNI on needle biopsy has no independent predictive value for the presence of EPE in RP specimens.

Several previous studies have reported a possible association between high Gleason scores on needle biopsy and EPE in the RP specimen.[16,17] Chaux and colleagues[16] found that the incidence of EPE was higher in patients with Gleason scores ≥8 on needle biopsy. Noguchi and colleagues[17] also found that a primary pattern of Gleason scores of 4/5 on biopsy is an independent predictor of the presence of EPE in RP specimens. Two published studies concerning EPE on biopsy also reported similar results.[6,7] In the study by Fleshner *et al*.[6] the most frequently occurring Gleason score in cores with EPE was 9. As for the study from JHU, the mean Gleason score in cores with EPE was 8, the mean highest Gleason score per patient being 8.4.[7] In concordance with this, in the present study, we found that most patients with EPE on biopsy had Gleason scores between 9 and 10, which was a significantly higher percentage than in those without EPE (87.1% *vs* 43.7%, $P < 0.001$). Besides, we identified an association between biopsy-detected EPE and the presence of IDC-P, which is an adverse prognostic indicator of survival in patients with either localized PCa or mPCa.[18,19]

The prognostic value of EPE in RP specimens is well established. However, the clinical significance of biopsy-detected EPE in patients with PCa, especially in those with mPCa, has not yet been fully determined. In the present study, we first reported that EPE on needle

biopsy is associated with significantly lower CFS and OS in patients with *de novo* mPCa. However, after adjustment for other prognostic indicators in multivariate analysis, EPE was no longer an independent prognostic factor. The strong association between EPE and other common risk factors such as high Gleason score and presence of IDC-P might be the main explanation for the absence of significant results in multivariate analysis. In addition, subgroup analyses revealed some interesting information. We found a correlation between EPE and poorer survival in patients with relatively favorable characteristics, such as negative NED status, absence of IDC-P, low baseline PSA concentrations, and low/intermediate Glass risk group. Furthermore, in patients with PSA <50 ng ml^{-1}, EPE was an independent predictor of shorter OS. Taken together, these results suggest that EPE, though not a strong prognostic indicator in all patients with mPCa, may be valuable in predicting poor prognosis in some subsets of patients. Even when the well-established prognostic indicators suggest that a patient will have favorable survival outcomes, clinicians should still pay attention to the finding of positive EPE on biopsy to avoid underestimation of the disease and to optimize treatment strategies.

This study had several limitations. Although the overall cohort was relatively large, when we stratified patients into subgroups, the sample sizes were small. In addition, as for any retrospective study, there was potential selection bias. Furthermore, biopsy techniques and variability in diagnosing and reporting EPE by pathologists may have had impacts on outcomes. Moreover, despite the fact that all patients were initially treated with MAB, the sequence of treatments after CRPC could have influenced the prognosis. Further studies with large patient cohorts are needed to verify our findings.

CONCLUSION

Extraprostatic extension on needle biopsy is common in patients with *de novo* mPCa. Although the presence of EPE in mPCa is not an independent prognostic indicator, this is the first study to report its association with shorter CFS and OS. Our findings indicate that we should pay more attention to the important potential predictive value of EPE in patients, otherwise considered as likely to have favorable survival outcomes on the basis of other prognostic factors.

AUTHOR CONTRIBUTIONS

JRC and JGZ designed the study, analyzed the data, and wrote and revised the manuscript. SZ helped statistical analyses and revised the manuscript. MNZ and NC collected and reviewed the pathologic data. GXS and JDL collected the clinical data and participated in patient follow-up. PFS and HZ supervised the project, participated its coordination, and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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