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ORIGINAL RESEARCH

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Enhancing androgen ablation response in metastatic hormone-sensitive prostate cancer: the benefits of transurethral resection of the prostate

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Abstract

Presently, there is limited data on the potential survival benefits of transurethral resection of the prostate (TURP) in patients with metastatic hormone-sensitive prostate cancer (mHSPCa). In this study, we aimed to assess the effects of TURP on the survival of mHSPCa patients. Of the 59 patients diagnosed with mHSPCa included, 28 received androgen deprivation therapy (ADT) alone, and the remaining received TURP plus ADT. Their time to biochemical progression (TBCP) and progression-free survival (PFS) were analyzed. Our results showed that for a median follow-up time of 15 (range, 3–40) months and 21 (range, 6–39) months for the ADT group and the TURP group, respectively, the TURP group exhibited significantly longer TBCP than the ADT group (p = 0.020). In addition, patients in the TURP group had numerically longer PFS, although the difference between the two groups was not significantly different (p = 0.110). Cox multivariate analysis indicated that longer TBCP was independently associated with TURP (p = 0.032) and lower Gleason scores (p = 0.001). Altogether this study showed that TURP could prolong TBCP and potentially improve the PFS of mHSPCa patients. However, further studies with a larger sample size are needed to confirm these findings.

Keywords

Metastasis prostate cancer; Hormone sensitive; Transurethral resection of the prostate; Progression-free survival; Time to castration resistance

1. Introduction

Prostate cancer remains a highly prevalent malignancy, comprising about 29% of all cancer diagnoses in men [1]. Despite advances in treatment, patients with metastatic prostate cancer (mPCa) still have poor survival prospects [2]. Although androgen deprivation therapy (ADT) remains the traditionally recommended therapy for metastatic hormone-sensitive prostate cancer (mHSPCa) [3], most of these patients eventually develop biochemical or clinical progression, resulting in a significant decline in survival outcomes [4]. Moreover, the growth of cancer cells and the occurrence of local complications such as bladder outlet obstruction (BOO) and hematuria are also contributory factors that further reduce their quality of life and survival [5]. In such instances, TURP is often performed to relieve these local complications [6].

Cytoreductive surgery of the primary tumor has been shown to confer survival benefits in several malignancies [7–10]. The potential for a similar impact on prostate cancer has been demonstrated with cytoreductive radical prostatectomy (CRP) in mPCa patients [11–13]. Mechanistically, reducing the overall tumor burden has been proposed to improve survival outcomes following CRP in mPCa patients [12]. Similar to CRP, TURP can be performed to manage local complications in mPCa patients to a certain extent, making it a form of cytoreductive surgery that could theoretically lead to better survival outcomes.

In this present study, we evaluated the survival of a well-selected cohort of mHSPCa patients who underwent TURP and ADT compared to ADT alone to shed light on strategies for improving the prognosis of patients with mPCa.

2. Methods

In this prospective study, 59 mHSPCa patients receiving ADT with or without TURP from Jun 2019 to July 2022 were assessed. Of them, 31 underwent TURP due to the indications of hematuria or BOO before ADT (TURP group), while the others received ADT alone (ADT group). TURP was performed by the same doctor. The procedure was the same as TURP for benign prostate hyperplasia, and the prostate tissues were resected till the level of the capsule. The diagnosis of PCa was confirmed by biopsy. Tissues were sampled during routine transrectal ultrasound-guided 12 to 18-core biopsy of

the prostate. Then, several parameters, including the number of positive biopsy cores and the Gleason score, were assessed. Metastatic disease was confirmed *via* routine imaging, including skeletal scintigraphy, magnetic resonance imaging (MRI), or abdominal/pelvic/chest computed tomography (CT). Positron emission tomography-computed tomography (PET/CT) was performed for unequivocal findings on skeletal scintigraphy, MRI or CT.

Study eligibility criteria were: (1) the diagnosis of PCa was based on tissue samples taken during transrectal-ultrasound guided core biopsy; (2) had metastasis to the bone or viscera including liver, cerebrum, or lung; (3) were initially hormone-sensitive; (4) had no prior radiation and systemic therapy; (5) provided written informed consent; and (6) had a life expectancy >1 year from the time of diagnosis.

2.1 TURP group

Thirty-one mHSPCa patients with BOO or hematuria who underwent transrectal-ultrasound-guided core biopsy were elected to receive TURP as the initial local therapy and were recommended ADT (3.6 mg goserelin once every month and 50 mg bicalutamide per day) as adjuvant therapy.

2.2 ADT group

Twenty-eight mHSPCa patients without local complications underwent ADT alone. Once diagnosed, they were started on goserelin (3.6 mg, s.c. AstraZeneca; once every month) and bicalutamide (50 mg, p.o. AstraZeneca; once every day).

2.3 Following-up

All patients were followed-up until biochemical progression, clinical progression, or death. In the first year, they were followed-up every month. Following successful ADT intervention, they were followed-up every 3 months for the next two years, then annually afterward. At each follow-up, the patients underwent testosterone, alkaline phosphatase, prostate-specific antigen (PSA), and digital rectal examinations. Prostate magnetic resonance imaging (MRI), skeletal scintigraphy, abdominal/pelvic/chest CT, or PET/CT were performed every three months to evaluate radiographic changes.

2.4 Definition of progression

Biochemical progression was described as a continuous increase in PSA levels, resulting in a 50% increase above the nadir value. The onset of new symptoms due to PCa progression or radiographic evidence of disease progression alone were used as indications for determining clinical progression. Time to biochemical progression (TBCP) was measured from the start of ADT until biochemistry progression. Progression-free survival (PFS) was defined as the time interval from the initiation of ADT to the first occurrence of biochemical progression and clinical progression.

2.5 Statistical analysis

The SPSS v18.0 (IBM Corp., Armonk, NY, USA) software was used for statistical analysis. Continuous variables were analyzed using independent-samples Student's *t*-test. The chi-square test was used for categorical variables. The primary endpoint was TBCP, and the secondary endpoint was PFS. Kaplan-Meier survival analysis and log-rank test were performed for survival analysis. Cox univariate and multivariate proportional hazard analyses were also performed to identify factors independently associated with patients' survival. A two-sided p-value < 0.05 was considered for statistical significance.

3. Results

3.1 Baseline characteristics of the patients

Our analysis showed no significant difference in baseline characteristics between the two study groups in regard to age, PSA at diagnosis, American joint Committee on cancer (AJCC) clinical stage, and biopsy Gleason score (Table 1).

3.2 Histopathology, clinical T stages, and complications related to TURP

The diagnosis of PCa was confirmed in all patients *via* pathological examination (Fig. 1).

Imaging examinations showed that 22 (70.9%) patients were staged as cT1 and cT2, six (19.4%) as cT3, and three (9.7%) as cT4 in the TURP group. In the ADT group, there were 18 (64.3%) patients staged as cT1 and cT2, four (14.3%) as cT3, and six (21.4) as cT4. Additionally, four (12.0%) in the TURP group and six (21.4%) in the ADT group had lymph node metastases (Table 1). No serious TURP complications, such as perineum hematoma, rectal injury or urethra-rectal fistula, occurred in any of the investigated patients. However, one patient in the TURP group suffered from stress incontinence, but symptoms resolved within 3 months. All patients in the TURP group could urinate after removing the catheter.

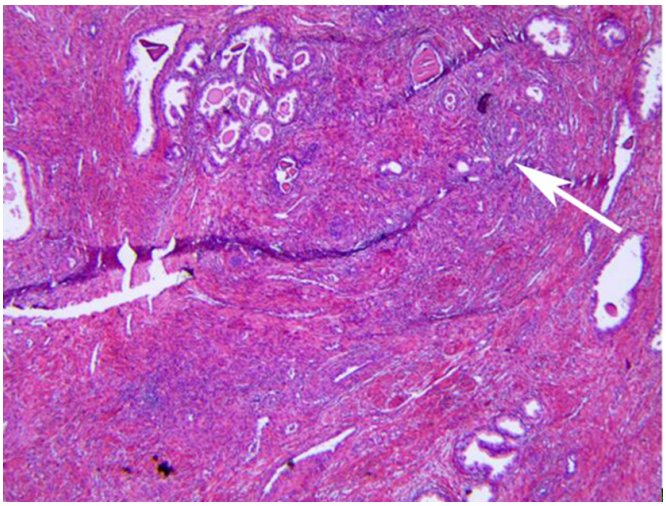

FIGURE 1. Representative pathology image of prostate cancer. The arrow indicates the tumor on gross histological slides.

3.3 Follow-up of oncologic parameters

TABLE 1. Baseline patient characteristics.

Baseline characteristics	TURP and ADT (n = 31)	ADT alone (n = 28)	*p* value
Mean age at diagnosis (range)	75.7 (56–89)	75.6 (55–89)	0.978
No. age (%)			
<60	1 (3.2)	1 (3.6)	
60–70	5 (16.1)	5 (17.8)	
Greater than 70	25 (80.7)	22 (78.6)	
Mean PSA level at diagnosis, ng/mL (range)	119.3 (2.37–416.0)	213.2 (4.16–654.0)	0.092
Mean PSA nadir, ng/mL (range)	0.33 (0.01–1.52)	0.87 (0.01–3.60)	0.015
Gleason score (%):			0.066
6 or less	10 (32.3)	5 (17.9)	
7	7 (22.6)	7 (25.0)	
8 or greater	14 (45.1)	16 (57.1)	
Clinical T stage (%):			0.082
≤cT2	22 (70.9)	18 (64.3)	
cT3	6 (19.4)	4 (14.3)	
cT4	3 (9.7)	6 (21.4)	
Lymph nodes status (%):			0.351
N0	27 (87.1)	22 (78.6)	
N1	4 (12.9)	6 (21.4)	
Clinical M stage (%):			0.062
M1a	0 (0)	0 (0)	
M1b ≤5a	21 (67.7)	14 (50.0)	
M1b >5b	6 (19.4)	9 (32.1)	
M1c	4 (12.9)	5 (17.9)	

a: skeletal metastases number is no more than five; b: skeletal metastases number is greater than five. TURP: transurethral resection of the prostate; ADT: androgen deprivation therapy; PSA: prostate-specific antigen.

3.3.1 TURP plus ADT

The overall follow-up time of the TURP group was 21 months (range, 6–39 months). Three patients died during follow-up, including one due to stroke and two from PCa progression. The mean TBCP was 12.6 months (95% confidence interval (CI): 10.5 to 14.6), and the mean PFS was 23.9 months (95% CI: 19.8 to 28.0). Of the 28 patients who developed biochemical progression, 18 underwent second-line treatment, and the remaining 10 received chemotherapy with docetaxel. Mean PSA at diagnosis was 119.3 ng/mL (range, 2.37–416.0 ng/mL). The mean nadir PSA in the TURP group during follow-up was 0.33 ng/mL (range, 0.01–1.52 ng/mL), which was significantly lower than that in the ADT group ($p = 0.015$) (Table 1).

3.3.2 ADT alone

The median follow-up time for this cohort of patients was 15 months (range, 3–40 months). Two patients died of prostate cancer progression during the follow-up period. The mean TBCP was 9.2 months (95% CI: 6.3 to 12.0), and the mean PFS was 17.4 months (95% CI: 13.0 to 21.8 months). Additionally, the mean PSA at diagnosis was 213.2 ng/mL (range, 4.16–654.0 ng/mL), and the mean nadir PSA during follow-up was 0.87 ng/mL (range, 0.01–3.60 ng/mL) (Table 1).

3.4 Survival and Regression analyses of TBCP

Kaplan-Meier survival analysis and log-rank test were conducted for survival analysis. The results showed that the TBCP of the TURP group was significantly longer than that of the ADT group ($p = 0.020$) (Fig. 2).

However, we found no significant difference in PFS between the two groups, though the TURP group tended to exhibit a longer PFS ($p = 0.110$) (Fig. 3).

Univariate analysis showed longer TBCP was associated with TURP, lower Gleason score, lower PSA at diagnosis, and lower clinical M staging. Subsequently, multivariate analysis indicated that longer TBCP was independently associated with TURP (HR (hazard ratio), 2.735; 95% CI: 1.091–6.858, $p = 0.032$) and lower Gleason score (HR, 1.947; 95% CI: 1.375–2.756) ($p = 0.001$) (Table 2).

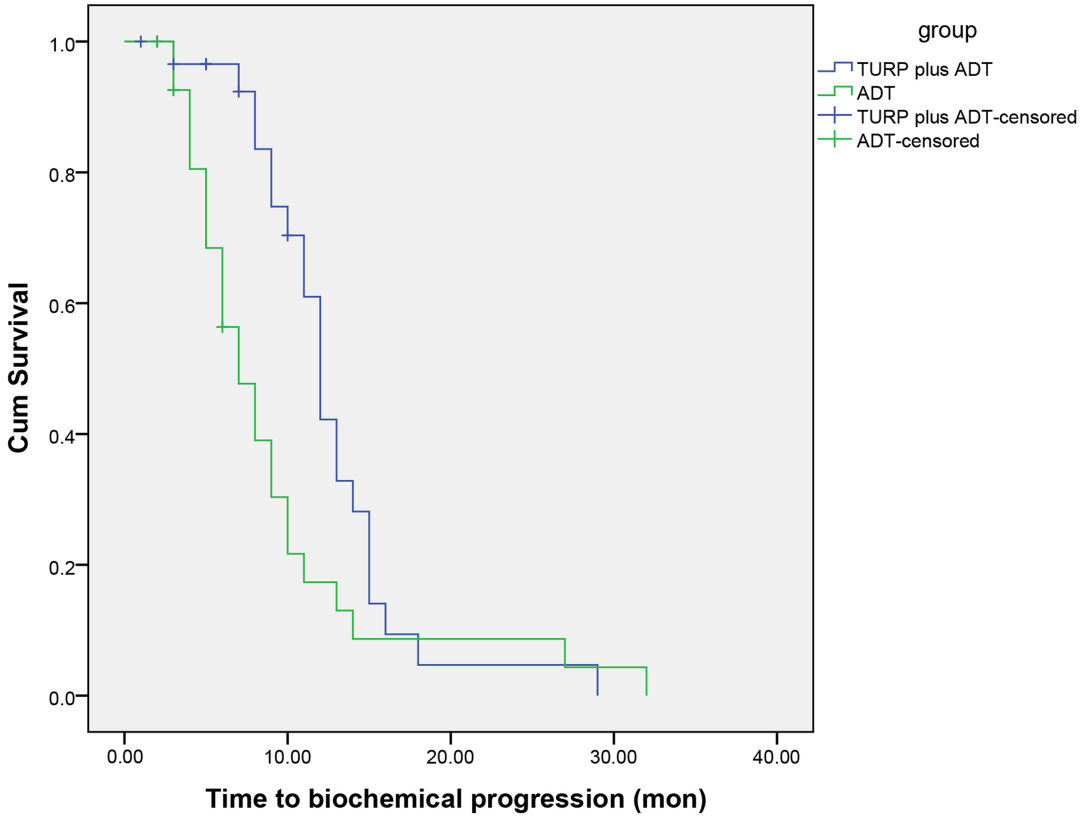

FIGURE 2. Time to biochemical progression of TURP plus ADT versus ADT alone. TURP: transurethral resection of the prostate; ADT: androgen deprivation therapy.

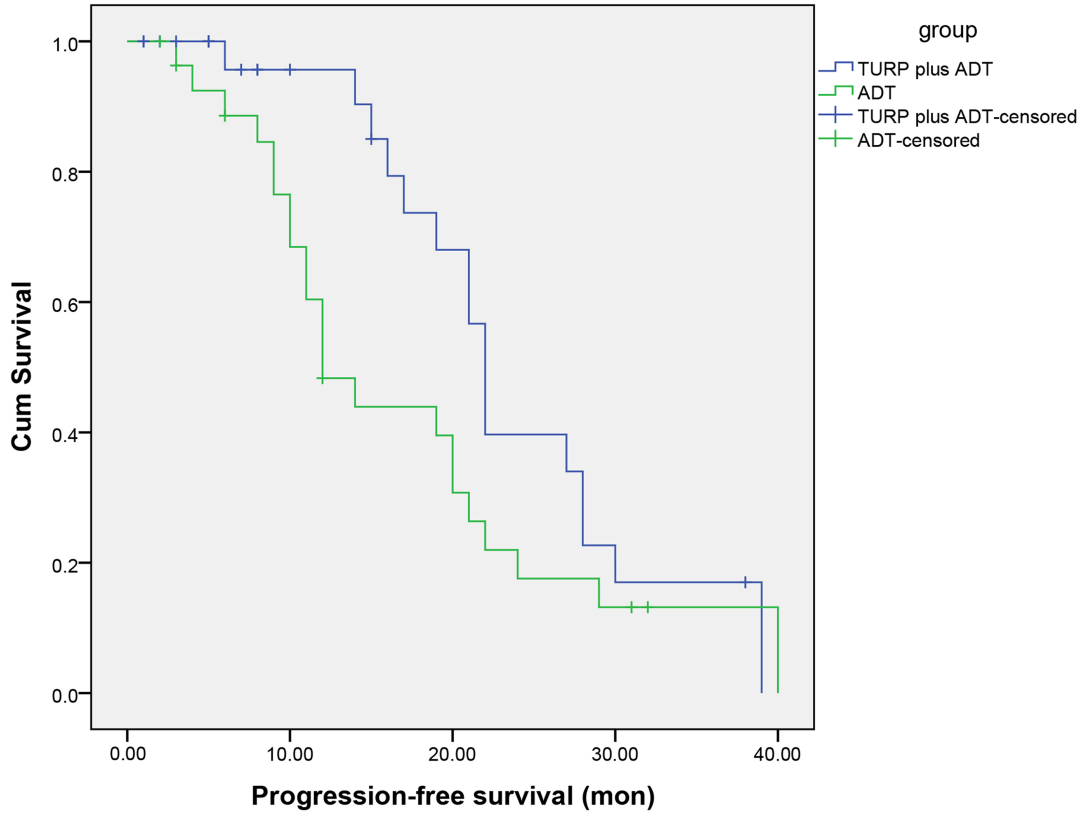

FIGURE 3. Progression-free survival of TURP plus ADT versus ADT alone. TURP: transurethral resection of the prostate; ADT: androgen deprivation therapy.

TABLE 2. Multivariate analyses of time to castration resistance prostate cancer.

Variables	HR	95% CI	*p* value
TURP (yes)	2.735	1.091–6.858	0.032
PSA at diagnosis	0.999	0.997–1.002	0.532
Biopsy Gleason score	1.947	1.375–2.756	0.001
M staging			
M1b $\leq$5a	1.603	0.339–7.580	0.551
M1b $>$5b	0.342	0.103–1.140	0.081
M1c	0.580	0.168–2.005	0.389

Note: a, skeletal metastases number $\leq$5; b, skeletal metastases number $>$5; HR, hazard ratio; CI, confidence interval; TURP, transurethral resection of the prostate; PSA, prostate-specific antigen.

4. Discussion

Prostate cancer is one of the most common malignancies of the male genitourinary system. According to epidemiological analyses, 268,490 new cases of prostate cancer were diagnosed in the United States in 2022, and 34,500 men died from this disease [14]. mPCa often leads to poor prognosis. Although systemic therapy remains the traditional treatment of mPCa, the therapeutic efficacy remains far from satisfactory [15]. In recent years, new therapeutic strategies have been explored for mPCa. In 2014, Antwi *et al.* [16] reported that CRP could reduce the mortality of mPCa patients. Recently, a meta-analysis and our previous results confirmed the survival benefit of CRP for mPCa [11, 17]. Collectively, these suggest that primary tumor reduction might be a promising approach that could improve the survival of mPCa patients.

Researchers have explored the underlying mechanisms influencing the outcomes of cytoreductive surgery in mPCa. They discovered that the "seed and soil" hypothesis might be pivotal during this process. Specifically, cytoreductive surgery offered a compelling advantage for mPCa by reducing the tumor load, shedding and metastasis of primary tumor cells, indicating the ideology that this intervention could effectively decrease the dissemination of prostate cancer ("seeds") to other organs ("soil"), whereby eliminating the tumor bank decreases the potential for future metastasis [18]. A similar phenomenon was reported in colorectal cancer, breast cancer, gastric cancer and renal cell carcinoma [7–10].

TURP has been proven to be safe and effective and is usually performed for relieving local complications such as BOO and hematuria in patients with mPCa [6, 19, 20]. As a special type of cytoreductive surgery, TURP may theoretically lead to a better prognosis for mPCa patients. Qin *et al.* [21] first explored the survival benefits of TURP in patients with mPCa. The results showed that TURP was associated with a significantly longer time to castration-resistance prostate cancer (CRPC) and trended toward better overall survival (OS) and cancer-specific survival (CSS). However, another study [22] revealed a worse CRPC-free survival, CSS and OS when TURP was performed in mPCa patients, suggesting that the oncological outcomes of TURP in advanced mPCa remain controversial. Hence, we performed this current research. Our results showed that mHSPCa patients in the TURP group benefitted from a significantly longer TBCP than the ADT group, indicating that TURP may result in a better prognosis.

According to the "seed and soil" hypothesis, the total amount of prostate tissues removed during TURP significantly impacts the survival and prognosis of mPCa patients. Therefore, when we performed TURP in mHSPCa patients, the prostate tissues were resected till the level of the capsule to achieve the greatest tumor reduction, which might be a reason for our reported different biochemical progression results between the two groups. In addition, though biochemical progression can explain the deterioration of mPCa to some extent, it is still insufficient. The impact on patient survival can be more fully explained when biochemical and clinical progression occurs. Thus, in this study, we defined PFS as the period from the start of ADT to the confirmed co-occurrence of biochemical and clinical progression. Our results showed that although there was a difference in TBCP between the two groups, no difference was observed between the PFS of both groups, suggesting that TURP might only benefit biochemical progression but not improve patient survival. Thus, more investigations are needed to clarify the underlying mechanisms to shed more light on this topic.

Recently, a prospective study [23] comprising 188 patients investigated the impact of TURP combined with ADT versus ADT alone on the survival of mHSPCa. The researchers revealed that TURP could prolong the CSS of mHSPCa patients, with PSA value, Gleason score and the number of bone metastases being the influencing factors, which were concordant with our findings and demonstrated the survival benefit of TURP in mHSPCa.

There were several limitations in this current study that should be considered. The investigated cohort size was relatively small, and the follow-up period was relatively short. Besides, only a few deaths were recorded. Due to these initially determined limitations, we chose TBCP and PFS as the outcome variables of this study.

5. Conclusions

Our results demonstrated that TURP could prolong TBCP and potentially improve the survival of mHSPCa patients. Further research using a larger sample size is needed to confirm our findings.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

YZ, JL and CSP—conceived and designed the experiments; QW, JYC, ZXY and HYF—performed the experiments; YHP and NXG—analyzed the data; YZ—wrote the paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was reviewed and approved by the Ethics Committee of Xuzhou Cancer Hospital (XCH20190016x). All study potential risks and procedures have been explained to the patients, and they gave their written informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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