Transurethral resection of the prostate is an independent risk factor for biochemical recurrence after radical prostatectomy for prostate cancer

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Biochemical recurrence (BCR) is important for measuring the oncological outcomes of patients who undergo radical prostatectomy (RP). Whether transurethral resection of the prostate (TURP) has negative postoperative effects on oncological outcomes remains controversial. The primary aim of our retrospective study was to determine whether a history of TURP could affect the postoperative BCR rate. We retrospectively reviewed patients with prostate cancer (PCa) who had undergone RP between January 2009 and October 2017. Clinical data on age, prostate volume, serum prostate-specific antigen levels (PSA), biopsy Gleason score (GS), metastasis stage (TNM), D’Amico classification, and American Society of Anesthesiologists (ASA) classification were collected. Statistical analyses including Cox proportional hazard models and sensitivity analyses which included propensity score matching, were performed, and the inverse-probability-of-treatment-weighted estimator and standardized mortality ratio-weighted estimator were determined. We included 1083 patients, of which 118 had a history of TURP. Before matching, the non-TURP group differed from the TURP group with respect to GS (P = 0.047), prostate volume (mean: 45.19 vs 36.00 ml, P < 0.001), and PSA level (mean: 29.41 vs 15.11 ng ml⁻¹, P = 0.001). After adjusting for age, PSA level, T stage, N stage, M stage, and GS, the TURP group showed higher risk of BCR (hazard ratio [HR]: 2.27, 95% confidence interval [CI]: 1.13–3.94, P = 0.004). After matching (ratio 1:4), patients who underwent TURP were still more likely to develop BCR according to the adjusted propensity score (HR: 2.00, 95% CI: 1.05–3.79, P = 0.034). Among patients with PCa, those with a history of TURP were more likely to develop BCR after RP. Asian Journal of Andrology (2020) 22, 217–221; doi: 10.4103/aja.aja_54_19; published online: 14 June 2019

Keywords: biochemical recurrence; prostate cancer; radical prostatectomy; transurethral resection

INTRODUCTION

Prostate cancer (PCa) is the most common malignant tumor found in elderly European males. PCa causes many health problems, especially in developed countries, with a large proportion of elderly males in the general population.1 Radical prostatectomy (RP) is the first-line option for treating patients with clinically localized PCa.2–4 Biochemical recurrence (BCR), defined as prostate-specific antigen (PSA) ≥0.2 ng ml⁻¹, is discovered in up to 40% of males treated with surgery.5 BCR does not invariably lead to systemic progression and death; however, patients who undergo BCR are at an increased risk of developing distant metastases and experiencing cancer-related mortality.6–8

Benign prostatic hyperplasia, one of the most common diseases among middle-aged to elderly males, can cause lower urinary tract symptoms.7,8 To treat and relieve the bothersome symptoms, transurethral resection of the prostate (TURP) is widely performed, and it is considered the gold standard.9 Several studies have evaluated the BCR after RP following TURP10–14 but no consensus has been reached on the postoperative oncological outcomes associated with RP after TURP. In this retrospective study of patients having received RP in West China Hospital (Sichuan University, Chengdu, China), we sought to determine if previous TURP affected the postoperative BCR rate.

PATIENTS AND METHODS

Study population
Given the retrospective nature of the study, requirement for informed consent was waived by the Institutional Review Board of West China Hospital (Sichuan University, Chengdu, China). This retrospective study was approved by the Institutional Ethics Review Board. We identified patients with PCa who had undergone RP between January 2009 and October 2017 at West China Hospital. Each participant was screened according to strict inclusion and exclusion criteria. The inclusion criteria were pathological diagnosis of PCa, receiving RP in our hospital, and being discharged from the hospital. The exclusion criteria were duration between TURP and RP <1 year and PCa confirmed by TURP specimen.

Outcomes
Clinical data on age, prostate volume, serum PSA levels, biopsy Gleason score (GS), metastasis stage (TNM), D’Amico classification, and American Society of Anesthesiologists (ASA) classification were

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collected. GS was assessed on the basis of 2014 International Society of Urological Pathology grading system.\textsuperscript{13} PSA was measured every month during the first 3 months, every 3–6 months for 5 years, and once a year thereafter. BCR was defined as two consecutive rising PSA values of ≥0.2 ng ml\textsuperscript{−1} postoperatively.\textsuperscript{14} We regarded BCR as the postoperative prognosis-related outcome. All data were collected from the hospital's register system.

**Statistical analyses**

Continuous variables were expressed as means with standard deviations or medians (quartile ranges). Categorical variables were expressed as frequencies with proportions. Student's $t$-test and Pearson's Chi-square test were used to determine between-group differences in means and proportions. The BCR rate was estimated using the Kaplan–Meier method with a log-rank test. A Cox proportional hazard model was used for univariate and multivariate analyses. To control confounders, another Cox proportional hazard model, including both nonadjusted and multivariate adjusted models, was performed to explore the relationship between the history of TURP and postoperative BCR further.

Based on patients' baseline characteristics, we generated propensity scores to estimate the probability that patients would be selected for TURP treatment and logistic regression to adjust for between-group differences in patients' baseline characteristics,\textsuperscript{15} including age, PSA, TNM stage, and GS. Results of propensity score matching (ratio 1:4 with a caliper set of 0.05) were used to emulate a randomized trial design, minimize residual bias, and increase precision.\textsuperscript{16} After matching, the differences in the above-mentioned confounders were represented by propensity scores. Then, we compared the baseline characteristics, using the same statistical approaches and multivariate regression analyses after adjusting for propensity scores, with the totality. In addition, we used the Kaplan–Meier method with patients who had propensity scores.

### Table 1: Characteristics of participants (unmatched and matched with a ratio of 4:1)

| Exposure                  | Unmatched |          |          |          |          |          |          |          |          |
|---------------------------|-----------|----------|----------|----------|----------|----------|----------|----------|----------|
|                           | Non-TURP  | TURP     | P        | Non-TURP | TURP     | P        | Non-TURP | TURP     | P        |
| Participants (n)          | 965       | 118      | 0.389    | 260      | 65       | 0.684    | 23.01±24.89 | 19.20±27.31 | 0.279 |
| Age (year), mean±s.d.     | 67.34±7.34| 66.73±7.01| <0.001   | 67.58±6.77| 67.20±6.68| 0.008    | 19.16±27.31 | 19.16±27.31 | 0.686 |
| Prostate volume (ml), mean±s.d. | 45.19±22.44 | 36.00±22.49 | <0.001   | 45.89±21.51 | 37.43±23.91 | 0.008    | 19.16±27.31 | 19.16±27.31 | 0.686 |
| PSA (ng ml\textsuperscript{−1}), mean±s.d. | 29.41±47.35 | 15.11±23.24 | 0.001    | 23.01±24.89 | 19.20±27.31 | 0.279    | 19.16±27.31 | 19.16±27.31 | 0.686 |
| Gleason score, n (%)      | 0.047     | 0.067    | 0.047    | 0.067    |          |          |          |          |          |
| 6                         | 157 (16.3)| 19 (16.1)|          | 21 (8.1) | 13 (20.0)|          |          |          |          |
| 7                         | 486 (50.4)| 54 (45.8)|          | 130 (50.0)| 32 (49.2)|          |          |          |          |
| 8                         | 125 (13.0)| 11 (9.3) |          | 47 (18.1)| 8 (12.3) |          |          |          |          |
| 9                         | 161 (16.7)| 23 (19.5)|          | 57 (21.9)| 11 (16.9)|          |          |          |          |
| 10                        | 36 (3.7)  | 11 (9.3) |          | 5 (1.9)  | 1 (1.5)  |          |          |          |          |
| T2a                       | 125 (13.0)| 15 (12.7)|          | 39 (15.0)| 14 (21.5)|          |          |          |          |
| T2b                       | 197 (20.4)| 22 (18.6)|          | 73 (28.1)| 21 (32.3)|          |          |          |          |
| T2c                       | 418 (43.3)| 23 (19.5)|          | 123 (47.3)| 19 (29.2)|          |          |          |          |
| T3a                       | 38 (3.9)  | 1 (0.8)  |          | 7 (2.7)  | 1 (1.5)  |          |          |          |          |
| T3b                       | 59 (6.1)  | 8 (6.7)  |          | 14 (5.4) | 7 (10.8) |          |          |          |          |
| T4                        | 25 (2.6)  | 3 (2.5)  |          | 4 (1.5)  | 3 (4.6)  |          |          |          |          |
| Missing data\textsuperscript{a} | 103 (10.7)| 46 (39.0)|          |          |          |          |          |          |          |
| N0                        | 905 (93.8)| 110 (93.2)|          | 246 (94.6)| 58 (89.2)|          |          |          |          |
| N1                        | 60 (6.2)  | 8 (6.8)  |          | 14 (5.4) | 7 (10.8) |          |          |          |          |
| M0                        | 928 (96.2)| 113 (95.8)|          | 252 (97.0)| 61 (93.9)|          |          |          |          |
| M1b                       | 37 (3.8)  | 5 (4.2)  |          | 8 (3.1)  | 4 (6.2)  |          |          |          |          |
| ASA classification, n (%) | 0.330     | 0.649    |          |          |          |          |          |          |          |
| 1                         | 4 (0.4)   | 0 (0)    |          | 0 (0)    | 0 (0)    |          |          |          |          |
| 2                         | 621 (64.4)| 69 (58.5)|          | 160 (61.5)| 38 (58.5)|          |          |          |          |
| 3                         | 340 (35.2)| 49 (41.5)|          | 100 (38.5)| 27 (41.5)|          |          |          |          |
| D’Amico classification, n (%) | <0.001     | 0.111    |          |          |          |          |          |          |          |
| Low risk                  | 27 (2.8)  | 5 (4.2)  |          | 7 (2.7)  | 5 (7.7)  |          |          |          |          |
| Mediate risk              | 226 (23.4)| 47 (39.8)|          | 66 (25.4)| 19 (29.2)|          |          |          |          |
| High risk                 | 712 (73.8)| 66 (55.9)|          | 187 (71.9)| 41 (63.1)|          |          |          |          |
| Follow-up duration, median (Q1–Q3) | 28.00 (12.00–48.00) | 36.00 (12.25–59.00) | 0.010 | 25.50 (11.75–44.25) | 24.50 (12.00–39.00) | 0.881 |
| PSM, n (%)                | 0.534     | 0.069    |          |          |          |          |          |          |          |
| Yes                       | 278 (28.8)| 36 (30.5)|          | 74 (28.5)| 38 (58.5)|          |          |          |          |
| No                        | 636 (65.9)| 72 (61.0)|          | 179 (68.8)| 20 (30.8)|          |          |          |          |
| Unknown                   | 51 (5.3)  | 10 (8.5) |          | 7 (2.7)  | 7 (10.8) |          |          |          |          |

\textsuperscript{a}Unclear defined T stage, for example, T3 stage at register but whether T3a or T3b was unknown. TURP: transurethral resection of the prostate; PSA: prostate-specific antigen; PSM: positive surgical margins; ASA: American Society of Anesthesiologists; s.d.: standard deviation; Q1–Q3: first and third quartiles
Sensitivity analyses were performed. The inverse-probability-of-treatment-weighted (IPTW) estimator determined the distribution of risk factors equal to that found in all patients. The second weighting method, known as the standardized mortality ratio-weighted (SMRW) estimator, was also performed to assure equal distribution of risk factors similar to those found in the treated group. The two weighting methods focused on treatment effects in different standard populations. Covariates for each model were identical to those in the propensity model described above. All the analyses were performed using the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA). P < 0.05 was considered statistically significant.

RESULTS
After the exclusion criteria were applied, 1083 patients were included, of which 118 patients had a history of TURP. The median follow-up duration was 28 months (interquartile range: 12–49 months). There were ten patients with follow-up durations of >100 months. Table 1 shows selected baseline characteristics of patients.

Before propensity score matching, the non-TURP group had a significantly lower GS than the TURP group (P = 0.047; Table 1). However, the non-TURP group had a larger prostate volume (mean: 45.19 vs 36.00 ml, P < 0.001) and a higher PSA level (mean: 29.41 vs 15.11 ng ml⁻¹, P = 0.001) than the TURP group. The D'Amico classification of the non-TURP group was more severe than that of the TURP group (high risk, 73.8% vs 53.9%, P < 0.001). The differences of age, T stage, N stage, M stage, and ASA classification were not statistically significant. After matching, the TURP and non-TURP groups had no significant differences, with the exception of prostate volume. Matching seemed balanced by the variables with a standardized difference of <0.05.

Table 2 shows results of the univariate and multivariate analyses. The multivariate Cox proportional hazard model showed that TURP (hazard ratio [HR]: 2.31, 95% confidence interval [CI]: 1.33–4.04, P = 0.003), PSA level (HR: 1.01, 95% CI: 1.00–1.02, P = 0.002), T stage of T3b (HR: 2.83, 95% CI: 1.16–6.87, P = 0.022), and GS of <10 were independent predictive factors of BCR (Table 2). Prostate volume (HR: 1.00, 95% CI: 0.99–1.01, P = 0.954), N stage (HR: 1.40, 95% CI: 0.66–2.99, P = 0.379), and M stage (HR: 0.70, 95% CI: 0.17–2.89, P = 0.619) were not associated with BCR.

After adjusting for age, PSA level, T stage, N stage, M stage, and GS, the TURP group still exhibited significantly more-frequent instances of BCR (HR: 2.27, 95% CI: 1.13–3.94, P = 0.004; Table 3). After propensity score matching, there were 65 patients in the TURP group and 260 in the non-TURP group. Even after propensity score adjustment, patients in the TURP group were more likely to experience BCR (HR: 2.00, 95% CI: 1.05–3.79, P = 0.034). Taking positive surgical margin and surgical procedures into consideration, we additionally performed another regression, and the result changed slightly (HR: 1.95, 95% CI: 1.08–3.53, P = 0.028) (Table 4). According to Kaplan–Meier curve, non-TURP group demonstrated obvious lower possibility of BCR (P = 0.016; Figure 1a). After matching, significant outcome was observed (P = 0.03; Figure 1b).

The IPTW and SMRW models were used to perform sensitivity analyses. The data were obtained from all the patients. Individuals in the TURP group were more likely to develop BCR (HR: 2.63, 95% CI: 1.50–4.63). The variables to perform both univariate and multivariate analyses included age, history of TURP, PSA, T stage, N stage, M stage, Gleason score, and prostate volume. The variables to perform both univariate and multivariate analyses included age, history of TURP, PSA, T stage, N stage, M stage, Gleason score, and prostate volume.

Table 2: Univariate and multivariate analyses of the comparison between the nontransurethral resection of the prostate group and the transurethral resection of the prostate group (before propensity score matching)

| Exposure         | Univariate | Multivariate |
|------------------|------------|--------------|
|                  | HR (95% CI)| P       | HR (95% CI) | P       |
| Age              | 0.99 (0.97–1.02) | 0.576 | 0.99 (0.96–1.02) | 0.509 |
| History of TURP  |            |         |            |         |
| Non-TURP         | 1 (reference) | 1 (reference) |           |         |
| TURP             | 1.72 (1.10–2.70) | 0.018 | 2.31 (1.33–4.04) | 0.003 |
| PSA              | 1.01 (1.01–1.02) | 0.001 | 1.01 (1.00–1.02) | 0.003 |
| T stage          |            |         |            |         |
| T2a              | 1 (reference) | 1 (reference) |           |         |
| T2b              | 1.70 (0.85–3.44) | 0.136 | 1.18 (0.57–2.45) | 0.653 |
| T2c              | 2.31 (1.21–4.43) | 0.012 | 1.41 (0.71–2.82) | 0.331 |
| T3a              | 2.57 (0.95–6.94) | 0.064 | 1.97 (0.70–5.56) | 0.203 |
| T3b              | 4.81 (2.04–11.33) | 0.001 | 2.83 (1.16–6.87) | 0.022 |
| T4               | 5.12 (0.65–40.07) | 0.120 | 2.13 (0.24–19.03) | 0.498 |
| Gleason score    |            |         |            |         |
| 6                | 1 (reference) | 1 (reference) |           |         |
| 7                | 2.42 (1.31–4.47) | 0.005 | 2.28 (1.09–4.75) | 0.028 |
| 8                | 3.53 (1.74–7.18) | 0.001 | 2.90 (1.24, 6.80) | 0.014 |
| 9                | 6.78 (3.38–13.61) | <0.001 | 5.55 (2.32–13.29) | <0.001 |
| 10               | 6.57 (2.29–18.88) | 0.001 | 4.21 (0.82–21.56) | 0.085 |
| Prostate volume  | 1.00 (0.99–1.01) | 0.597 | 1.00 (0.99–1.01) | 0.954 |
| M stage          |            |         |            |         |
| N stage          |            |         |            |         |
| N0               | 1 (reference) | 1 (reference) |           |         |
| N1               | 1.50 (0.73–3.06) | 0.269 | 1.40 (0.66–2.99) | 0.379 |
| M stage          |            |         |            |         |
| M0               | 1 (reference) | 1 (reference) |           |         |
| M1b              | 0.55 (0.14–2.24) | 0.408 | 0.70 (0.17–2.89) | 0.619 |

The variables to perform both univariate and multivariate analyses included age, history of TURP, PSA, T stage, N stage, M stage, Gleason score, and prostate volume.
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| Exposure     | Crude model (before PS matching) | Adjusted model (before PS matching) | After PS matching (ratio 1:4) |
|--------------|----------------------------------|------------------------------------|-----------------------------|
|              | HR (95% CI)                      | P                                  | HR (95% CI)                 | P                          |
| Non-TURP     | 1 (reference)                    |                                    | 1 (reference)              |                            |
| TURP         | 1.72 (1.10–2.70)                 | 0.018                              | 2.27 (1.31–3.94)           | 0.004                      |
|              |                                  |                                    | 2.00 (1.05–3.79)           | 0.034                      |

Variables are adjusted for age, PSA, Gleason score, T stage, N stage, and M stage. TURP: transurethral resection of the prostate; PS: propensity score; PSA: prostate-specific antigen; HR: hazard ratio; CI: confidence interval.

| Exposure     | Nonadjusted model | Adjusted model I | Adjusted model II |
|--------------|-------------------|------------------|------------------|
|              | HR (95% CI)       | P                | HR (95% CI)      | P                |
| Non-TURP     | 1 (reference)     | 1.72 (1.10–2.70) | 0.018            | 2.27 (1.31–3.94) | 0.004            |
| TURP         | 1 (reference)     | 1 (reference)    | 1 (reference)    | 1.95 (1.08–3.53) | 0.028            |

Model I adjusted for age, PSA, TNM stages, and GS. Model II adjusted for age, PSA, TNM stages, GS, PSM, and surgical procedures. TURP: transurethral resection of the prostate; BCR: biochemical recurrence; PS: propensity score; PSA: prostate-specific antigen; HR: hazard ratio; CI: confidence interval; GS: Gleason score; PSM: positive surgical margin.

Table 3: Multivariate regression models of biochemical recurrence in the comparison between the nontransurethral resection of the prostate group and the transurethral resection of the prostate group (before and after propensity score matching)

Table 4: Multivariate regression models of biochemical recurrence in the comparison between the nontransurethral resection of the prostate group and the transurethral resection of the prostate group (before propensity score matching)

Table 5: Multivariate regression of overall survival with the use of inverse-probability-of-treatment-weighted and standardized mortality ratio-weighted models comparing the nontransurethral resection of the prostate group and the transurethral resection of the prostate group

DISCUSSION

Patients with a history of TURP were at a higher risk of developing BCR after RP. After eliminating the influence of confounders including age, PSA level, TNM stages, prostate volume, and GS by using propensity score matching, TURP still promoted the risk of BCR compared with the non-TURP group. Using the IPTW model, the distribution of characteristics were assumed to be in accordance with that of total patients, indicating that this result was suitable for the study population as a whole. On using the SMRW model, the distribution of characteristics were assumed to be similar with those of the intervention group (the TURP group), indicating that if patients in the non-TURP group received TURP treatment, the same results would be found. The BCR rate was worse in the TURP group among patients whose propensity scores were most consistent with the selected patients in the non-TURP group.

Our findings should be evaluated in the context of results from other studies. A retrospective study featuring a smaller sample size (n = 158) revealed that patients with a history of TURP had a higher risk of BR after robot-assisted RP (RARP), which was in agreement with our findings.²² Although no significant difference in the margin positivity rates between two groups was found in this study, others have reported higher rates of positive surgical margins (PSM) after RARP in patients who underwent TURP previously.²³ Our results showed no obvious difference in the PSM rate. This might be because of the occurrence of a vast majority of PCa in the peripheral zone, an area that TURP minimally resects.²⁴,²⁵ In a study involving patients who received androgen deprivation therapy (n = 614), the TURP group exhibited worse oncological outcomes for castration-resistant PCa-free survival, cancer-specific survival, and overall survival.²⁶ This indicates that TURP was an independent risk factor of cancer-specific and all-cause mortalities.

Conversely, several studies reported no difference in the biochemical rate between the TURP and non-TURP groups. These studies were small and featured a short follow-up duration; therefore, they may be less accurate.²⁷–²⁹ Menard et al.²⁰ reported that the 5-year BCR freedom survival rate was similar between the two groups (TURP and non-TURP) after laparoscopic RP (n = 640). This study included additional patients (GS <6, T1 stage) who were not suitable for RP but were recommended for active surveillance. Furthermore, the postoperative PSA index was only collected every 6 months, indicating that BCR results were not observed in a timely fashion.

Another similar study found that patients with a history of TURP presented with lower PCa-related mortality.²¹ This outcome contributed to frequent PCa screen and more biopsies after TURP, thus facilitating early diagnosis of cancer. In the present study, the results suggested that the patients’ anatomy changed after TURP, and the incidence of PSM and BCR increased owing to the difficulty of the surgical procedure. Briefly, differences in the selected study populations, between the two research studies, could have contributed to differences in the observed outcomes. Except for a higher incidence of PSM, the probable mechanisms of high BCR rate after TURP included: (i) tumor cells that spread easily via the ejaculatory ducts may increase seminal vesicular reactions in and around the prostate, making the microenvironment changed, thus increasing the possibility of BCR.

Regarding the analyses, our study took potential bias into account and controlled for potential confounders. However, evidence of increased risk remained, even after adjusting for potential confounders. Furthermore, sensitivity analyses were performed to verify the results. Finally, we confirmed that TURP increased the chance of a patient developing BCR after RP.

There are several limitations to our study. First, as a retrospective study, selection bias could not be avoided. A history of TURP might influence a doctor’s decision of whether to perform RP. To overcome this, we performed propensity score matching and used two weighted models; however, the bias still exists. Second, although the duration
between TURP and RP was >1 year, the specific duration was not clear. Third, the huge difference in sample size between the two groups caused imbalance in the number of patients in each group after propensity score matching. Fourth, cancer-specific and all-cause mortalities were not assessed because of the relatively short follow-up duration. Furthermore, we lacked a nerve-sparing technique during RP, which could influence the outcome accuracy. However, the effect was still significant, indicating that a reduced sample size would not obscure the true effects of TURP.

CONCLUSION
Among patients with PCa, those with a history of TURP were more likely to develop BCR after RP.

AUTHOR CONTRIBUTIONS
KJ, LY, and SQ designed the study; KJ, XYL, and SQ wrote this article in cooperation; KJ and SQ performed the data analyses; LY and QW were responsible for study supervision and were the guarantor of the article; and KJ, XYL, SQ, XT, XNZ, and LST collected the data. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declare no competing interests.

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