BMC Cancer

RESEARCH

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Efficacy of brachytherapy versus radical prostatectomy for localized prostate cancer–propensity score-matched comparison

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Abstract

Objective The brachytherapy (BT) and radical prostatectomy (RP) are two methods recommended in current guidelines for the treatment of localized prostate cancer (PCa). It is difficult to compare the oncological results of these two treatments because of differences in baseline characteristics and treatment selection.we sought to compare the efficacy of BT and RP after propensity score matching(PSM)analysis.

Methods Between January 2009 and December 2021, our institution treated 657 patients with localized PCa (BT: $n=198$; RP: $n=459$)and followed up for > 2 years. Biochemical recurrence was defined as prostate-specific antigen (PSA) levels of nadir plus 2 ng/ml or higher (Phoenix definition) for BT, and as PSA0.2 ng/ml or greater for RP. PSM was applied based on the age, body mass index, PSA, prostate volume, clinical T-stage, Gleason grade, percentage of positive puncture needles ≥ 1/2, maximum tumor diameter ≥ 5 mm, and follow-up period.

Results Median follow-up was 63 months for BT and 52 months for RP. After propensity score adjustment, a total of 294 (147 each) patients remained for further analysis.Kaplan–Meier curves showed no statistically significant difference in clinical relapse-free survivals (cRFS) ($p=0.637$),overall survival (OS) ($p=0.726$),and cancer-specific survival (CSS) ($p=0.505$).BT was associated with improved biochemical relapse-free survivals (bRFS) compared to RP ($p=0.022$), Logistic multivariate analysis based on the whole cohort revealed that clinical T stage ≥ T_{2b} ($p=0.043$) and tumor maximum diameter ≥ 5 mm ($p=0.044$) were associated with significantly bRFS.

Conclusion The BT and RP group patients exhibited similar cRFS, OS, and CSS. However, patients in the BT groups exhibited better bRFS than those in the RP group.Clinical T stage ≥ T_{2b} and a maximum tumor diameter ≥ 5 mm were independent prognostic factors.

Keywords Prostate cancer, Brachytherapy, Radical prostatectomy, Efficacy, Propensity score matching (PSM)

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Introduction

Prostate cancer (PCa) is one of the most common malignant tumors of the genitourinary system. It is prevalent in middle-aged and old-aged men [1]. The incidence and mortality of PCa in China have rapidly increased; this is due to the late-disease stage at presentation and a poor prognosis [2, 3]. For localized prostate cancer, there is no difference in overall survival (OS) or prostate cancer-specific survival (CSS) between low-dose brachytherapy (BT), radical prostatectomy (RP), and external beam radiation therapy (EBRT). The difference in OS and prostate CSS between RP and EBRT was statistically non-significant [4–6]. The National Comprehensive Cancer Network (NCCN) guidelines recommend making treatment choices based on tumor characteristics, patient age, comorbidities, life expectancy, quality of life, and the patient's preference [7, 8]. In this study, we retrospectively analyzed 657 cases of patients with stage T_{1c}-T_{3a} localized PCa who underwent BT or RP between January 2009 and December 2021 at Jinhua Hospital, Zhejiang University School of Medicine, and were followed up. The prognostic factors imbalance between the two groups was reduced using propensity score matching. The efficacy of the two treatments was compared to provide a reference for the treatment choices of patients with localized prostate cancer.

Materials and methods

Population data

The inclusion criteria were as follows: (1) Patients with clinical stage T_{1c}-T_{3a} prostate cancer; (2) patients with a follow-up period of at least 2 years; (3) patients without distant metastasis. The treatment regimen (BT or RP) was selected after informing the patients about the advantages and disadvantages of both regimens and consulting with their physicians. All patients were pathologically diagnosed with prostate adenocarcinoma using prostate aspiration biopsy before surgery, and metastasis was excluded using chest radiograph or computed tomography (CT), abdominal and pelvic CT or magnetic resonance imaging, and whole-body bone scan. The exclusion criteria were as follows: (1) patients with incomplete clinical information; (2) patients who underwent androgen deprivation therapy (ADT) immediately after surgery.

Demographic and propensity score matching (PSM)

This study included 1022 patients with clinically localized PCa who underwent BT ($n=355$) or RP ($n=667$) between January 2009 and December 2021. Of the 1022 patients, 48 patients did not have complete clinical information (22 in the BT group and 26 in the RP group), 93 patients were followed up for less than 2 years (27 in the BT group and 66 in the RP group), 224 underwent adjuvant ADT immediately after surgery (108 in the BT group and 116 in the RP group), and 365 were excluded from the study cohort. The remaining 657 patients (198 in the BT group and 459 in the RP group) were included in the study and compared using PSM.

A multivariate logistic regression model was utilized to calculate a propensity score for each patient, using age, body mass index (BMI), pretreatment prostate-specific antigen (PSA) level, prostate volume, clinical T-stage (according to the TNM staging system [9]), Gleason grade, percentage of puncture-positive needles ≥ 1/2, cases with puncture tumors ≥ 5 mm in maximum diameter, and follow-up time. The PSM ratio was 1:1, and the matching tolerance between the two groups was 0.02.

All prostate biopsy specimens were verified by a single pathologist (SHI), and tumor grading subgroups were determined according to the International Society of Urological Pathology grading subgroups [10] and graded according to the NCCN recommended prognostic risk of PCa (D-Amico scale) [7, 11] subgroups.The study protocol was approved by the Ethics Committee of Jinhua Hospital (ethics number: 2021-ethics-250).

Treatment

BT treatment

Patients in the BT group received iodine-125 radioactive particles. Epidural or general anesthesia was employed, the high truncated position was taken, and the Foley catheter was left in place after routine disinfection and toweling. An intraoperative particle distribution plan map was made, and a transrectal ultrasound probe was fixed using a brachytherapy device. Prostate ultrasound images were acquired under real-time transrectal ultrasound guidance, and a treatment plan was achieved using the treatment planning system with a treatment dose of 145–160 Gy. One month after implantation, dose analysis was performed using CT, and D90 (minimum dose to cover 90% of the prostate) was obtained for each patient, with a mean D90 of approximately 144 Gy. Additionally, 103 (52.3%) patients were treated with neoadjuvant androgen deprivation therapy (NADT) in this group before matching.

Radical prostatectomy

Of the 459 patients in the RP group, 33 underwent open RP, and 426 underwent laparoscopic RP. Furthermore, 63 (13.7%) patients underwent pelvic lymph node dissection, and 25 (5.4%) patients underwent NADT before matching.

ADT treatment

Maximal androgen blockade therapy was utilized for ADT treatment. Oral bicalutamide tablets 50 mg QD) were administered in combination with goserelin acetate

extended-release (3.6 mg, administered subcutaneously) or treprostinil acetate (3.75 mg, administered intramuscularly) every four weeks. Additionally, NADT therapy was administered preoperatively for 2–7 months.

EBRT treatment

A 3-D conformal or intensity-modulated radiation therapy was used for EBRT treatment. The total external radiation dose was 40 Gy, 2.0 Gy daily, administered five days weekly.

Follow-up and study endpoints

Patients were monitored for serum PSA every month for the first three months after treatment and reviewed every three months after that. If PSA levels were stable, follow-up was performed every six months after two years of treatment. Chest, abdominal, pelvic, and whole-body bone CT scans were performed if PSA was elevated or if bone pain developed, as recommended by the European Society of Urology and NCCN guidelines [7, 8].

The primary endpoints for determining efficacy were biochemical recurrence-free survival (bRFS), clinical relapse-free survival (cRFS), CSS, and OS. When a BT patient experienced a postoperative PSA decrease that reached its lowest point and was subsequently elevated by 2.0 ng/mL, biochemical relapse was considered (Phoenix definition) [12]. The RP patients were those with two consecutive postoperative serum PSA > 0.2 ng/mL [13]. Clinical relapse was defined as a local recurrence or distant metastasis confirmed using medical imaging or pathological examination of a biopsied specimen.

Statistics

PSM and statistical analysis were processed using a statistical package for social science (version 27.0; IBM). Factors affecting study endpoints were analyzed at baseline, differences in means of continuous variables were assessed using student's *t*-tests, and comparisons of baseline data were performed using the χ^2 test and Fisher's exact test. Survival curves for bRFS, cRFS, CSS, and OS after treatment were analyzed using the Kaplan–Meier analysis, and the significance of differences was tested using the log-rank test. Logistic regression models were established to analyze the factors associated with bRFS. A $p < 0.05$ was considered statistically significant.

Results

Comparison of clinical base

Table 1: shows the clinical baseline statistics of the PSM patients. We successfully matched 294 patients (147 each for BT and RP groups). No statistically significant difference was observed between patients in the matched BT and RP groups based on age, BMI, pretreatment PSA, prostate volume, clinical T-stage, Gleason grade, percentage of puncture-positive needles ≥ 1/2, patients with a maximum tumor diameter ≥ 5 mm, and follow-up period ($p > 0.05$). Furthermore, after matching, NADT was performed in 77 (52.4%) and 12 (8.2%) patients in BT and RP groups, respectively. The median duration of treatment was 3.5 months (range: 3–7 months) and 3 months (range: 2–5 months), respectively, which was significantly more among patients in the BT group than among those in the RP group ($\chi^2 = 68.082$, $p < 0.001$). Salvage treatment after biochemical recurrence was performed in 20 (13.6%) patients and 32 (21.8%) patients in the BT and RP groups, respectively, and no significant difference was

Table 1 Characteristics of patients with localized prostate cancer before and after matching

Variables[Mean ± SD, or *n* (%)]	Before propensity score matching			After propensity score matching		
	BT (*n* = 198)	RP (*n* = 459)	*p*-value	BT (*n* = 147)	RP (*n* = 147)	*p*-value
Age (years)	75.61 ± 7.54	68.90 ± 6.76	< 0.001	72.73 ± 6.40	73.07 ± 5.54	0.620
BMI (kg/m^2)	22.82 ± 3.18	22.91 ± 2.69	0.694	22.91 ± 3.26	23.17 ± 2.93	0.476
PSA (ng/mL)	24.81 ± 27.55	23.05 ± 21.90	0.383	26.00 ± 28.61	24.41 ± 24.66	0.610
Prostate volume (ml)	38.55 ± 15.82	38.80 ± 16.44	0.861	38.40 ± 15.83	38.14 ± 14.31	0.881
Biopsy Gleason grading grouping (n, %)			0.079			0.887
1	54 (27.3)	134 (29.2)		45 (30.6)	47 (32.0)	
2–3	74 (37.4)	202 (44.0)		53 (36.1)	49 (33.3)	
4–5	70 (36.3)	123 (26.8)		49 (33.3)	51 (34.7)	
NCCN risk classification (n, %)			0.546			0.492
low risk	22 (11.1)	48 (10.5)		16 (10.9)	20 (13.6)	
Intermediate risk	61 (30.8)	124 (27.0)		40 (27.2)	32 (21.8)	
high risk	115 (58.1)	287 (62.5)		91 (61.9)	95 (64.6)	
Percentage of biopsy-positive needles ≥/2 (n, %)	67 (33.8)	204 (41.8)	0.011	56 (38.1)	63 (42.9)	0.406
Maximum diameter of biopsied tumor ≥ 5 mm (n, %)	76 (38.4)	216 (43.1)	0.040	62 (42.2)	75 (51.0)	0.129
Follow-up time M(Q1,Q3 months)	59 (45, 84)	57(40,88)	0.072	63 (45.5, 87)	52 (42,80)	0.108

BT: iodine 125-endo-radiotherapy; RP: radical prostatectomy; BMI: body mass index; PSA: prostate-specific antigen; NCCN: National Comprehensive Cancer Network

observed between the two groups (χ^2=3.364, p=0.067). The number of patients that received salvage ADT was 15 (10.2%) and 30 (20.4%), which was significantly more among patients in the RP group than among those in the BT group (χ^2=5.904, p=0.015) and the number of patients that received salvage EBRT was 5 (3.4%) and 2 (1.4%), which did not differ significantly between the two groups (p=0.447).

Oncologic findings

Survival: The median follow-up period was 63 (29–178) and 52 (24–175) months in BT and RP groups, respectively. Additionally, 20 (13.6%) patients developed biochemical recurrence, 9 (6.1%) patients developed clinical recurrence, and 23 (15.6%) patients died in the BT group, of which 6 (4.1%) died of prostate cancer. Furthermore, 32 (21.8%) patients developed biochemical recurrence, 9 (6.1%) patients developed clinical recurrence, and 21 (14.3%) patients died in the RP group, of which 3 (2.0%) died of prostate cancer.

The 5-year and 10-year bRFSs were 90.1% and 85.0% in the BT group and 79.4% and 79.4% in the RP group, respectively. The log-rank test showed that the bRFS in the BT group was better than that in the RP group (Fig. 1A, p=0.022), and the difference was statistically significant. The 5-year and 10-year cRFSs were 95.0% and 87.8% in the BT group and 94.4% and 81.1% in the RP group, respectively (Fig. 1B, p=0.637); 5-year and 10-year CSSs were 97.2% and 92.3% in the BT group and 98.4% and 92.9% in the RP group, respectively (Fig. 1C, p=0.505); and 5-year and 10-year OSs were 91.3% and 74.3% in the BT group and 89.7% and 77.4% in the RP group, respectively (Fig. 1D, p=0.726); the differences in survival curves between the two groups were statistically non-significant (p>0.05) (Fig. 1).

Factors affecting bRFS correlation

According to the difference in pretreatment variables between the BT and RP groups of patients matched, a log-rank test was used to compare the bRFS curves of BT and RP under the conditions of different variables (Table 2). Pre-matched factors associated with bRFS were surgical approach(p=0.019), pretreatment PSA (p<0.001), clinical T-stage T2b (p<0.001), the puncture biopsy

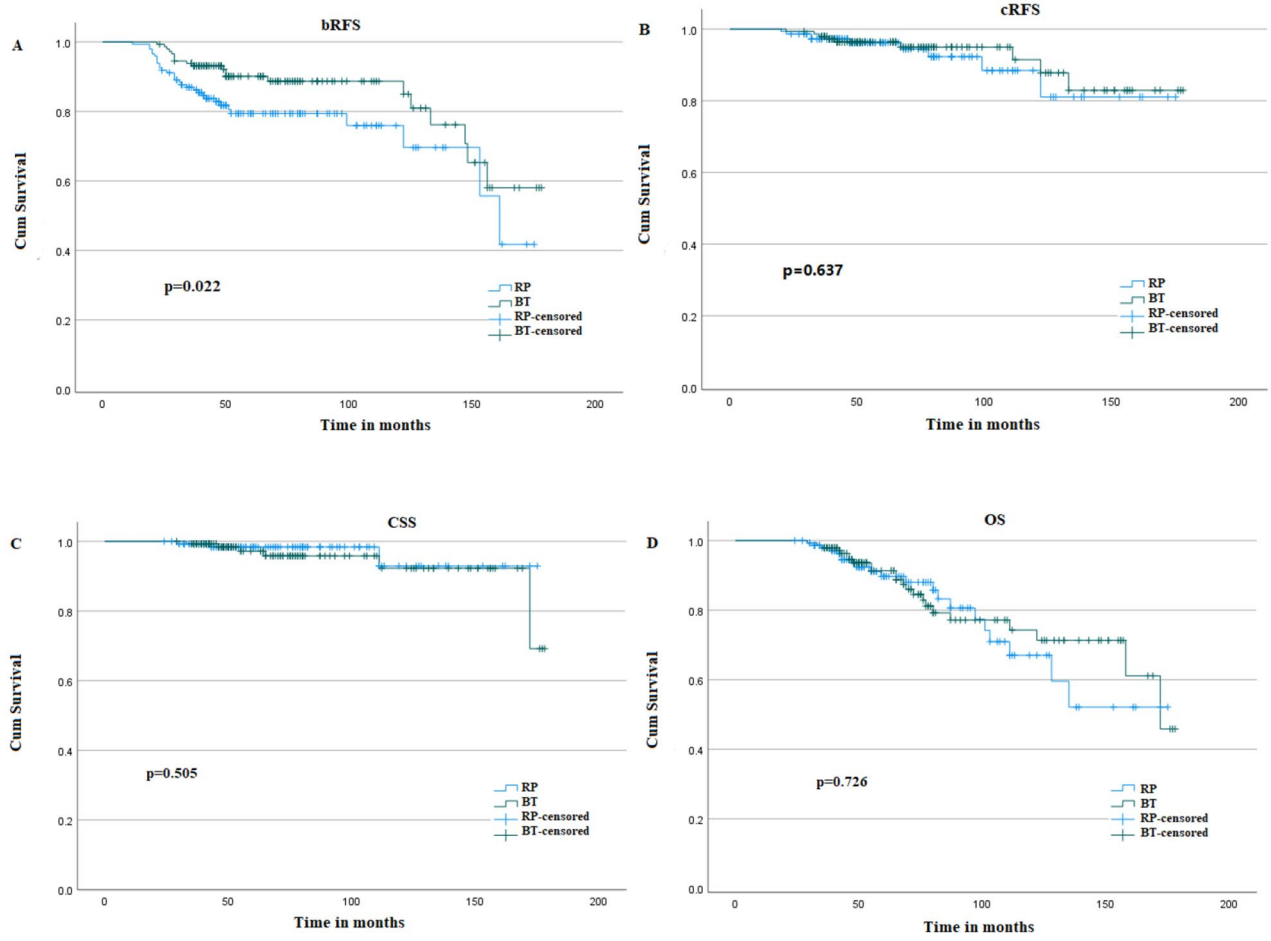

Fig. 1 **bRFS**(Biochemical recurrence-free survival, **A**), **cRFS**(Clinical relapse-free survival,**B**), **CSS**(Caner-specific survival,**C**); **OS**(Overall survival,**D**)

Table 2 Log-rank test for the correlation factors of bRFS between TB and RP before matching

Variables[Mean ± SD, or *n* (%)]	OR (95% CI)	*p*-value
Surgical approach (BT/RP n, %)	1.805 (1.102–2.955)	0.019
Age (years)	0.986 (0.960–1.013)	0.309
BMI (kg/m^2)	1.040 (0.968–1.117)	0.281
PSA (ng/mL)	1.021 (1.013–1.028)	< 0.001
Prostate volume (ml)	0.996 (0.983–1.009)	0.515
Clinical staging cT (n, %)		
T1-T2a	1	
T2b	1.195 (1.115–1.329)	< 0.001
T2c-T3a	1.597 (1.316–2.128)	0.112
Biopsy Gleason grading grouping (n, %)		
1	1	
2–3	1.103 (1.051–1.208)	< 0.001
4–5	1.250 (1.156–1.399)	< 0.001
NCCN risk classification (n, %)		
low risk	1	
Intermediate risk	1.188 (1.067–1.529)	0.002
high risk	1.159 (1.078–1.332)	< 0.001
Percentage of biopsy-positive needles ≥ 1/2 (n, %)	5.973 (3.739–9.539)	< 0.001
Maximum diameter of biopsied tumor ≥ 5 mm (n, %)	7.810 (4.669–13.062)	< 0.001
NADT (n, %)	0.800 (0.488–1.311)	0.376

BT: iodine 125-endoradiotherapy; RP: radical prostatectomy; bRFS: biochemical recurrence-free survival; BMI: body mass index; PSA: prostate-specific antigen; NCCN: National Comprehensive Cancer Network; NADT: neoadjuvant androgen blockade therapy

Table 3 Univariate and multivariate analysis of bRFS after matching

Variables[Mean ± SD or *n* (%)]	univariate analysis		multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Surgical approach (BT/RP n, %)	1.697 (0.917–3.142)	0.092		
PSA (ng/mL)	1.016 (1.006–1.026)	0.001	1.008 (0.966–1.019)	0.181
Clinical T staging cT (n, %)				
T1-T2a	1		1	
T2b	1.186 (1.089–1.392)	< 0.001	1.355 (1.130–1.996)	0.043
T2c-T3a	1.076 (1.010–0.576)	0.013	1.145 (1.016–2.290)	0.083
Biopsy Gleason grading grouping (n, %)				
1	1		1	
2–3	1.128 (1.047–1.346)	< 0.001	1.551 (1.126–3.075)	0.348
4–5	1.384 (1.192–1.767)	0.007	2.109 (1.474–3.596)	0.811
NCCN risk classification (n, %)				
low risk	1		1	
Intermediate risk	1.179 (1.041–1.774)	0.021	2.438 (1.196–11.546)	0.721
high risk	1.132 (1.040–1.441)	< 0.001	1.509 (1.117–3.204)	0.366
Percentage of biopsy-positive needles ≥ 1/2 (n, %)	4.141 (2.166–7.915)	< 0.001	1.250 (0.469–3.330)	0.655
Maximum diameter of biopsied tumor ≥ 5 mm (n, %)	4.809 (2.398–9.644)	< 0.001	2.926 (1.030–8.257)	0.044

BT: iodine 125-endoradiotherapy; RP: radical prostatectomy; bRFS: biochemical recurrence-free survival; PSA: prostate-specific antigen; NCCN: National Comprehensive Cancer Network

Gleason grouping 2–3 ($p<0.001$) or 4–5 ($p<0.001$), NCCN risk classification intermediate risk ($p=0.002$) or high risk ($p<0.001$), biopsy-positive needles as a percentage of ≥1/2 ($p<0.001$) and biopsy tumors with maximal diameters ≥ 5 mm ($p<0.001$). Based on the pre-matched relevant variables, a post-matched logistic regression model was developed to identify the factors associated with bRFS (Table 3). The univariate analysis of the entire cohort revealed that surgical approach ($p=0.092$) did not have a significant effect on bRFS. However, pretreatment PSA ($p=0.001$), clinical T-stage T2b ($p<0.001$) or T2c–T3a ($p=0.013$), puncture biopsy Gleason grouping group 2–3 ($p<0.001$) or 4–5 ($p=0.007$), NCCN risk classification intermediate-risk ($p=0.021$) or high-risk ($p<0.001$), biopsy-positive needles as a percentage of ≥1/2 ($p<0.001$), and a maximum biopsy tumor diameter ≥ 5 mm ($p<0.001$). Multivariate analysis showed that clinical T stage ≥ T_{2b} stage ($p=0.043$) and biopsy tumor

maximum diameter ≥ 5 mm ($p=0.044$) were associated with significantly bRFS.

Discussion

The current NCCN guidelines recommend RP and BT treatments for T_{1c} ~ T_{3a} stage PCa [7, 8]. There is no statistically significant difference between the two treatments based on OS and CSS [5, 6]. The choice of treatment options for PCa depends greatly on the conditions of each medical center, physician preference, and patient perception. Differences in baseline characteristics, such as age, comorbidities, tumor risk profiles, and treatments used, make it more difficult to compare the efficacy advantages and disadvantages of the two treatments [5, 14–17]. Randomized controlled trials are ideal for comparing competing treatment modalities [18]. Currently, reported comparisons of the efficacy of BT and RP are primarily limited to retrospective analyses [5, 19]. Most patients treated with BT are older and have more comorbidities than RP patients, making it more difficult to conduct randomized trials in clinical studies [15, 17].

This study used PSM for longer-term follow-up of patients with clinically localized PCa treated with BT versus RP. The results showed that patients in the BT group exhibited better bRFS than those in the RP group. The two groups did not differ significantly based on cRFS, CSS, and OS. The results showed that the overall outcome of both treatments was good. This result is consistent with those of previous studies [20, 21].

Oncologic outcomes

Several studies have compared the oncologic outcomes of RP and BT treatment modalities in patients with PCa. Kupelian et al. compared RP, EBRT, BT, and BT with EBRT and reported that similar bRFS were achieved when higher radiation doses were administered [22]. Hayashi et al. compared the outcomes of RP, EBRT, and BT in patients with localized PCa using PSM analysis and reported that, in intermediate-risk patients, the bRFS of BT was superior to that of RP ($p=0.003$). There was no significant difference in OS between the two groups [20] ($p=0.429$). Goy et al. performed a retrospective follow-up analysis of 1,503 patients with intermediate-risk PCa over a long period (median follow-up time of 9.8 years for BT and 10.0 years for RP). Adjusted 10-year bRFSs were 80.2% in the BT group and 57.1% in the RP group ($p=0.0003$). However, distant metastasis-free survival and tumor-specific survival were similar [21]. The median follow-up period in the BT and RP groups in this study was 63 and 52 months, respectively, and the 10-year bRFS was 85% and 79.4%, respectively ($p=0.022$), which showed that the bRFS in the BT group was better than that in the RP group. It was closer to that of Goy et al. [21]; however, their enrolled patients were all intermediate-risk patients, whereas our study included all patients from low risk to high risk, and the proportion of patients in the BT group who underwent NADT preoperatively was greater, and the duration of administration was longer. Previous studies reported that ADT is not an independent prognostic factor [23, 24], and our group also found no significant effect of NADT on bRFS.

Additionally, two patients were found to have pulmonary metastases 22 and 29 months of BT, respectively, which were not found in the RP group. These two patients demonstrated multiple concurrent NCCN high-risk risk factors [7, 9]. A previous study reported the possibility of tumor metastasis during particle implantation, especially in high-risk patients [25]. Although the number of cases of tumor metastasis with this modality is small, the possibility of this risk should be considered.

Independent prognostic factors

Several factors have been reported in a previous study to influence the prognosis of prostate cancer, including the patient's age, clinical T-stage of the tumor, Gleason grading of the tumor, PSA, and bone scan status [26] Taussky et al. [27] reported that the younger the age, the higher the percentage of biopsy-positive needles, and the higher the PSA at the time of diagnosis, the higher the risk of biochemical recurrence. Univariate analysis using propensity score-matched cohorts in this study revealed that pretreatment PSA, clinical T-stage, Gleason grading subgroups for puncture biopsy, NCCN risk classification, biopsy-positive needle count percentage ≥ 1/2, and biopsy tumor maximal diameter ≥ 5 mm were associated with bRFS. This finding is consistent with those of previous studies [26, 27]. Multivariate analysis revealed that only clinical T stage ≥ T_{2b} and biopsy tumor maximum diameter ≥ 5 mm were significantly associated with bRFS and were independent prognostic factors.

Limitations of this study

(1) This retrospective study was inevitably flawed. Although prognostic factor imbalances between some treatment groups were eliminated by PSM, a randomized controlled trial would be the ideal method. (2) Surgical procedures are essentially operator-dependent, and the surgeon's surgical technique will significantly impact outcomes. Herein, all BT surgeries were performed by the same team (DONG), and RP was performed by senior (> 100 RP surgeries) physicians (ZHU) to ensure quality. (3) The different definitions of biochemical recurrence after BT and RP affected their comparability to a certain extent, and although this study used the most commonly used international standard and comparison method [26, 28, 29], it might have caused a certain bias to the final results.

Conclusion

For localized prostate cancer, BT and RP treatments demonstrated equivalent cRFS, CSS, and OS. However, bRFS was better among patients in the BT group than among those in the RP group. Patients with clinical T stage ≥ T_{2b} stage and biopsy tumor maximum diameter ≥ 5 mm indicated a poor prognosis. The results of this study must be validated with multicenter and longer follow-up.

Acknowledgements
Not applicable.

Author contributions
Zaisheng Zhu(A): Study design, completed RP surgery, data analysis and manuscript writing. Yiyi Zhu(B): Article writing.Hongqi Shi(C), Penfei Zhou(D) & Yadong Xue(E): Data collection and data analysis. Ke Dong(F) & Shengye Hu(G): Completed BT surgery and statistical analysis. All authors reviewed the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported by grants from the Zhejiang Provincial Medical and Health Program Project (2022KY1332), Zhejiang Jinhua City (Social Development Category) Major Science and Technology Research Program Project (2021-3-022).

Data availability
The datasets generated and analysed during the current study are not publicly available due to do not have consent from all patients to publish this data, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by Jinhua Hospital, The Aflicated Hospital of Zhejiang University Medical School Medical Ethics Committee of No. 2021 – 250. All patients have signed informed consent forms. All methods were performed following the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 28 June 2024 / Accepted: 11 September 2024
Published online: 27 September 2024

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