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ORIGINAL ARTICLE

Efficacy of brachytherapy combined with endocrine therapy and external beam radiotherapy in the treatment of intermediate and high-risk localized prostate cancer

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Summary

Purpose: *To explore the efficacy and safety of brachytherapy combined with endocrine therapy (ET) and external beam radiotherapy (EBRT) in the treatment of patients with intermediate- and high-risk localized prostate cancer (PCa).*

Methods: *A total of 128 patients with intermediate- and high-risk localized PCa treated in our hospital, were included, encompassing 64 cases undergoing brachytherapy combined with ET (control group), and 64 cases undergoing intensity-modulated EBRT on the above basis (combination group). The clinical efficacy, adverse reactions, the serum prostate specific antigen (PSA) level before and after treatment, maximum urinary flow rate (Q_{max}), and expanded prostate cancer index composite (EPIC) score were compared between the two groups. The overall survival (OS) of patients was analyzed using the Kaplan-Meier method and log-rank test.*

Results: *After treatment, the EPIC scores of urinary function, intestinal function, sexual function and hormone function declined significantly in both groups, and they were significantly higher in the combination group than in the control group. At 12 months after treatment, the combination group had an obviously lower serum PSA level, and obviously higher Q_{max} than the control group. All patients were followed up for 12-60 months. In the combination and control group, OS was 87.5% and 81.3%, disease-specific survival (DSS) was 89.1% and 78.1%, the biochemical progression-free survival (bPFS) was 76.6% and 60.9%, and distant metastasis free survival (DMFS) was 87.5% and 71.9%, respectively. Log-rank test showed no statistically significant differences in OS and DSS between the two groups, but both bPFS and DMFS in the combination group were remarkably superior compared with the control group.*

Conclusions: *Brachytherapy combined with ET and EBRT has definite efficacy in intermediate- and high-risk localized PCa, which can significantly improve the physiological function, raise the quality of life of patients, and effectively control the disease progression.*

Key words: *prostate cancer, brachytherapy, endocrine therapy, external beam radiotherapy, efficacy*

Introduction

The morbidity rate of prostate cancer (PCa), one of the common malignant tumors threatening the health of elderly men, ranks 2nd among all malignant tumors in males around the world, and it has rapidly risen in China in recent years [1]. With the popularization of prostate specific antigen (PSA) test, more cases of early localized PCa have been found [2]. According to the PSA level before puncture, clinical stage and Gleason score, PCa patients can be classified into different

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risk levels. Low-risk PCa patients can be treated with radical prostatectomy, internal radiotherapy alone, external beam radiotherapy (EBRT) and active monitoring [3,4]. According to the *EAU Guidelines on Prostate Cancer*, transperineal continuous low-dose brachytherapy alone is considered as a definite, reliable and well reproducible treatment method for low-risk PCa [5]. However, brachytherapy alone is less effective for intermediate- and high-risk localized PCa [6-8]. In recent years, the clinical research results have shown that the combined surgery, radiotherapy or endocrine therapy (ET) can raise the efficacy and improve the long-term prognosis of patients [9,10].

In this study, the clinical data of 128 patients with intermediate- and high-risk localized PCa treated in our hospital from January 2013 to October 2014 were retrospectively analyzed, and the efficacy and safety of brachytherapy combined with ET and EBRT in the treatment of intermediate- and high-risk localized PCa were explored, so as to provide a solid basis for selecting the clinical therapeutic regimen for such patients.

Methods

Objects of study

A total of 128 patients with intermediate- and high-risk localized PCa treated in our hospital from January 2013 to October 2014 were collected. All patients were pathologically diagnosed with prostate adenocarcinoma via prostate biopsy before operation, and those with metastatic lesions were excluded via chest X-ray, abdominal and pelvic CT, or MRI and whole body bone scan. According to the classification of PCa risk of the NCCN, intermediate-risk PCa is defined as 10 ng/mL < PSA ≤ 20 ng/mL, Gleason score of 7 points and clinical stage T_{2b}, and high-risk PCa is defined as PSA >20 ng/mL, Gleason score >7 points and clinical stage T_{2c} or above. PCa can be definitely diagnosed if at least one of the above three criteria is met [11]. Patients who used to undergo brachytherapy, radiotherapy or adjuvant ET, had distant metastasis or could not tolerate the treatment were excluded. Based on the different treatment methods, the patients were divided into the combination group (n=64, treated with brachytherapy combined with ET and intensity-modulated radiotherapy EBRT) and the control group (n=64, treated with brachytherapy combined with ET). The patient age was 56-82 years (mean 71.33±10.45), and there were 53 cases of intermediate-risk PCa (41.4%) and 75 cases of high-risk PCa (58.6%). No statistically significant differences in baseline data between the two groups were observed (p>0.05) (Table 1). This study was approved by the Ethics Committee of Jinchang Central Hospital of Gansu Province. Signed written informed consents were obtained from all participants before the study entry.

Treatment methods

Brachytherapy

All patients underwent PCa brachytherapy. At 3-5 days before operation, transrectal ultrasonography was performed in a lithotomy position. The image of prostate was acquired from the bottom to the tip of the gland at an inter-slice spacing of 5 mm. The outline of the prostate and urethra was delineated using software, the radiation dose was designed, the particle distribution planning chart was plotted, and the number of radioactive particles required during operation was calculated. One day before operation, the particle activity was measured and the particles were disinfected for later use. During operation, under epidural anesthesia, subarachnoid anesthesia or general anesthesia, the particle distribution planning chart was plotted again, based on which the particles were inserted into the prostate using MICK200 particle implantation device under the guidance of transrectal B ultrasound. The intraoperative prescribed dose was 145 Gy, and the planned time was 15-35 min, with an average of 25 min. The particles were implanted for 20-48 min, with an average of 26 min. The particle activity was 0.35-0.50 mci, and the total activity was 15.0-44.5 mci, with an average of 25.1 mci. The 90% target volume absorbed dose (D_{90}) was 140-155 Gy, with an average of 144 Gy.

ET

According to the recommendation of the American Brachytherapy Society (ABS) [8], intermediate-risk patients were treated with brachytherapy combined with maximal androgen blockade (MAB) for more than 6 months. It was decided that combined EBRT should be based according to the change of postoperative PSA level. High-risk patients were treated with brachytherapy combined with MAB for more than 6 months. Based on the changes in the postoperative PSA level combined EBRT was determined. At the same time, the anti-androgenic Bicalutamide (Tablets, 50 mg, once a day), or Flutamide (250 mg, 3 times a day) were orally taken, and the luteinizing hormone-releasing hormone analogue (3.6 mg of Goserelin, 3.75 mg of Leuprolide or 3.75 mg of Triptorelin) were injected once a month.

EBRT

2-3 months after brachytherapy, intensity-modulated EBRT was performed. The seminal vesicle and pelvic lymph node regions were irradiated under routine fraction radiation (1.8-2.0 Gy a day, 5 times a week). Four-field radiotherapy was adopted every day at a prescribed dose of 45.0 Gy.

Observation indexes

Within 24 h after operation, pelvic anteroposterior X-ray examination was performed to evaluate whether there was particle displacement. At 4-6 weeks after operation, the particle distribution was detected via chest X-ray and pelvic plain CT scan, and the dose was evaluated. The maximum urinary flow rate (Q_{max}) was compared between the two groups before and af-

ter treatment, based on which the peak of flow curve during continuous urination was recorded. The level of serum PSA was also compared between the two groups before and after treatment, and the complications were observed and recorded in both groups.

The quality of life of patients was evaluated using the expanded prostate cancer index composite (EPIC). The questionnaire was composed of a total of 51 items of the urinary function, intestinal function, sexual function and hormone function. The score of each function was given according to the function and symptom evaluation. The total score was converted into the hundred-mark system (0-100 points), and the higher score corresponded to the better quality of life. The questionnaire survey was made before radiotherapy and 3 years after radiotherapy.

If there was disease progression during follow-up, chest, abdominal and pelvic CT or MRI and whole body bone scan were performed at any time, so as to determine whether local or distant metastasis occurred. The overall survival (OS), disease-specific survival (DSS), biochemical progression-free survival (bPFS) and distant metastasis-free survival (DMFS) of patients were recorded. Biochemical recurrence was defined as the decline in PSA to the bottom and then rise again to 2.0 ng/mL.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was used to detect survival differences between two groups. P<0.05 suggested statistically significant difference.

Results

Comparison of EPIC score between the two groups before and after treatment

There were no statistically significant differences in the EPIC scores of urinary function, intestinal function, sexual function and hormone function between the two groups before treatment (p=0.775, p=0.768, p=0.502, p=0.675). After treatment, the EPIC scores of urinary function, intestinal function, sexual function and hormone function declined significantly in both groups, and they were significantly higher in the combination group than those in the control group (p<0.001, p=0.009, p=0.007, p=0.002) (Table 2).

Comparison of serum PSA and Q_{max} between the two groups before and after treatment

There were no statistically significant differences in the serum PSA level (32.25±8.20 ng/mL *vs.* 33.04±8.03 ng/mL) and Q_{max} (11.2±1.8 mL/s *vs.* 10.8±1.7 mL/s) between the two groups before treatment (p=0.424, p=0.199). At 12 months after treatment, the combination group had an obviously lower serum PSA level (10.47±2.42 ng/mL *vs.* 16.89±2.65 ng/mL, p<0.001), and obviously higher Q_{max} (13.4±1.9 mL/s *vs.* 11.9±1.5 mL/s, p<0.001) than the control group (Figure 1).

Adverse reactions after comprehensive treatment

In the combination group there were 5 cases (7.8%) of particle displacement after treatment, including 3 cases of single particle displacement and 2 cases of 2 particle displacement. Two par-

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*Combination group (n=64)*	*Control group (n=64)*	*p value*
Age (years)	70.63±9.89	71.90±10.41	0.481
PSA (ng/ml)	32.25±8.20	33.04±8.03	0.424
Q_{max} (ml/s)	11.2±1.8	10.8±1.7	0.199
Prostate volume (ml)	30.8±2.8	31.3±3.0	0.332
Gleason Score (points), n (%)			0.510
4-6	11 (17.2)	15 (23.4)	
7-9	53 (82.8)	49 (76.6)	
TNM stage, n (%)			0.830
$T_{2a}N_0M_0$	12 (18.8)	10 (15.6)	
$T_{2b}N_0M_0$	15 (23.4)	14 (21.9)	
$T_{2c}N_0M_0$	21 (32.8)	26 (40.6)	
$T_{3a}N_0M_0$	16 (25.0)	14 (21.9)	
Clinical risk stratification, n (%)			0.370
Moderate risk	29 (45.3)	24 (37.5)	
High risk	35 (54.7)	40 (62.5)	

PSA: prostate specific antigen; Q_{max}: maximum flow rate; TNM: tumor, lymph node, metastasis

ticles were transferred to the lungs, 4 particles to the subcutaneous or retropubic region, and 1 particle out of the body. No subjective symptoms were found in the patients. During the follow-up period, lower urinary tract irritation in varying degrees occurred in 52 cases (81.3%) and 47 cases (73.4%), respectively, in the combination group and the control group, mainly manifested as frequent urination, urgent urination, dysuria and mild urge urinary incontinence. The symptoms were severest at 4-8 weeks, and then were gradually relieved. After symptomatic treatment for 6-12 months, the patients returned to the conditions before treatment. After treatment, there were 6 cases (9.4%) and 4 cases (6.3%) of urinary retention in the two groups, and autonomous urination was restored after urinary catheter indwelling was prolonged. Long-term urethral stricture occurred in 1 case (1.6%) and 2 cases (3.1%), and it was improved after transurethral prostatic resection (TURP). Mild radiation proctitis occurred in 2 case (3.1%) and 1 case (1.6%), manifested as aching pain or burning pain in the anorectum and tenesmus, and it was spontaneously relieved within 1 month after operation. No severe complications such as urinary fistula and rectal fistula occurred. It can be seen that the incidence of adverse reactions had no statistically significant difference between the two groups after treatment (p>0.05) (Table 3).

Follow-up results of patient survival

As of October 2019, all patients were followed up for 12-60 months, with a median of 43.3 months. In the combination group and the control group, there were 8 and 12 deaths, respectively, among

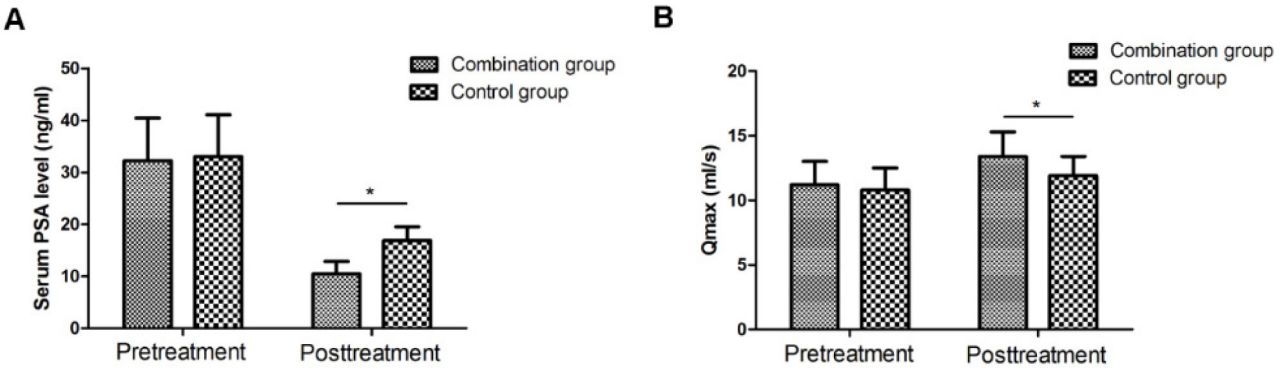

Figure 1. Comparison of serum PSA level and maximum flow rate of patients in the two groups. Pretreatment PSA level **(A)** and maximum flow rate **(B)** of patients had no significant difference between Combination group and Control group (p=0.424, p=0.199). Serum PSA level of patients dramatically decreased and maximum flow rate of patients dramatically increased after treatment. Posttreatment serum PSA level **(A)** of patients in the Combination group was significantly lower than that of the Control group, while maximum flow rate **(B)** of patients in the Combination group was significantly higher than that of the Control group (*p<0.001).

Table 2. Comparison of pretreatment and posttreatment EPIC score (points) of the studied patients in two different groups

	Combination group (n=64)	*Control group (n=64)*	*p value*
Urinary subscales (points)			
Pretreatment	92.21±8.20	92.64±8.73	0.775
Posttreatment	88.16±7.09	82.20±7.17	0.001
Bowel subscales (points)			
Pretreatment	97.20±9.84	97.71±9.64	0.768
Posttreatment	89.63±6.76	85.65±5.99	0.009
Sexual subscales (points)			
Pretreatment	55.29±4.17	54.72±5.34	0.502
Posttreatment	43.50±4.75	38.67±5.85	0.007
Hormonal subscales (points)			
Pretreatment	88.21±7.31	87.84±7.30	0.675
Posttreatment	80.28±7.79	75.02±7.82	0.002

EPIC: Expanded prostate cancer index composite

which 2 and 3 cases died of recurrence of PCa at 12-56 months after operation, and 6 and 9 cases died of non-related diseases at 14-59 months after operation, including non-surgical infection, primary lung cancer, primary rectal cancer, primary gastric cancer, cardio-cerebrovascular accidents and fractures. In the combination and control group, OS was 87.5% (56/64) and 81.3% (57/64), DSS was 89.1% (57/64) and 78.1% (50/64), bPFS was 76.6% (49/64) and 60.9% (39/64), and DMFS was 87.5% (56/64) and 71.9% (46/64), respectively. The Kaplan-Meier survival curves of both groups are shown in Figure 2. According to the log-rank test, no statistically significant differences were found in OS and DSS between the two groups (p=0.229, p=0.067), but both bPFS and DMFS in the combination group were remarkably superior to those in the control group (p=0.033, p=0.016).

Table 3. Comparison of adverse reactions of patients in the two groups

Adverse reactions	*Combination group (n=64) n (%)*	*Control group (n=64) n (%)*	*p value*
Urinary irritation symptoms	52 (81.3)	47 (73.4)	0.291
Urinary retention	6 (9.4)	4 (6.3)	0.510
Hematuria	12 (18.8)	17 (26.6)	0.291
Anemia	5 (7.8)	8 (12.5)	0.380
Urethrostenosis	1 (1.6)	2 (3.1)	0.559
Radiation proctitis	2 (3.1)	1 (1.6)	0.559

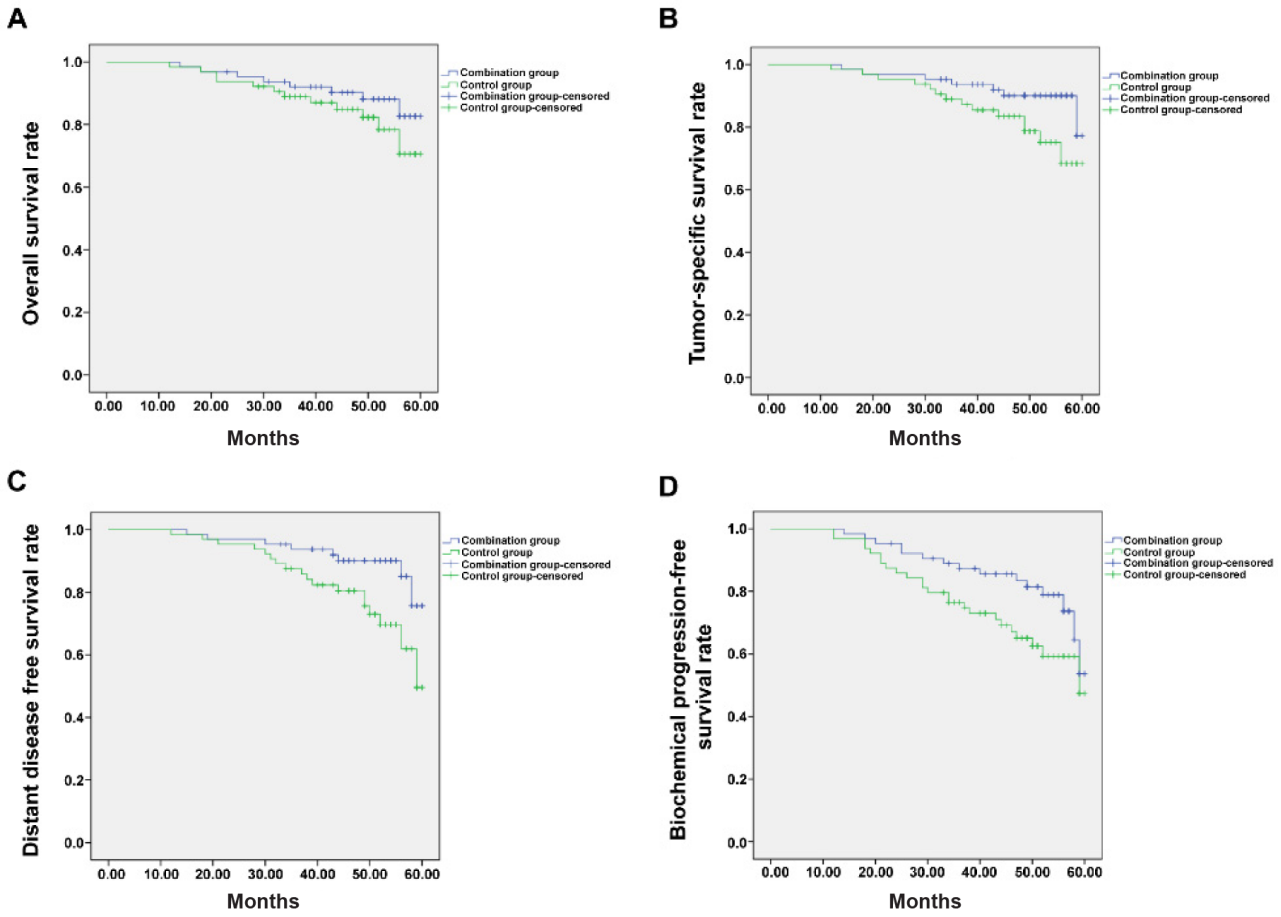

Figure 2. Kaplan-Meier survival curves of patients in the Combination group and the Control group. **A:** The difference between overall survival rate of patients in the two groups had no statistical significance (p=0.229). **B:** The difference between tumor-specific survival rate of patients in the two groups had no statistical significance (p=0.067). **C:** The distant disease-free survival rate of patients in the Combination group was significantly higher than that of the Control group (p=0.016). **D:** The biochemical progression-free survival rate of patients in the Combination group was significantly higher than that of the Control group (p=0.033).

Discussion

According to the *EAU Guidelines on Prostate Cancer*, localized PCa refers to PCa in clinical stage cT_1-$T_2N_0M_0$ (stage cT_3 for locally advanced PCa). Radical prostatectomy, radical EBRT and radioactive particle implantation in brachytherapy are all curative treatment methods for PCa [12]. Due to minimal invasion and good prognosis, brachytherapy has become one of the standard treatment means for PCa [13]. Compared with EBRT, brachytherapy has fewer adverse reactions, so it is easily accepted by the patients [14]. It is recommended by the *ABS Guidelines* that localized PCa can be treated with brachytherapy. Moreover, low-risk PCa can be treated with brachytherapy without EBRT, combined treatment of brachytherapy, EBRT and MAB can be adopted for high-risk PCa, and it is needed to determine whether EBRT and ET should be applied for intermediate-risk PCa according to the specific conditions of the patients [15].

A large amount of literature can be found about the treatment of patients with intermediate- and high-risk localized PCa with brachytherapy combined with ET and EBRT. In 2004, Stock et al [16] reported for the first time that brachytherapy combined with ET and EBRT is effective in controlling the PSA level and improving bPFS in high-risk localized PCa. In the study of Mason et al 1205 high-risk PCa patients without distant metastasis were randomly divided into long-term ET group and ET + radiotherapy group. They were followed up for 8 years, and it was found that ET + radiotherapy markedly increased the OS of patients (85% *vs.* 57%) and lowered the PCa-specific mortality (34% *vs.* 61%) [17]. Marshall et al [18] studied 2495 localized PCa patients treated with brachytherapy who were followed up for 12 years. The results revealed that overall bPFS is 83% (90% in low-risk group, 84% in intermediate-risk group, and 64% in high-risk group), DMFS was 95%, DSS was 95% and OS was 70%, indicating that combined MAB can reduce the biochemical recurrence rate of patients with PCa (especially intermediate- and high-risk PCa) after brachytherapy. In the study of Stock et al [19] involving 27 patients with stage T_3 high-risk PCa, the 8-year bPFS of patients with PSA >20 ng/mL was 58%. Besides, Chen et al [2] treated 85 patients with stage T_1-T_3 PCa, and they confirmed that the 4-year bPFS was 100%, 91%, 81% and 25%, respectively, in low-, intermediate-, high- and very high-risk groups. In this study, all patients were followed up for 12-60 months. In the combination group, the OS, DSS, bPFS and DMFS were 87.5% (56/64), 89.1% (57/64), 76.6% (49/64) and 87.5% (56/64), respectively. Both bPFS and DMFS in the combination group were remarkably superior to those in the control group (p=0.033, p=0.016). The above findings are similar to those in previous studies, but some results are biased, which may be related to the higher level of PSA before operation and the higher proportion of high-risk patients.

Q_{max} can reflect the bladder and urethral function of subjects during urination, based on which the functional status of prostate can be analyzed. In this study, Q_{max} in the combination group was obviously higher than in the control group at 1 year after treatment, suggesting that the efficacy was better and the quality of life was higher in the combination group, similar to the findings of other investigators [20,21]. At 1 year after treatment, the EPIC scores of urinary function, intestinal function, sexual function and hormone function declined in both groups, more significantly in the control group, demonstrating that the quality of life in the combination group was higher than in the control group. Moreover, the incidence of complications had no statistically significant difference between the two groups during treatment (p>0.05), indicating that the combined EBRT does not increase the incidence of adverse reactions.

There were some limitations in this study, such as limited sample size, short follow-up period and no random grouping. In the future, the conclusion in this study needs to be confirmed by more rigorous large-sample prospective multicenter randomized studies.

Conclusions

Brachytherapy combined with ET and EBRT has definite efficacy on intermediate- and high-risk localized PCa, which can significantly improve the physiological function, raise the quality of life of patients, and effectively control the disease progression.

Conflict of interests

The authors declare no conflict of interests.

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