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ORIGINAL ARTICLE

Efficacy of ^{125}I seed implantation combined with intermittent hormonal therapy on moderate- and high-risk non-metastatic prostate cancer

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Summary

Purpose: *To explore the efficacy and safety of ^{125}I radioactive seed implantation combined with intermittent hormonal therapy (IHT) in the clinical treatment of moderate- and high-risk non-metastatic prostate cancer.*

Methods: *A total of 136 patients were divided into observation group (n=68) and control group (n=68). In observation group, ^{125}I radioactive seed implantation was performed, bicalutamide capsules were taken orally immediately after operation, and leuprorelin was injected from 1 week after operation. In control group, IHT alone was performed. The level of serum prostate specific antigen (PSA), maximum urine flow rate (Q_{max}) and international prostate symptom scale (IPSS) score were compared between the two groups before and after treatment. Moreover, the overall survival (OS), tumor-specific survival (TSS), distant metastasis-free survival (DMFS) and progression-free survival (PFS) of patients were recorded.*

Results: *There were no statistically significant differences in the PSA level, Q_{max} and IPSS score between the two groups before treatment (p>0.05). At 6, 12 and 24 months after treatment, the level of PSA in observation group was significantly lower than that in control group (p=0.005, p<0.001, p<0.001). At 24 months after treatment, Q_{max} in observation group was significantly higher than that in control group (p=0.025). At 12 and 24 months after treatment, the IPSS score in observation group was significantly lower than that in control group (p=0.013, p=0.002). During the follow-up period, the intermission time of hormonal therapy and progression-free survival time in observation group were obviously longer than those in control group (p<0.001). In the two groups, OS was 97.1% and 94.1%, TSS was 95.6% and 92.6%, DMFS was 82.4% and 66.2%, and PFS was 72.1% and 51.5%, respectively. It can be seen that OS and TSS had no statistically significant differences between the two groups (p=0.405, p=0.496), while DMFS and PFS in observation group were remarkably superior to those in control group (p=0.037, p=0.022).*

Conclusions: *^{125}I seed implantation combined with IHT is safe and effective in the clinical treatment of patients with moderate- and high-risk non-metastatic prostate cancer. Compared with IHT alone, combination therapy can significantly prolong the intermission time of hormonal therapy and effectively control the progression of disease.*

Key words: *prostate cancer, internal radiotherapy, hormonal therapy, efficacy*

Introduction

In 2016 there were about 180,890 new cases and 26,120 deaths of prostate cancer in the United States, ranking 1st among all new-onset malignant tumors in males [1-5]. In East Asia, the morbidity rate of prostate cancer has also rapidly risen, and Japan and mainland China are high-prevalence areas [6-8]. According to the prostate specific antigen (PSA) before puncture, clinical stage and Gleason

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score, the prostate cancer patients can be divided into different risk levels, among which those with clinical low-risk prostate cancer can be treated with radical prostatectomy, internal radiotherapy alone, external radiotherapy and active monitoring [9,10]. However, hormonal therapy alone was previously dominating in the treatment of patients with moderate- and high-risk non-metastatic prostate cancer. In recent years, related clinical research results have shown that combined surgery or radiotherapy can prolong the sensitization time of hormonal therapy and improve the long-term prognosis of patients [11,12].

According to the EAU Guidelines on Prostate Cancer, continuous low-dose transperineal brachytherapy alone is considered as a definite, reliable and well reproducible therapeutic method for low-risk prostate cancer [13]. Since the 1970s, seed implantation brachytherapy has been widely applied in the treatment of prostate cancer, and its efficacy on moderate- and low-risk prostate cancer is comparable to that of radical prostatectomy. However, the efficacy of brachytherapy alone is poor for localized moderate- and high-risk prostate cancer [14-16].

In the present study, the clinical data of 136 patients with moderate- and high-risk non-metastatic prostate cancer treated in our hospital from July 2013 to July 2015 were analyzed, and the clinical significance of ^{125}I seed implantation combined with intermittent hormonal therapy (IHT) was explored in the treatment of moderate- and high-risk non-metastatic prostate cancer.

Methods

Objects of study

In this study, the patients were enrolled using a prospective non-randomized method. Inclusion criteria: patients diagnosed with prostate cancer via prostate biopsy, those with non-metastatic prostate cancer according to clinical evaluation, those with any clinico-laboratory risk factors (cT ≥ stage T2b, Gleason score ≥7 points, and PSA before puncture ≥10 ng/mL), and those who agreed to undergo ^{125}I radioactive seed implantation and hormonal therapy. Exclusion criteria: patients who received neoadjuvant or adjuvant hormonal therapy, those with distant tumor metastasis, or those who failed to tolerate hormonal therapy. The patients enrolled were divided into the observation group (n=68, ^{125}I radioactive seed implantation combined with IHT) and the control group (n=68, IHT alone) according to different therapeutic methods. The patients were aged 60-84 years with an average of 71.22±9.85 years. The level of PSA before the puncture was 4.0-122.0 ng/mL with an average of 34.89±18.18 ng/mL. The Gleason score was 6 points in 21 cases (15.4%), 7 points in 50 cases (36.8%) and ≥8 points in 65 cases (47.8%). The clinical stage was T2a in 25 cases (18.4%), T2b in 30 cases (22.1%), T2c in 47 cases (34.6%) and T3a in 34 cases (25.0%). There were 65 cases (47.8%) of moderate-risk prostate cancer and 71 cases (52.2%) of high-risk prostate cancer. The clinical baseline data had no statistically significant differences between the two groups (p>0.05) (Table 1). All patients enrolled adhered to the *Declaration of Helsinki* and signed the informed consent, and this study was approved by the Ethics Committee of the Central Hospital of Wuhan.

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

Parameters	*Observation group (n=68)*	*Control group (n=68)*	*p value*
Age, years	70.23±9.85	71.71±10.11	0.389
PSA (ng/mL)	35.21±13.20	34.64±14.03	0.808
Q_{max} (mL/s)	11.0±1.7	10.7±1.5	0.277
IPSS score (points)	20.8±2.9	20.2±2.8	0.222
Gleason score (points), n (%)			0.776
6	11 (16.2)	10 (14.7)	
7	23 (33.8)	27 (39.7)	
≥8	34 (50.0)	31 (45.6)	
TNM stage, n (%)			0.844
$T_{2a}N_0M_0$	13 (19.1)	12 (17.6)	
$T_{2b}N_0M_0$	16 (23.5)	14 (20.6)	
$T_{2c}N_0M_0$	21 (30.9)	26 (38.2)	
$T_{3a}N_0M_0$	18 (26.5)	16 (23.5)	
Clinical risk stratification, n (%)			0.607
Moderate risk	31 (45.6)	34 (50.0)	
High risk	37 (54.4)	34 (50.0)	

PSA: prostate specific antigen, Q_{max}: maximum flow rate, IPSS: international prostate symptom score, TNM: tumor, lymph node, metastasis

Treatment methods

^{125}I radioactive seed implantation: The radioactive seed implantation three-dimensional treatment planning system and quality verification system were manufactured by SSGI, USA. The auxiliary equipment such as puncture holder, template, stepper, 18G seed implantation needle and Mick gun was produced by Mick Radio-Nuclear, USA, and the rectal ultrasound diagnostic apparatus was produced by B-K, Denmark. The ^{125}I radioactive seeds (nickel-titanium cladding, activity: 11.9-16.6 MBq) were manufactured by China Institute of Atomic Energy. The intestine was cleansed one day before seed implantation. The prostate CT or MRI examinations were routinely performed, the three-dimensional treatment planning system was used for pre-planning, and the number of seeds to be implanted and the irradiation dose were initially determined.

After epidural anesthesia in lithotomy position, Foley catheter was indwelled routinely, and 15 mL of water were injected into the balloon. The stepper, template and rectal ultrasound probe were fixed, the stepper was moved to the ultrasound probe into the rectum, and the transversal ultrasonic images (slice thickness: 5 mm) were obtained from the prostatic basal layer to the apex. The images were then transmitted to the treatment planning system to reconstruct the three-dimensional shape of the prostate. Under the ultrasonic guidance, the implant needle was punctured to the predetermined position of the prostate, the seeds were pushed to the tip of needle using the implant gun, and the implant needle was withdrawn to longitudinally release seeds into the prostate. The seeds were implanted in each needle position in the same way. Three days after operation, pelvis anteroposterior and lateral X-ray and prostate CT examination were performed to evaluate the distribution of seeds.

IHT: In the observation group, bicalutamide capsules were taken orally (50 mg, once daily) immediately after operation, and leuprorelin was injected (3.75 mg, once every 28 d) from 1 week after operation for total androgen blockade. When the level of serum PSA declined to <0.2 ng/mL for 3 months, the drugs were withdrawn for intermission. When the PSA concentration exceeded 0.5 ng/mL, intermission was ended and treatment began again as above. In the control group, only hormonal therapy was performed in the same way as observation group.

Observation indexes

The level of serum PSA was detected in all patients every month, based on which the hormonal therapy regimen was developed and the efficacy was evaluated. Chest X-ray and whole-body bone scan were conducted every 6 months. The international prostate symptom scale (IPSS) score was recorded before treatment and every 3 months after treatment. The level of PSA, maximum urine flow rate (Q_{max}), IPSS score and stabilization time (intermission) after initial hormonal therapy were compared between the two groups before and after treatment, and overall survival (OS), tumor-specific survival (TSS), progression-free survival (PFS) and distant metastasis-free survival (DMFS) of patients were calculated in both groups. Biochemical recurrence was defined as the elevation of PSA to 2.0 ng/mL again after falling to the bottom.

The urethral and rectal adverse reactions of patients were evaluated in the observation group every 3 months after operation. Urination and urinary tract symptoms were graded according to the recommendation of the American Society for Radiation Oncology: grade 0: no symptom, grade I: mild burning sensation and frequent

Table 2. Comparison of pretreatment and posttreatment serum PSA level (ng/mL), Q_{max} (mL/s) and IPSS score (points) of the studied patients in two different groups

	Observation group (n=68)	*Control group (n=68)*	*p value*
PSA (ng/mL)			
Before treatment	35.21±13.20	34.64±14.03	0.808
6 months after treatment	0.16±0.09	0.20±0.07	0.005
12 months after treatment	0.21±0.12	0.59±0.38	0.001
24 months after treatment	0.29±0.17	0.72±0.34	0.001
Q_{max} (mL/s)			
Before treatment	11.0±1.7	10.7±1.5	0.277
6 months after treatment	17.1±1.9	16.6±1.8	0.118
12 months after treatment	16.5±2.0	16.0±1.9	0.137
24 months after treatment	16.2±2.1	15.4±2.0	0.025
IPSS score (points)			
Before treatment	20.8±2.9	20.2±2.8	0.222
6 months after treatment	12.9±2.1	13.4±2.0	0.157
12 months after treatment	11.8±1.8	12.6±1.9	0.013
24 months after treatment	12.0±1.7	12.9±1.9	0.002

PSA: prostate specific antigen, Q_{max}: maximum flow rate, IPSS: international prostate symptom score

urination (twice to 3 times/night), grade II: moderate burning sensation, frequent urination (4-6 times/night) and gross hematuria, grade III: severe burning sensation and frequent urination (7-10 times/night), and grade IV: obstruction of urinary tract, and catheter indwelling needed. Rectal adverse reactions were evaluated based on the recommendation of the Radiation Therapy Oncology Group: grade I: tenesmus and mucous stool, grade II: intermittent rectal bleeding, grade III: ulceration, and grade IV: intestinal obstruction, intestinal fistula and blood transfusion needed.

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 x2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method accompanied with log-rank test. P<0.05 suggested statistically significant difference.

Results

Comparisons of therapeutic indexes between the two groups after treatment

There were no statistically significant differences in the PSA level, Q_{max} and IPSS score between the two groups before treatment (p>0.05). At 6, 12 and 24 months after treatment, the level of PSA in the observation group was significantly lower than that in the control group, showing a statistically significant difference (p=0.005, p<0.001, p<0.001). At 24 months after treatment, Q_{max} in the observation group was significantly higher than that in the control group (p=0.025), while there was no statistically significant difference at other time points (p>0.05). At 12 and 24 months after treatment, the IPSS score in the observation group was significantly lower than that in the control group, showing a statistically significant difference (p=0.013, p=0.002), while it had no statistically significant difference at 6 months after treatment between the two groups (p=0.157) (Table 2).

Comparisons of adverse reactions between the two groups

In the observation group, 44 out of 68 (64.7%) patients had urethral adverse reactions within 6 months after operation, mainly including frequent urination, urgent urination, dysuria and mild urge incontinence, which were the most severe at 4-8 weeks and then gradually relieved, and returned to normal after symptomatic treatment for 6-12 months. Among them, there were 29 cases (42.6%) in grade I, 11 cases (16.2%) in grade II, 3 cases (4.4%) in grade III, and 1 case (1.5%) in grade IV. The voluntary urination could be restored in patients with urinary retention after prolonging the time of catheter indwelling. Besides, rectal adverse reactions occurred in 11 patients, mainly including aching pain or burning pain in the anal-rectal region and tenesmus, which were spontaneously relieved within 1 month after operation, and severe complications such as urinary fistula and rectal fistula were not observed. Among them, there were 9 cases (13.2%) in grade I and 2 cases (2.9%) in grade II. Seed displacement was found in 5 cases (7.4%), without any symptoms. There was no statistically significant difference in the incidence of adverse reactions between the two groups (p>0.05) (Table 3).

Follow-up results

As of May 2019, all patients were followed up for 13-60 months (median 38 months). Among 68 patients in the observation group, there was one death of prostate cancer recurrence and 1 death due to myocardial infarction. No pulmonary metastasis was found in chest X-ray examination, while

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

Parameters	*Observation group (n=68)* *n (%)*	*Control group (n=68)* *n (%)*	*p value*
Urinary adverse reactions			0.544
I	29 (42.6)	15 (22.1)	
II	11 (16.2)	4 (5.9)	
III	3 (4.4)	0 (0)	
IV	1 (1.5)	0 (0)	
Rectal adverse reactions			0.360
I	9 (13.2)	4 (5.9)	
II	2 (2.9)	0 (0)	
III	0 (0)	0 (0)	
IV	0 (0)	0 (0)	

bone metastasis was observed in 12 cases (17.6%) in whole body bone scan. OS was 97.1%, TSS 95.6%, and DMFS 82.4%. Among 68 patients in the control group, there were 2 deaths of prostate cancer recurrence, 1 death due to myocardial infarction and 1 death due to car accidents. No pulmonary metastasis was found, while bone metastasis was observed in 23 cases (33.8%). OS was 94.1%, TSS 92.6%, and DMFS 66.2%. It can be seen that OS and TSS had no statistically significant differences between the two groups (p=0.405, p=0.496), whereas DMFS in the observation group was remarkably superior compared to the control group (p=0.037). During the follow-up period, the intermission time of hormonal therapy and PFS in the observation group were obviously longer than those in the control group [(23.8±7.1) months *vs.* (12.7±5.2) months, p<0.001, (32.3±6.6) months *vs.* (25.7±5.9) months, p<0.001]. In the two groups, PFS was 72.1% and 51.5%, respectively, which was remarkably superior in the observation group to that in the control group (p=0.022). The Kaplan-Meier survival of both groups is shown in Figure 1.

Discussion

Prostate tumors have obviously different biological behaviors in different patients. Based on the D'Amico classification system, appropriate therapeutic regimens are recommended for patients at different risk levels in the treatment guidelines for prostate cancer in European and American countries and China [9,10]. Hormonal therapy alone was dominating previously in the treatment of patients with moderate- and high-risk prostate cancer. In recent years, related clinical research results have shown that combined surgery or radiotherapy can prolong the sensitization time of hormonal therapy and improve the long-term prognosis of patients [11,12].

Prostate radioactive seed implantation is a kind of minimally invasive brachytherapy for prostate cancer. Whitemore et al [17] pioneered the permanent ^{125}I seed implantation into the prostate for internal radiotherapy through the open retropubic approach in 1972. Since then, new techniques such as transrectal ultrasonic technique, and new

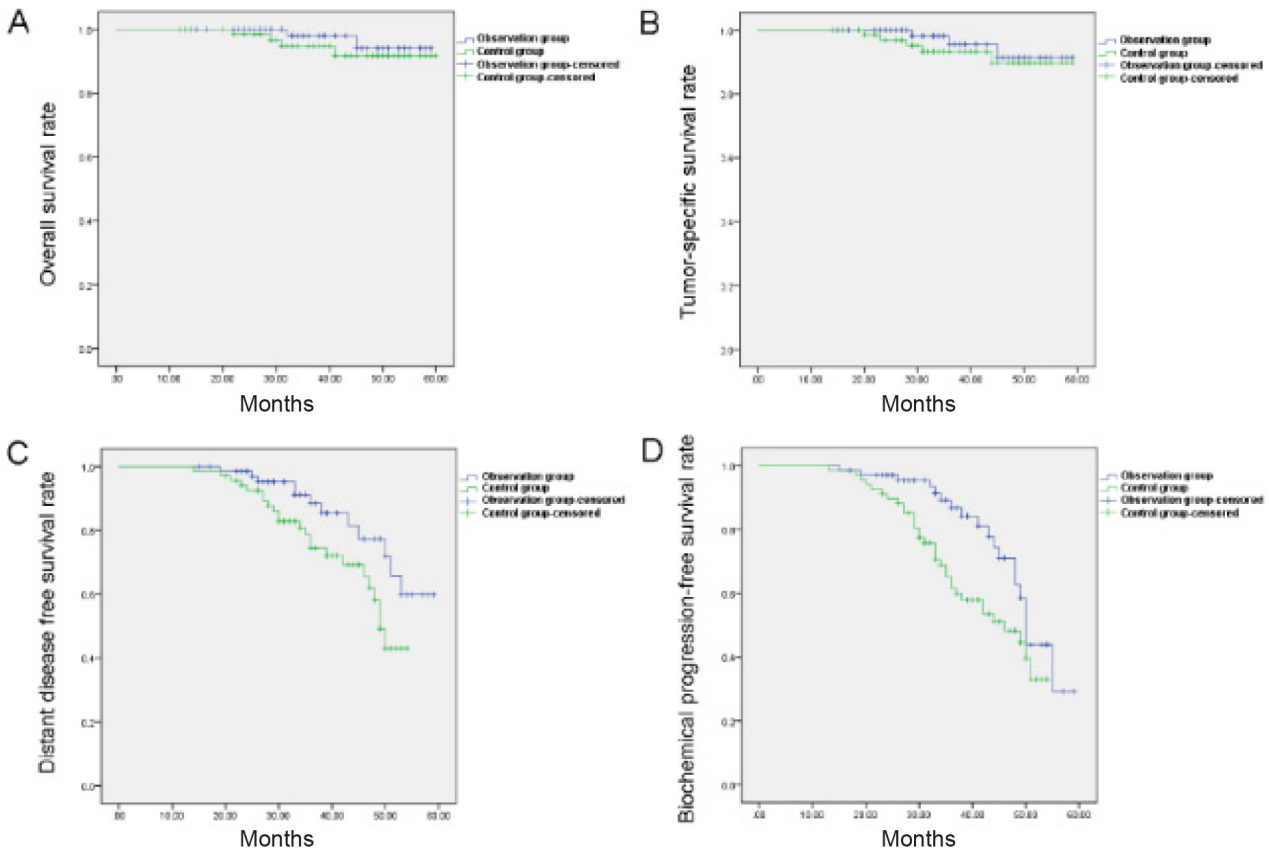

Figure 1. Kaplan-Meier survival curves of patients in the observation and the control group. **A:** The difference between overall survival rate of patients in the two groups had no statistical significance (p=0.405). **B:** The difference between tumor-specific survival rate of patients in the two groups had no statistical significance (p=0.496). **C:** The distant disease free survival rate of patients in the observation group was significantly higher than that of control group (p=0.037). **D:** The biochemical progression-free survival rate of patients in the observation group was significantly higher than that of the control group (p=0.022).

radionuclide and computer treatment systems have constantly emerged, and prostate radioactive seed implantation has been gradually improved and become an important treatment method for prostate cancer. Radioactive seed implantation can allow the prostate and surrounding tissues to obtain the same intensity of irradiation as external irradiation, with less damage to adjacent organs and a lower incidence rate of related adverse reactions [18,19].

Some authors have applied seed implantation in the treatment of moderate- and high-risk localized prostate cancer, but hormonal therapy should be supplemented [20,21]. Animal experiments have proved that IHT, one of the hormonal therapies, can prolong the time of hormone dependence in tumors, reduce the adverse reactions of hormonal therapy and improve the quality of life [22]. As a prospective non-randomized controlled study, this study aimed to evaluate the efficacy and safety of radioactive seed implantation combined with IHT in the clinical treatment of moderate- and high-risk non-metastatic prostate cancer. It was found that the improvement of PSA, Q_{max} and IPSS score in the observation group was superior compared to the control group, and both intermission time of hormonal therapy and PFS in the observation group were obviously longer than those in the control group.

Widmark et al [23] reported that the 10-year OS and TSS are evidently improved after horsmonal therapy combined with radioactive seed implantation compared with those after hormonal therapy alone. Lilleby et al [24] applied ^{125}I seed brachytherapy combined with androgen blockade in the treatment of moderate- and high-risk prostate cancer, and found that the efficacy of combination therapy is significantly better than that of internal irradiation alone, which is basically consistent with the results in this study. In this study, OS and TSS had no statistically significant differences between the two groups (p=0.405, p=0.496), whereas DMFS and PFS in the observation group were remarkably superior to those in the control group (p=0.037, p=0.022), demonstrating that the combined application of seed implantation can effectively control the progression of tumor into bone metastatic prostate cancer, thereby improving the long-term prognosis of patients.

In this study, the IPSS score declined at each time point after treatment compared with that before treatment in both groups, and the possible reason is that hormonal therapy can reduce the prostatic cancer volume. In the observation group there was a certain proportion of urethral and rectal adverse reactions after operation, which may be related to radioactive seed-induced radiation urethritis and radiation proctitis. The postoperative urethral adverse reactions in the observation group were mostly of grade I-II, which were generally severe at 2-3 months after seed implantation, and the therapeutic effect of α-receptor blockers was better [25]. Cosset et al [26] found through the follow-up of 675 patients treated with prostate seed implantation that 5.8% of patients had grade III-IV urethral adverse reactions after operation, similar to the results in this study. In this study, no grade III-IV rectal adverse reactions occurred, and there was no statistically significant difference in the incidence of adverse reactions between the two groups (p>0.05).

This study presents some limitations. For example, the sample size was limited, the follow-up time was not long enough, and the patients were not divided randomly. In the future, multicenter large-sample prospective randomized studies are needed to confirm the conclusions in this study.

Conclusions

^{125}I seed implantation combined with IHT is safe and effective in the clinical treatment of patients with moderate- and high-risk non-metastatic prostate cancer. Compared with IHT alone, combination therapy can significantly prolong the intermission time of hormonal therapy and effectively control the progression of disease.

Conflict of interests

The authors declare no conflict of interests.

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