·Clinical Research·

^{125}I versus ^{103}Pd brachytherapy for low risk prostate cancer: a systematic review

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[Abstract] **Background and Objective:** Permanent interstitial prostate brachytherapy is the main treatment for early-stage prostate cancer. ^{125}I and ^{103}Pd are the most commonly used radionuclides for prostate brachytherapy, which are different in complications and clinical efficacy. This study was to compare the effectiveness and adverse effects of ^{125}I and ^{103}Pd for patients with low risk prostate cancer using transperineal prostate seed implantation. **Methods:** Systematic literature retrieval was carried out to obtain articles of randomized controlled trials comparing ^{125}I and ^{103}Pd brachytherapy for low risk prostate cancer before May 2008. Study selection, data collection and quality assessment of studies were performed by two individual reviewers according to the Cochrane Handbook for systematic reviews of interventions 4.2.6. Statistic analyses were calculated using RevMan5.0 software. **Results:** Six randomized controlled trials, a total of 1 406 patients, were included. There was no significant difference in biochemical progression free survival between patients treated with ^{125}I brachytherapy and those treated with ^{103}Pd brachytherapy [RR=0.97, 95%CI (0.93,1.01)]. At one month after seed implantation, the adverse effects were more severe in ^{103}Pd group than in ^{125}I group. At six months after seed implantation, the adverse effects were more severe in ^{125}I group than in ^{103}Pd group. No significant difference in adverse effects was found between the two groups at 12 months after seed implantation. **Conclusion:** The individual effects of ^{125}I and ^{103}Pd brachytherapy for low risk prostate cancer are similar. However, the side effects are different at different time points after treatment.

Key words: brachytherapy, implant radiotherapy, ^{125}I, ^{103}Pd, prostate cancer, meta analysis, systematic review

Prostate cancer is a malignant tumor with a high incidence and mortality rate among men in USA. Epidemiologists estimate that there will be 186,320 new cancer cases and 160,390 deaths from prostate cancer in 2008.[1] The incidence and mortality rates of prostate cancer vary considerably among different racial and ethnic groups, which are much higher in North American and Southwestern Europe than in Asian and South American, and its mortality rates in African Americans and African Jamaican are the highest.[2] The risk factors include age, race/ethnicity, family history and so on.[2]

Nowadays, operation, external radiation, brachytherapy and co-hormonal therapy are the main treatments for early-stage prostate cancer. The role of seed-embedding brachytherapy, which started in the 20th century, has been scrutinized for a long term to treat prostate cancer. Brachytherapy navigated by CT or hypersound has been widely used in treating early prostate cancer, particularly in low-risk patients.[3,6] ^{125}I and ^{103}Pd are the most commonly used radionuclides for prostate brachytherapy. The half-life of ^{125}I is 60.2 days and the initial dose rate is 7.7cGy/h. The half-life of ^{103}Pd is 60.2 days and the initial dose rate is 18-20cGy/h. To balance their relative biological effectiveness for prostate cancer therapy, the currently prescribed doses used for clinical therapy are ^{125}I (145 Gy) and ^{103}Pd (115 Gy).[7,8] Peschel et al.[9] reported that the biochemical disease-free survival rate (bPFS) for those treated with ^{125}I was 92%, as the same as that of those treated with ^{103}Pd. The bPFS was 72% and 74% for those in the intermediate and poor prognosis group treated with ^{125}I and ^{103}Pd respectively.[9] A study group at the Department of Therapeutic Radiology, Yale University School of Medicine reported that the adverse reaction of brachytherapy for prostate cancer included intestinum rectum, urethral injury, urinific and sexual disturbance. The incidence rates of severe adverse reaction of ^{125}I and ^{103}Pd treatment were rare.[7] However, the selection of the prescribed dose for ^{125}I and ^{103}Pd has not been confirmed by extensively randomized controlled trials and biological experiments, and the difference in therapeutic effects and adverse reaction between these two particles has not been obtained based on evidence-based medicine.[7-9]

This study compared the effectiveness and adverse effects of ^{125}I and ^{103}Pd for patients with low risk prostate cancer using transperineal prostate seeding implantation.

Materials and Methods

Including criterion. Investigative category: randomized controlled trials, concealed or blinded.

Subjects: patients with low risk prostate cancer (including the clinical stage of T1c or T2a, prostate-specific antigen (PSA) level of ≤ 10ng/ml, and Gleason score of ≤ 6).

Intervention: ^{125}I (a prescribed dose of 144Gy, TG-43) or ^{103}Pd (a prescribed dose of 125Gy, IST-99) brachytherapy. Clinical trails for brachytheapy combined with operation or external radiation were excluded.

Observation indices: bPFS (PSA≤ 0.5ng/ml at the last follow-up) was used to estimate the therapeutic effect. American Urologic Association (AUA) Score, Radiation Therapy Oncology Group Score (RTOG) were used for estimating the adverse reaction.

Searching methods . To use "(I 125 OR ^{125}I) AND (Pd 103 OR ^{103}Pd) AND (prostate cancer OR prostate tumor)" to search for literature data bases from China National Knowledge Infrastructure (Jan,1994-May,2005), China Biology and Medicine database (Jan, 1978-May,2008), Chinese Science Periodical Full-text Database (Jan,1989~May,2008) and to use " (^{125}I OR iodine 125) AND (palladium 103 OR ^{103}Pd) AND (prostatic neoplasm* OR prostate cancer* OR prostatic cancer*) " to search for literature data bases from PubMed (Jan, 1966-May,2008) and Cochrane library (The first phase in 2008) and EMBASE (Jan,1974-May, 2008).

Searching words, including two parts of targeting disease and interventions, were adjusted in specific database. Main subject words [Medline (MeSH), EMBAE (EMTREE)] self-selected words were used for all searches methods of which were determined by multiple pre-searching.

We manually searched for the data base from "Chinese Journal of Radiation Oncology", " International Journal of Radiation Medicine and Nuclear Medicine", "Journal of Nuclear and Radiochemistry ", " Chinese Journal of Radiological Medicine and Protection", "International Journal of Urology and Nephrology", "Journal of Clinical Urology", " Chinese Journal of Urology", and " Journal of Modern Urology". The publication date was from January, 1994 to May,2008. We use other search engines, such as Google Scholar, and

Medical Martix, to further search for literatures from internet, and to investigate the references which had been used in the study . We contact with domain expert and corresponding author in order to obtain in other information. We mailed the authors to acquire additional information if the experimental report is unknown or its information lacked.

Lliterature screening and information extraction. Two researchers read the titles and abstracts separately. Read the full text of selected articles after no requirement experiments excluded, in order to find whether the article was suitable. Two researchers check the result of experiment each other. The third researcher determined whether the experiment was suitable when there were controversial between the two researchers. The deficiency information can be supplemented by the telephone or the mail.

The requirement information generally included (1) general characteristics : title, author's name, publication date, literature reference; (2) investigative characteristics: age, pre-therapeutic PSA level, pre-therapeutic AUA score, pre-therapeutic prostate size, administration statu of α -receptor blocking agent and hormone treatment; (3) end point : bPFS, AUA score, the complication of rectum and urinary system.

Quality evaluation. The Cochrane manual 4.2.6 "Quantity evaluation standard for randomized controlled trial" [11] provided technologic methods for evaluating the included literature. (1) Tthe method of random allocation method was correctly or incorrectly used, (2) The method of conceal assignment was correct or incorrect. (3) Was blinding method used? and who was used? (4) Were the patients lost to follow up or withdraw from treatment? Was intention-to-treat (ITT) used?

Three levels were divided on basis of above-mentioned evaluating criterion, level A (low bias): all the evaluated indexes were correct; level B (moderate bias): one or more index (es) had not been described; level C (high bias): one or more index was incorrect or unused.

Statistical analysis. Meta-analysis was performed using RevMan5.0 software. Risk ratio (RR) was used for assess therapeutic effect in the enumeration data, and weighted mean difference (WMD) and standard mean difference (SMD) were used in the measurement data, and 95% confidence interval (CI) was calculated. We assessed the heterogeneity of the included finding with the χ 2 tests. If there was significant homogeneity ($p>0.1$, $I^2<50\%$) in each investigation, fixed effect model is used for meta-analyses. If there was significant heterogeneity ($p<0.1$, $I^2>50\%$), then the source of heterogeneity was searched, and the possible factors were analyzed in the sub-group. If there was significant heterogeneity but not clinical heterogeneity between two groups, the stochastic effect model was used to analyze the data. Heterogeneity was from low quality investigation and sensibility analysis was performed. If there was too large significant heterogeneity between two groups to find the source of the data, descriptive study was used to analyzed the data.

Results

Retrieval results of quality evaluation and general characters. In total 158 related articles were searched out and 124 were weighted. One hundred and ten articles without the related substantial content, duplication, and clinical investigation or remedial investigation were withdrawn after reading of the titles and abstracts. Eight of the left 14 retrieved original articles were excluded due to non-compliance. Six randomized controlled trials[12-17] were finally selected in which a total of 1406 patients with average age of 65-66 years were followed up for more than 12 months (Table 1).

Quantity evaluation. Random method: six trials were randomized.[12-17] Three of them[12,13,15] were computerized randomization and the random allocation method of the other three[14,16,17] were not mentioned.

Allocation concealment: allocation concealment was not mentioned in six trials. [12-17] Blinding: blinding was not used in three trials, [12,13,15] and was not mentioned in other three trials. [14,16,17] Lost, drop out and ITT: lost was mentioned in two trials,[13,15] but ITT was not used (Table 2).

Biological progression-free survival time. The bPFS was reported in three articles[14-16] There was no significant heterogeneity in the articles

Table 1 Characteristics of enrolled studies

Study	Group	Cases	Age range(yrs)	Follow-up(months)	Preimplant PSA(ng/mL)
Herstein.A/2005[12]	I-125	159	65±7	24	7.0±1.9
	Pd-103	155	66±6	24	6.7±1.7
Wallner.K/2002[13]	I-125	55	Approximately 66	at least 12	Approximately 34
	Pd-103	55	Approximately 71	at least 12	Approximately 33
Gretory S/2007[14]	I-125	127	66.4±7.2	52.6(±11.4)	6.4±1.7
	Pd-103	136	65.1±6.6	52.0(±11.4)	6.7±1.9
Wallner.K/2003[15]	I-125	57	65±7	at least 36	7.0±1.9
	Pd-103	58	66±6	at least 36	6.7±1.7
Herstein.A/2008[16]	I-125	130	Not mentioned	at least 24	Not mentioned
	Pd-103	135	Not mentioned	at least 24	Not mentioned
Ghaly. M/2003[17]	I-125	54	66±7	at least 12	Not mentioned
	Pd-103	51	65±6	at least 12	Not mentioned

Study	Preimplant AUA scores	Hormonal therapy(cases)	TRUS volume(cc)	a-blocker taken 6 months after implant(%)
Herstein.A/2005[12]	7.6±7	29/159	34±15	68
	8.2±7	26/155	34±10	63
Wallner.K/2002[13]	Approximately 9.2	Not mentioned	Approximately34.4	44
	Approximately 8.8	Not mentioned	Approximately35.2	41
Gretory S/2007[14]	Not mentioned	No	34.4±11.0	Not mentioned
	Not mentioned	No	34.4±9.5	Not mentioned
Wallner.K/2003[15]	Not mentioned	9/57(pre-implant)0/57(post-implant)	34±15	Not mentioned
	Not mentioned	11/58(pre-implant)0/58(post-implant)	34±10	Not mentioned
Herstein.A/2008[16]	Not mentioned	Not mentioned	Not mentioned	Not mentioned
	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Ghaly. M/2003[17]	7.5±5.7	Not mentioned	36±12	70
	6.9±6.1	Not mentioned	35±10	57

Table 2 Quality assessment of enrolled studies

Study	Randomization	Allocated concealment	Blinding	Loss of follow-up	ITT	Drop out(cases)	Quality grade
Herstein.A/2005[12]	Adequate	Unclear	Not used	No	–	No	C
Wallner.K/2002[13]	Adequate	Unclear	Not used	1(Pd-103) died of cardiac cause	No	Not mentioned	C
Gretory S/2007[14]	Adequate	Unclear	Unclear	Not mentioned	–	Not mentioned	B
Wallner.K/2003[15]	Adequate	Unclear	Not used	4 died of unrelated cause	No	2 were excluded for nonmedical reasons	C
Herstein.A/2008[16]	Adequate	Unclear	Unclear	Not mentioned	–	Not mentioned	B
Ghaly. M/2003[17]	Adequate	Unclear	Unclear	Not mentioned	–	Not mentioned	B

(χ^2= 0.16, p= 0.92, I□ = 0%). The result of meta-analysis in fixed effect model showed that there was no significant difference between ^{125}I group and ^{103}Pd group (RR=0.97, 95% CI = 0.93-1.01) (Fig. 1).

Adverse reactions. Rectal complications. Two articles[13,17] reported that there were rectal complications at one months after seeding implantation. Ghaly et al.[17] reported that rectal complications incidence was higher in the ^{103}Pd group than in the ^{125}I group (p =0.0029). Walner et al.[13] reported that there was no significant difference between these two groups (p =0.39). There were rectal complications at six months after seed implantation in the three articles.[12,13,17] Two of them[12,13] were treated by meta-analysis, there was no significant heterogeneity between the other two literatures (χ^2= 0.49, p = 0.02,

I² = 0%).[12,13] The result of meta-analysis in fixed effect model showed that rectal complications incidence was higher in the ^{125}I group than in the ^{103}Pd group [RR=2.49,95% CI (1.18,5.26)] (Fig. 2). Ghaly et al.[17] reported that there was no significant difference between these two groups (no p value provided). There were rectal complications at 12 months after seed implantation in two articles,[12,13] and there was no significant heterogeneity between them (χ^2= 0.09, p = 0.76, I² = 0%). The result of meta-analysis in fixed effect model showed that there was no significant difference in complications of the urinary system incidence between these two groups (RR=1.53, 95% CI = 0.68-3.45, Fig. 2).

Complications of the urinary system. There were complications of the urinary system at 1 months after seed implantation in two literatures.[13,17] There was no significant heterogeneity between articles (χ^2=1.21, p = 0.27, I² = 21%). The result of meta-analysis in fixed effect model showed that there was no significant difference in complications of the urinary system incidence between two groups (RR=0.69, 95% CI =0.39-1.21, Fig. 3). There were complications of the urinary system at 6 months after seed implantation in two literatures.[13,17] And there was significant heterogeneity between two articles (χ^2= 4.70 , p = 0.03, I² = 79%).The result of meta-analysis in random effect model showed that there was no significant difference in complications of the urinary system incidence between two groups [RR=2.20, 95% CI (0.39, 12.30)] (Fig. 4). One of the articles[13] reported that there were complications of the urinary system at 12 months after seed implantation. There was no significant difference between ^{125}I group and ^{103}Pd group (P=0.37).

AUA score. Three articles[12,13,17] reported the score at 1 months after seed implantation. The AUA score was higher in the ^{103}Pd group than in

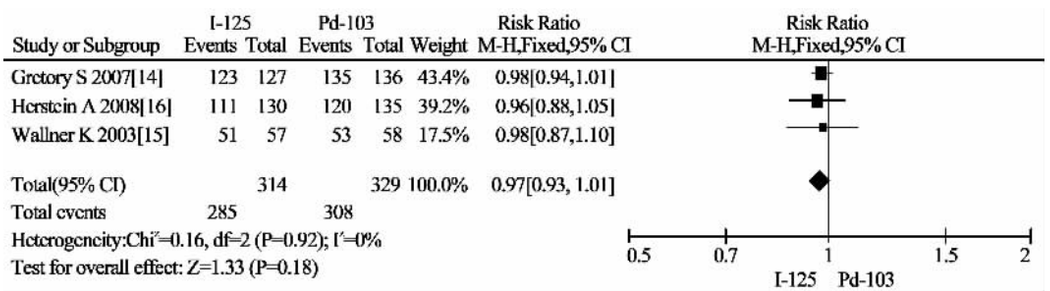

Figure 1 Forest plot of biochemical progression free survival after ^{125}I and ^{103}Pd brachytherapy in low risk prostate cancer

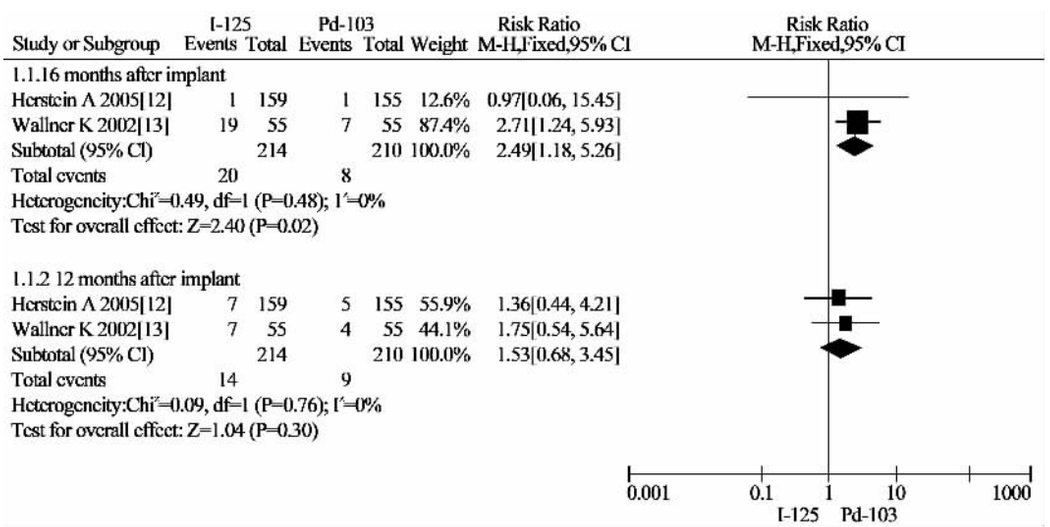

Figure 2 Forest plot of rectal morbidity after ^{125}I and ^{103}Pd brachytherapy in low risk prostate cancer

the ^{125}I group. Herstein et al.[12] (P=0.0009) and Ghaly et al.[17] (P=0.035) reported that there was significant difference in AUA score. But Wallner et al.[13] reported there was no significant difference in AUA score at 1 months after seed implantation (p =0.2). Three articles[12,13,17] reported the AUA score at six months after seed implantation. Two of them treated with meta-analysis, there was no significant difference in heterogeneity between them (χ^2= 2.11, p = 0.15, I^2 = 53%). The result of meta-analysis in fixed effect model showed that the AUA score was higher in the ^{125}I group than in the ^{103}Pd group (RR=2.83, 95% CI=1.13-4.54). Ghaly et al.[17] reported a similar result (no p value). Two articles[12,13] reported the AUA score at 12 months after seed implantation., and there was no significant difference in heterogeneity between them (χ^2= 0.01, p = 0.92, I^2 = 0%). The result of meta-analysis in fixed effect model showed that there was no significant difference in AUA score between two groups (RR=0.85, 95% CI=-0.75-2.46, Fig. 5).

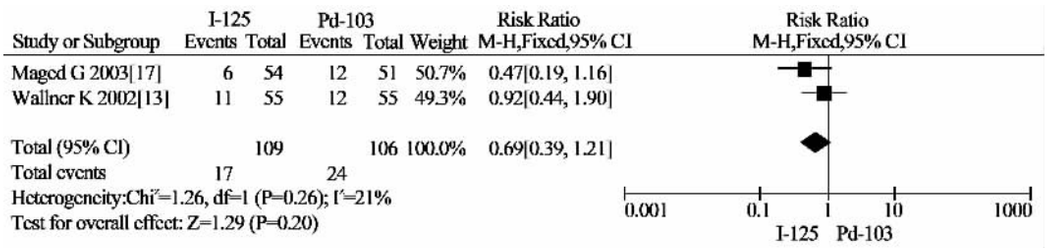

Figure 3 Forest plot of urinary morbidity one month after ^{125}I and ^{103}Pd brachytherapy in low risk prostate cancer

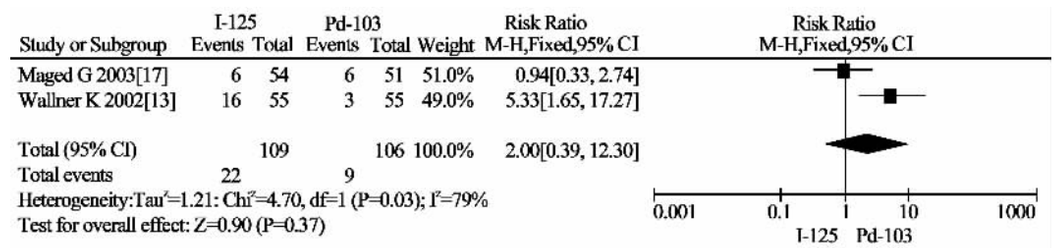

Figure 4 Forest plot of urinary morbidity six months after ^{125}I and ^{103}Pd brachytherapy in low risk prostate cancer

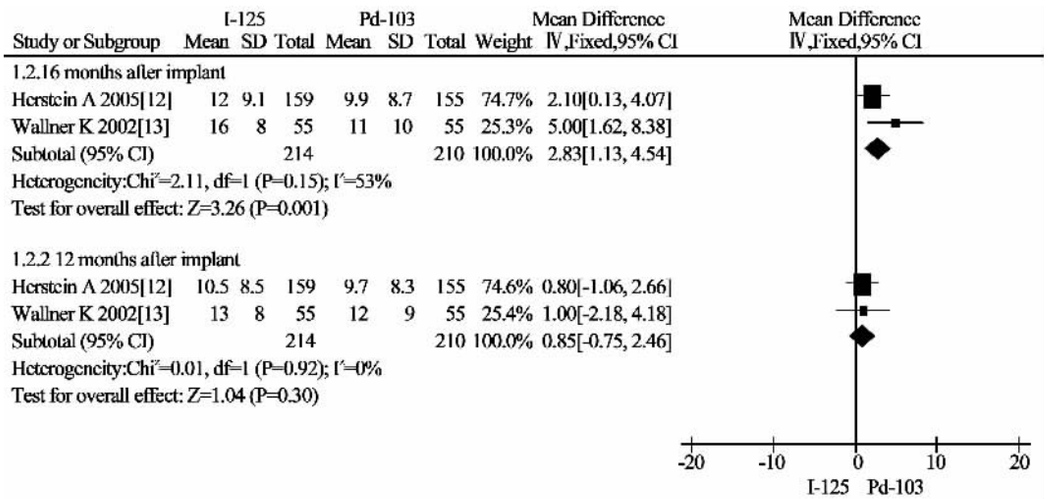

Figure 5 Forest plot of AUA scores after ^{125}I and ^{103}Pd brachytherapy in low risk prostate cancer

Discussion

Brachytherapy is the main treatment for early-stage prostate cancer since 20th century. ^{125}I and ^{103}Pd are the most commonly used radionuclides for prostate brachytherapy. This study demonstrates that the individual effects of ^{125}I and ^{103}Pd brachytherapy for bPFS were similar. At one month after seed implantation, the adverse effects were more serious in the ^{103}Pd group than in the ^{125}I group. At six months after seed implantation, the adverse effects were much more serious in the ^{125}I group than in the ^{103}Pd group. This would be attributed to a shorter half-life in ^{103}Pd group. No significant difference in adverse effects was found between the two groups at 12 months after seed implantation.

The quality of the articles selected in this study was not satisfied. The finding would be biased by different factors: (1) the blinding method was used in three of the studies included,[12,13,15] the other three[14,16,17] was unclear whether the blinding method was used or not. It maybe result in implementation bias or measurement bias; (2) Random allocation was used in studies included. Three of them[12,13,15] were computerized randomization, The random allocation method of the other three[14,16,17] were not mentioned; (3) Allocation concealment was not mentioned in all studies, and it maybe result in selection bias; (4) Lost was mentioned in two articles,[13,15] but ITT was not mentioned, it may result in bias of losing in the follow-up; (5) All studies included were come from the USA, and it may result in a lower general adaptability of result. Prostate cancer incidence and death rates vary considerably among region and ethnic groups. The systematic review should included clinical studies from different country and race, in order to reflect differences in efficacy from different radionuclides brachytherapy for prostate cancer.

The study included a small number of clinical studies, which influenced the universality of result. Some of measurement index was not reported sufficiently, it may influence demonstration intension. Wallner et al.[13] and Maged et al.[17] s studies showed AUA score with line graph or column diagram. It was not use of meta-analysis because the specific value was not provided. Hormonal therapy is one of the fundamental treatments for prostate cancer. But there was no descriptive analysis about hormonal therapy in three[13,16,17] clinical trials included. It is necessary to equilibrate the hormonal level in different group, because the dose of hormone may affect therapeutic efficacy, and then we could identification the difference of particles. Otherwise, the adverse reaction, such as urinary system obstruction, can be relieved by α -receptor block agent, and further influenceed AUA score. Three studies[12,13,17] about adverse reaction mentioned the patients in-took α -receptor block agent in the ^{125}I group and the ^{103}Pd group. And it was demonstrated with line graph and column diagram or demonstrated similar situation but no statistical analysis. There were different follow-up time in different studies. Merrick et al.[14] provided bPFS in six years, Wallner et al.[15] and Herstein et al.[16] provided bPFS in three years. The randomized controlled trial should provide survival results every year in the future with long term of following-up and report the detail of end-point. In addition, the randomized controlled trial should investigate and report the clinical economics, survival quality of the patients with cancer and negative result incidence of ^{125}I and ^{103}Pd brachytherapy for prostate cancer. Finally, we could understand the pros and cons of two nuclide sand provide guidance for clinical decision.

In all, this study demonstrates that the individual effects of ^{125}I and ^{103}Pd brachytherapy for low risk prostate cancer are similar; however the side effects are different at different time points after treatment. The clinical economics must be considered in clinical seed selection

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