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Analysis of postoperative PSA changes after ultrasound-guided permanent [^{125}I] seed implantation for the treatment of prostate cancer

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ABSTRACT. The aim of this study was to explore postoperative changes in prostate-specific antigen (PSA) levels and risk factors that influence the clinical effects of ultrasound-guided permanent [^{125}I] seed implantation in the treatment of prostate cancer. From July 2009 to December 2012, 41 prostate cancer patients who underwent transrectal ultrasound-guided [^{125}I] seed implantation were followed up for 3-56 months. The patients were divided into 2 groups according to their results: group A, benign rebound group, 31 cases; and group B, biochemical relapse group, 10 cases. A blood analysis of group A showed that the initial PSA rise after a nadir occurred postoperatively at 16.8 ± 1.2 months, and in 65.8% (27/41) patients the rise occurred during 15-27 weeks. For group B, the initial PSA rise after a nadir occurred postoperatively at 30.2 ± 2.1 months, and the difference in the time parameter of the initial PSA rise after the nadir was statistically significant between the 2 groups ($P < 0.01$). During treatment, age was shown to be a risk factor for group

A ($P = 0.0027$, $P < 0.01$). Postoperative changes in PSA levels after ultrasound-guided permanent [^{125}I] seed implantation contributed to the assessment of the clinical treatment effects.

Key words: [^{125}I] prostate cancer; Radiotherapy; Ultrasound guidance; PSA

INTRODUCTION

In recent years, prostate cancer has become a common diagnosis in urology departments because of the wide application of screening technology. The incidence of prostate cancer is increasing, and according to 2010 U.S. statistics, it accounts for approximately 28% of cancer cases in men (Jemal et al., 2010). Treatment for middle- and advanced-stage prostate cancer is mainly endocrinotherapy, and for early stage prostate cancer, radiotherapy, surgery, and observation and expectation treatments are employed. For low-risk prostate cancer patients with early stage disease (T1-T2a), a well-differentiated tumor (Gleason score, 2-6), and low prostate-specific antigen (PSA) levels (<10 μg/L), ultrasound-guided permanent [^{125}I] seed implantation is increasingly used (Ash et al., 2000; Morris et al., 2009). This is an effective treatment (Heidenreich et al., 2008), as there is no statistically significant difference between the clinical effects of external radiotherapy and radical surgery for prostate cancer (Potters et al., 2004; Block et al., 2006), and changes in PSA levels are important for evaluating treatment efficacy. A large number of clinical studies in other countries (Chira et al., 2013) have shown that after ultrasound-guided permanent [^{125}I] seed implantation, blood PSA shows a transient elevation, which is a benign rebound, and not a biochemical relapse of the tumor. However, there are few reports examining this problem. We carried out a retrospective analysis of 41 patients treated with permanent [^{125}I] seed implantation for prostate cancer, and examined changes in blood PSA levels to evaluate its clinical therapeutic effects.

MATERIAL AND METHODS

Cases

From July 2009 to December 2012, we carried out a retrospective analysis of 41 prostate cancer patients from the Tumor Hospital Affiliated to Zhengzhou University who were treated with transrectal ultrasound-guided [^{125}I] seed implantation. The patients were aged 54-83 years and had a mean age of 69.2 ± 0.9 years. This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Zhengzhou University. Written informed consent was obtained from all participants.

The patients had pathologically confirmed prostate cancer and preoperative PSA levels of 5.79-35.72 ng/mL, (mean, 14.52 ± 0.77 ng/mL), clinical stage T1c-T2b, a Gleason score of 4-7 points, and a follow-up period of 3-56 months. The patients were divided into 2 groups according to their follow-up results: group A, the benign rebound group consisted of 31 cases, where blood PSA temporarily increased to ≥0.2 ng/mL after treatment, and then decreased to the nadir and remained stable; group B, the biochemical relapse group consisted of 10 cases, where the blood PSA gradually dropped to the nadir after treatment. Patients were also included in this latter group if the blood PSA value achieved a nadir, increased to at least 0.2 ng/mL greater than

that nadir, and then showed no decrease or need for remedial treatment following clinical assessment. Exclusion criteria included synchronous hormone therapy or radiotherapy.

Permanent [^{125}I] seed implantation

Three days before particle implantation, oral antibiotics were administered to the patients, and a cleaning enema was performed 1 day before or on the day of surgery. A prostate ultrasound, CT, or MRI was performed initially to evaluate each patient and to determine the number of particles that needed to be implanted. The patients underwent routine preoperative preparations including intramuscular injections of analgesic drugs, sacral anesthesia, placement in the dorsal lithotomy position, and insertion of a conventional indwelling Foley catheter with the appropriate filling of the bladder, after which a Philips HD11 color Doppler ultrasound instrument with a via-rectum diplane probe (Philips Electronics, Amsterdam, Holland) was employed. Guided by transrectal ultrasound, 18G seed implantation needles were inserted side-by-side into different parts and planes of the prostate (Figure 1). The prostate cross section in color Doppler ultrasound after implantation of [^{125}I] seeds was shown in Figure 2. The patients received postoperative symptomatic treatment and infection prevention, and had an indwelling catheter for 1 week. The activity of the [^{125}I] radioactive seeds (nickel titanium alloy jacketing; Chinese Atomic Energy Research Institute, Beijing, China) was 11.9-16.6 MBq.

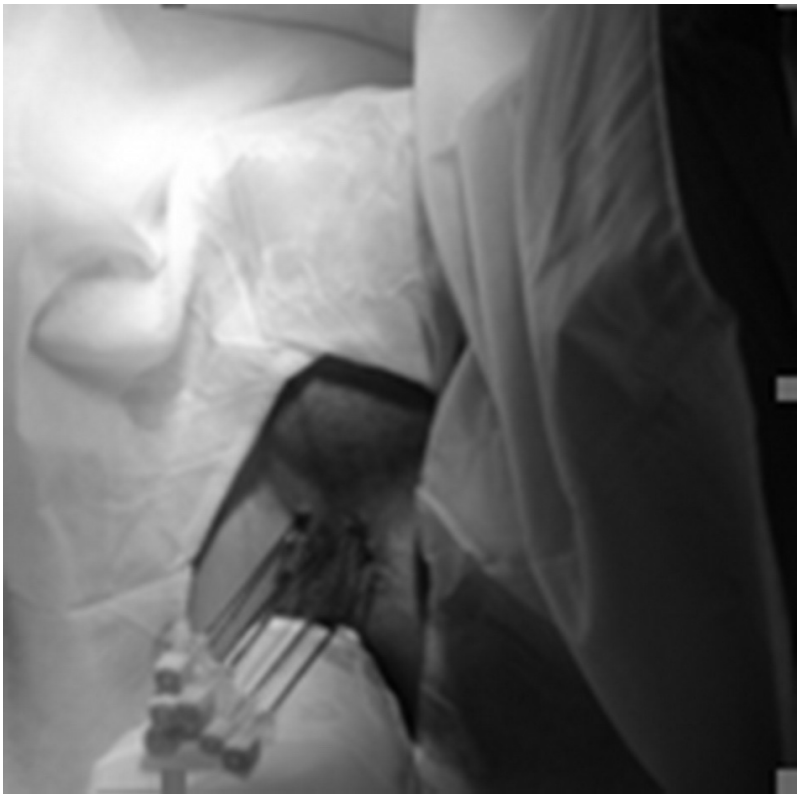

Figure 1. Tissue appearance after the 18G seed implantation needles were punctured into the prostate.

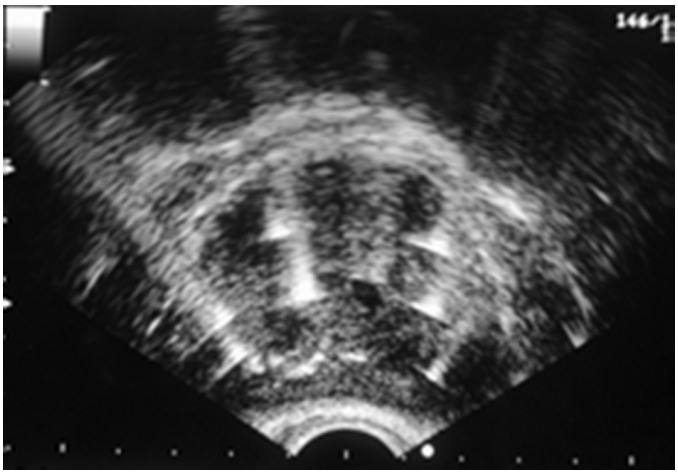

Figure 2. Prostate cross section in color Doppler ultrasound after implantation of [^{125}I] seeds. The [^{125}I] seeds were evenly implanted into the whole prostate tissue at distance intervals of 0.5 cm.

Here, postoperative follow-up: the changes in blood PSA levels were analyzed in the first month and checked once every 3 months during the first year, and finally once every 3-6 months. The patients underwent a radionuclide bone scan, B ultrasound, chest X-ray, and prostate examination every 6-12 months. All the follow-up data were obtained by full-time nurses.

Statistical analysis

Using the SPSS version 17.0 statistical software for data processing, all measurement data are reported as means ± standard deviation; the count data were analyzed using the chi-square test; and the risk factors for treatment effect analysis were examined by using logistic regression analysis. $P < 0.01$ was considered to be significant.

RESULTS

General data

The patients all had preoperative pathologically confirmed prostate cancer, and were aged 54-83 years (mean, 69.2 ± 0.9 years), with preoperative PSA levels of 5.79-35.72 ng/mL (mean 14.52 ± 0.77 ng/mL), clinical stage T1c-T2b, a Gleason score of 4-7 points, and a follow-up period of 3-56 months (Table 1).

Changes in blood PSA levels

Benign rebound group (A): 31 cases (68.9%) experienced benign rebound; 1 patient experienced 3 benign rebounds; and 2 had 2 benign rebounds. Then, PSA gradually decreased to a normal level and remained stable at the nadir value. The initial PSA rise after the nadir occurred postoperatively at 16.8 ± 1.2 months, and in 65.8% (27/41) of patients the rise occurred during 15-27 weeks. After 36 weeks, the PSA of group A (4.8%, 2/41) barely increased. The

duration of the PSA rise was 2.9 ± 0.3 months; the rise velocity was 0.12 ± 0.06 ng/month; and the rise amplitude was 1.2 ± 0.8 ng (Figure 3A).

Biochemical relapse group (B): 10 patients (22.2%) experienced biochemical recurrence (pathologically confirmed as tumor relapse or metastasis), including 2 cases of metastasis and 3 cases of external radiation remedial treatment. The initial PSA rise after the nadir occurred postoperatively at 30.2 ± 2.1 months. The duration of the PSA rise was 2.8 ± 0.6 months; the rise velocity was 0.13 ± 0.04 ng/month; and the rise amplitude was 1.4 ± 0.6 ng (Figure 3B).

Table 1. Patients, characteristics.

Variables	Value
Age (years)	69.2 ± 0.9
Volume of the prostate (cm^3)	30.4 ± 1.7
Preoperative PSA* (ng/mL)	14.52 ± 0.77
Gleason score	
≤6 score	36 (80.0%)
7	9 (20.0%)
Clinical stage	
T1c	24 (53.3%)
T2a	17 (37.7%)
T2b	4 (0.9%)
Implanted seeds (seeds)	65.7 ± 3.2
Density of the implanted seeds (seeds/cm^3)	2.1 ± 0.3
Follow-up (months)	19.3 ± 1.7
Follow-up results	
Benign rebound (group A)	31 (68.9%)
Biochemical relapse (group B)	10 (22.2%)
Clinical effect stable	4 (0.8%)

*PSA: Prostate-specific antigen.

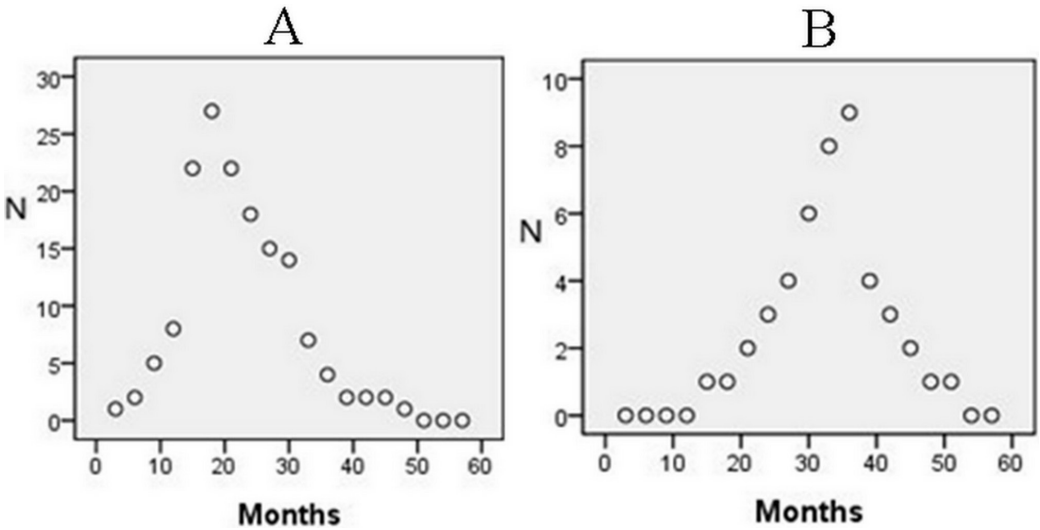

Figure 3. N represents the change in the number of cases in each group corresponding with the variations of the follow-up time. **A.** Benign bounce group. **B.** Biological relapse group.

Logistic regression

During treatment, age was a risk factor for benign rebound (P = 0.0027, P < 0.01), while prostate volume, number of implanted seeds, implanted seed density, preoperative PSA, PSA velocity (PSAV), Gleason score, and clinical stage did not affect the occurrence of benign rebound or biochemical relapse (P > 0.01; Table 2).

Table 2. Factors possibly predictive of bounce or bioquemical failure by logistic regression.

C	Group A			Group B		
	OR	P	95%CI	OR	P	95%CI
Age	0.852	0.0027	0.753-0.926	0.901	0.1628	0.875-1.104
Prostate volume	0.702	0.8526	0.637-0.827	0.826	0.2535	0.601-0.996
Number of seeds	1.143	0.6532	0.843-1.579	0.609	0.3727	0.403-0.829
Density of seeds	0.952	0.1725	0.724-1.235	1.004	0.7186	0.945-1.124
Preoperative PSA	1.032	0.1836	0.679-1.325	0.996	0.3152	0.886-1.214
PSAV[#]	0.953	0.7773	0.476-1.543	0.927	0.5237	0.712-1.135
Gleason score						
≤6 *vs* 7	0.856	0.3623	0.632-1.315	1.034	0.4125	0.876-1.214
Clinical stage						
≤2a *vs* 2b	0.793	0.4324	0.589-1.453	0.965	0.3126	0.705-1.146

[#]PSAV (PSA increasing velocity) = (postoperative PSA bounce peak - postoperative PSA peak vellay) / T, where *T* = interval of postoperative PSA peak valley to bounce peak.

Comparison of groups A and B (Table 3): the difference in the time parameter for the initial rise of PSA after the nadir was statistically significant between the 2 groups (P < 0.01).

Table 3. Comparison between bounce and biochemical failure.

Variables	Group A	Group B	P
PSA nadir before increase (ng/mL)	0.4 ± 0.03	0.5 ± 0.02	P > 0.01
PSA increase time after nadir (month)	16.8 ± 1.2	30.2 ± 2.1	P < 0.01
PSA velocity (ng/month)	0.12 ± 0.06	0. 13 ± 0.04	P > 0.01
PSA delay* (months)	8.2 ± 0.3	7.9 ± 0.6	P > 0.01

*PSA rise after the period duration = lowest value to benign PSA bounce (or biochemical recurrence) peak.

There was no significant difference when parameters such as postoperative PSA nadir, PSAV rise, PSA duration rise, and PSA amplitude rise were compared between the 2 groups (P > 0.01).

DISCUSSION

Ultrasound-guided [^{125}I] radioactive seed implantation is an effective, minimally invasive brachytherapy for prostate cancer (Mitchell et al., 2008; Aaltomaa et al., 2009; Zwahlen et al., 2011). [^{125}I] radioactive seed implantation increases local radiation within the prostate tumor tissue and ensures maximum exposure of the tumor tissue to continuous irradiation while limiting the exposure of surrounding tissues. Therefore, tumor cells are destroyed, but the reaction is localized and not as severe as systemic treatment.

According to Bai et al. (2004), patients that meet the following criteria should be considered for [^{125}I] seed implantation: stage T1 or T2 prostate cancer; cancer confined to the

prostate capsule; tumor diameter of <2 cm; highly or moderately differentiated prostate cancer; advanced age; severe heart and lung disease; and uncontrolled diabetes or other chronic diseases that prevent radical prostatectomy. However, if patients who have undergone transurethral resection of the prostate receive brachytherapy, sphincter damage could lead to urinary incontinence after treatment, which is a relative contraindication for this treatment.

Analysis of postoperative changes in blood PSA levels is important for evaluating treatment effects. According to previous reports (Ciezki et al., 2006), approximately 46.3% of prostate cancer patients will experience postoperative blood PSA benign rebound after [^{125}I] radioactive seed implantation, which is a stress response of prostate tissue to the operation, but does not indicate treatment failure or relapse (Jeon et al., 2012). A number of studies (Todor et al., 2011; Guarneri et al., 2013) have reported that age is an important factor that may influence whether benign rebound occurs, and that the younger the patient the more likely that postoperative blood PSA will show benign rebound. Critz et al. (2003) found that the incidence of benign rebound in patients ≤60 years is twice that of those ≥71 years (57 *vs* 26%; $P < 0.0001$). Thompson et al. (2010) found that 60% of PSA-positive rebound occurred in patients <59 years.

We carried out a retrospective analysis of 41 cases of permanent [^{125}I] seed implantation for the treatment of prostate cancer (follow-up, 3-56 months) and analyzed changes in blood PSA levels. Thirty-one cases (68.9%) experienced benign rebound; 1 patient experienced 3 benign rebounds; and 3 experienced 2 benign rebounds. Ten patients (22.2%) experienced biochemical relapse (pathologically confirmed as tumor recurrence or metastasis), including 2 cases of metastasis, and 3 cases of external radiation for salvage therapy. This study analyzed changes in blood PSA levels, which provide an important reference for the clinical assessment of treatment effects.

Through this retrospective analysis, we found that 67.6% of PSA-positive rebound occurred in patients with an average age of 66.3 years, consistent with the results of Crook et al. (2007), which showed that benign rebound occurred at an average age of 66 years. Statistical analysis revealed that in group A, the initial PSA rise after the nadir occurred postoperatively at 16.8 ± 1.2 months. In 65.8% (27/41) of patients the rise occurred during 15-27 weeks, and after 36 weeks, the PSA level of group A (4.8%, 2/41) barely rose. However, in group B (biochemical relapse group), the initial PSA rise after the nadir occurred postoperatively at 30.2 ± 2.1 months, and there was a statistically significant difference between the 2 groups ($P < 0.01$). This is consistent with the results of Mazeron et al. (2012) where the follow-up of 198 prostate cancer patients who underwent [^{125}I] radioactive seed implantation showed that the difference in the time parameter of the initial PSA rise after the nadir was statistically significant between the benign rebound and the biological relapse groups ($P < 0.0001$), while parameters such as postoperative PSA nadir, PSAV rise, PSA duration rise, and PSA amplitude rise showed no significant difference between the 2 groups ($P > 0.01$), consistent with our results. Zhang et al. (2012) found that 17 of 18 patients with [^{125}I] radioactive seed implantation had no PSA upward trend during the 3-57 month follow-up period, and no postoperative PSA benign rebound was observed, which was inconsistent with our study, and may be due to differences in the clinical stage of the patients and the reaction conditions following [^{125}I] radioactive seed implantation.

Among the cases of recurrence in this study, the Gleason scores of the patients were relatively high when the different biological characteristics of individual tumors were taken into account. Increasing the radiation dose or combining the treatment with an adjuvant thera-

py might improve the therapeutic effects, but further studies are needed to confirm this.

Traditionally, it was thought that prostate resection would result in the best long-term survival rate for early localized prostate cancer. However, postoperative complications, such as urinary incontinence, sexual dysfunction, and reduced quality of life made patients and doctors cautious of choosing radical resection. Current international clinical observations of prostate brachytherapy suggest that a long-term survival rate similar to radical prostatectomy has been achieved. This therapy is also preferred for its lower rates of urinary incontinence and sexual dysfunction (Marcu and Gowda, 2013), and is especially suitable for young or frail elderly patients who are too weak to tolerate radical surgery.

There are some limitations of this study; we need larger samples of follow-up patients for statistical analysis, and we did not statistically analyze preoperative and postoperative clinical manifestations in patients, such as improvement of urethral symptoms or rectal complications, both of which would be required for more comprehensive and thorough research.

CONCLUSIONS

Radioactive seed implantation has a number of advantages for the treatment of prostate cancer, such as fewer complications, less trauma, a clinical curative effect, and low risk, which are worth promoting. Changes in postoperative blood PSA levels can be useful in preliminary assessments of the clinical effect of ultrasound-guided [^{125}I] radioactive seed implantation, and can provide a reference point and basis for further treatment.

Conflicts of interest

The authors declare no conflict of interest.

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