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Six-year Experience of Permanent Prostate Brachytherapy for Clinically Localized Prostate Cancer

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ABSTRACT

This report presents the outcome of prostate permanent brachytherapy (PPB). One hundred and seventy-two patients with clinically localized prostate cancer were treated with permanent brachytherapy using iodine-125 seeds (125-I) at Hiroshima University Hospital from July 2004 to June 2010. This study evaluated the efficacy of PPB in these patients. The median patient age was 69 years (range 53 to 82 years), the median prostate-specific antigen (PSA) value before biopsy was 6.75 ng/ml (range 3.5 to 47.9 ng/ml), and the median prostate volume was 23.1 ml (range 10.1 to 57 ml). The median follow-up was 37 months (range 1 to 72 months). The serum PSA levels decreased continuously after PPB throughout the entire follow-up period in 97% of patients without neoadjuvant hormonal therapy. No relapse occurred during the follow-up period in patients at low risk. Our 6-year experience suggests that PPB is effective for localized prostate cancer. Patients with prostate cancer that does not require combined External beam radiation therapy (EBRT) have the best chance of responding to treatment.

Key words: *Brachytherapy, Localized prostate cancer, Iodine-125 seed*

Prostate cancer is the second leading cause of male cancer death in the United States, and has become one of the most common types of cancers among Japanese men[12)]. Clinically localized cancer has risen steadily since the beginning of the Prostate specific antigen (PSA) era[2,21)].

Treatment options other than a radical prostatectomy must address both cancer control and quality of life. The use of prostate permanent brachytherapy (PPB) with iodine-125 (125-I) seed has increased steadily in the United States since Holm et al[10)] reported the technique of transrectal echo-guided seed implantation to the prostate in 1983, and several studies have demonstrated the efficacy and safety of PPB[3,7,9)]. The Japanese government legalized the use of 125-I seed source in July 2003, and PPB was first performed at Tokyo Medical Center in September 2003[20)]. It has since become a powerful treatment for clinically localized prostate cancer as an alternative to radical prostatectomy and external beam radiation therapy (EBRT). There is still insufficient evidence about the efficacy, morbidity and safety of PPB in Japan, because PPB was started much later in comparison to the United States and other countries. Therefore, further accumulation of data from patients treated with PPB is required. This center started PPB using 125-I seeding in July 2004, and PPB has been administered in 172 cases with prostate cancer. The present study evaluates the efficacy of PPB 172 patients with localized prostate cancer.

MATERIALS AND METHODS

1) Patients

One hundred and seventy-two patients with clinically localized prostate cancer were treated with permanent brachytherapy using 125-I seeds at Hiroshima University Hospital from July 2004 to June 2010.

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2) Seeds

The treatment used 125-I seeds (Oncoseed ™). The activity of the seeds was 13.1 MBq for cases treated with PPB alone, and 11.0 MBq for cases combined with EBRT, respectively.

3) Treatment procedures

Pre-planning: Pre-planning was performed 1 month before seed implantation. Images of the prostate gland were captured by transrectal ultrasonography (TRUS) at 5mm intervals in the high lithotomy position from the base to the apex.

The captured images were used to make the ideal treatment plan, using the brachytherapy planning system VariSeed 7.1 (Varian Medical Systems, Palo Alto, CA, USA) to calculate a well-designed dose volume histogram (DVH). The planning target volume (PTV) was determined from the margin of the prostate plus 3 mm in the lateral and anterior, and 2 mm in the posterior direction. The locations of seeds were determined according to the modified peripheral loading technique.

Cases with a prostate volume more than 35 ml were evaluated again after 3 or more months of androgen deprivation therapy (ADT).

Intraoperative planning and seed implantation:We captured Ultrasonographic images of the prostate and surrounding organs once more just before seed implantation to determine the most adequate position of seeds based on the results of pre-planning. The seeds were implanted into the prostate under spinal anesthesia, with the patient in the high lithotomy position, using a Mick applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY, USA).

Dose prescription: The indications for PPB alone with a dose of 144 Gy were patients defined as the low risk group based on the D'Amico risk classification[4] (PSA < 10 ng/ml and Gleason score ≤6 and ≤ T2a) or patients with a Gleason score 3+4 and ≤ T2a and PSA <10 ng/ml. EBRT with 45 Gy was added at 1 month in patients with higher risk after 100Gy PPB.

A prescribed dose of 144 Gy was planned to cover ≥ 95% of the planning target volume (PTV) as mono-therapy. The minimal dose received by 90% of the prostate (D90) was 110-120% of the prescribed dose. The percentages of prostate volume receiving 100% and 150% of the prescribed minimal peripheral dose (Vp100 and Vp150, respectively) were calculated. The volume of urethra receiving 150% of the prescribed dose (Vu150) and that of rectum receiving 100% dose (Vr100) were also evaluated. Targeted values of these parameters were Vp150 < 50%, Vu150 = 0% and Vr100 = 0%.

PSA evaluation and morbidity: All patients were followed up at 1 month and every 3 months for 3 years after PPB and every 6 months thereafter. Clinical follow-up was started the day following the completion of radiation therapy including combined EBRT. PSA was evaluated and post-treatment morbidity was recorded at each visit.

Post-planning: Pelvic X-ray, chest X-ray and Pelvic Computed Tomography were performed in order to evaluate the position of the implanted seeds, DVH and seed migration at 1 month after seed implantation.

4) Statistical analysis

Biochemical disease-free survival and overall survival curves were generated using the Kaplan-Meier method, and the logrank test was used for comparison. The level of significance was set at $p<0.05$.

RESULTS

The clinical characteristics of the patients are shown in Table 1. The median age was 69 years old (range 53 to 82), the median initial PSA value was 6.75 (range 3.5 to 47.9) ng/ml, and the median prostate volume was 23.1 (range 10.1 to 57) ml. The median follow-up was 37 (range 1 to 72) months and that for 16 patients at risk was 60 months.

Table 1. Characteristics of Patients

Age	53-82 (median 69.5)
Initial PSA (ng/ml)	3.5 - 47.9 (median 6.75)
≤10	137 pts
10-20	29 pts
20<	6 pts
Clinical T stage	
T1c	125 pts
T2a	37 pts
T2b	8 pts
T2c	2 pts
Prostate volume (ml)	10.1-57 (median 23.1)
Gleason score	
6≥	95 pts
7(3+4)	46 pts
7(4+3)	19 pts
8≤	12 pts
UICC risk classification	
Low	61 pts
Intermediate	93 pts
High	18 pts
Pre-implant ADT	73 pts
Combined EBRT	46 pts
Follow-up (month)	1-72 (median 37)

The median PSA level in 99 patients without neoadjuvant androgen deprivation therapy gradually decreased to 0.42 ng/ml at 4 years and 0.19 ng/ml at 5 years after PPB. In 96 of 99 patients (97.0%), the PSA level decreased even at 36 months after PPB.

The 5-year overall survival and biochemical freedom from recurrence (BFR) were 96.9% and 95.8%, respectively (Fig. 1). Biochemical

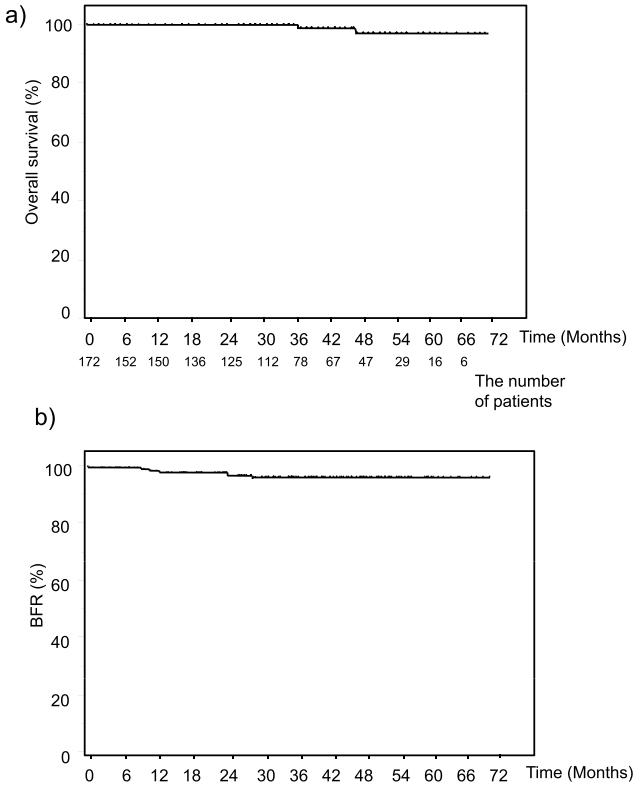

Fig. 1. (a) Overall survival in 172 patients. (b) Biochemical freedom from recurrence in 172 patients.

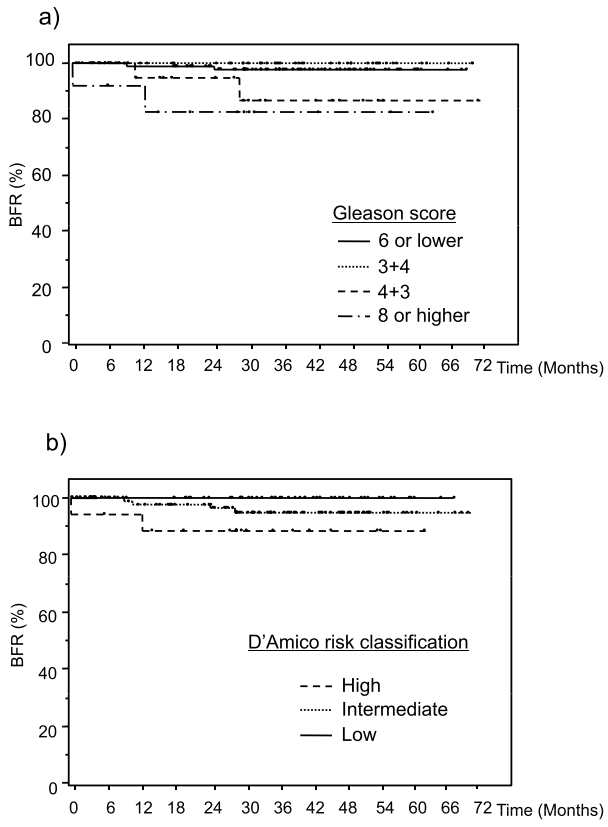

Fig. 2. (a) Biochemical freedom from recurrence based on a Gleason score of 6 or lower, 3+4, 4+3 and 8 or higher. (b) Biochemical freedom from recurrence based on a D'Amico risk classification of high, intermediate and low.

recurrence was observed in 6 patients. Androgen deprivation therapy was initiated in all of them after the detection of recurrence and the serum PSA decreased to an undetectable level. Three of those patients relapsed and were treated with chemotherapy using docetaxel. During the follow-up period, 2 patients died from other malignancies, lung cancer and malignant lymphoma, respectively. No patient died from progression of prostate cancer. No patient died within a year after the seeds were implanted.

Fig. 2 shows BFR after PPB based on the Gleason score. The 5-year BFR was 97.4%, 100%, 86.8% and 80.8% in patients with a Gleason score 6 or lower, 7 (3+4), 7 (4+3), and 8 or higher, respectively (p=0.0053, Gleason score 6 or lower versus 8 or higher; p=0.0018, Gleason score 7 (3+4) or lower versus 7 (4+3) or higher; Fig. 2a). Fig. 2b shows the BFR based on the D'Amico risk classification[4]. 5-year BFR in patients at low, intermediate and high risk were 100%, 94.7% and 88.5%, respectively. While all patients at low risk and 66 of those at intermediate risk were treated with monotherapy, all of those at high risk and 27 of those at intermediate risk were treated with EBRT combined therapy. The 5-year BFR in those treated with monotherapy was 98.9%, significantly higher than in those treated with EBRT combined therapy (88.3%, p=0.0027; Fig. 3).

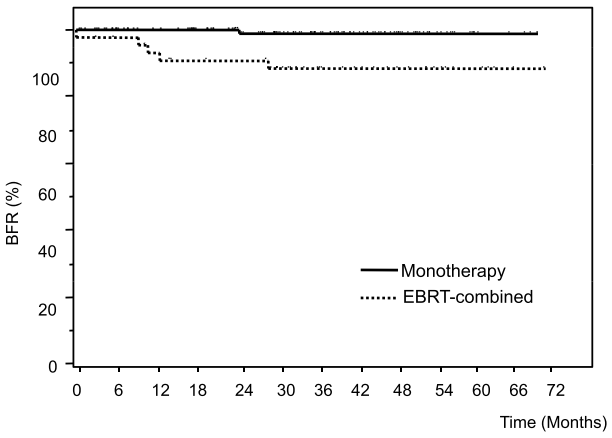

Fig. 3. Biochemical freedom from recurrence based on monotherapy or EBRT combined therapy.

DISCUSSION

The present study showed the outcomes of patients over a 6-year period treated with PPB for clinically localized prostate cancer. Several studies have shown the long-term outcome of PPB. Grimm et al[7] showed that the 10-year BFR of patients with low risk prostate cancer after PPB without combined EBRT was 87%. Taira et al[26] and Potters et al[19] reported that the 12-year

overall survival after PPB for their entire cohorts were 72.6% and 81%, the disease-specific survival rates were 98.2% and 93%, and the BFR were 72.6% and 78%, respectively. Although documentation of longer term follow-up is required in the future, the current results of biochemical control for patients treated with PPB alone are consistent with those previous studies. Iannuzzi et al[11] showed that the nadir of serum PSA level continued to decrease for 4-5 years after PPB, and the nadir was 0.2-0.5 ng/ml. The median PSA level in the current series gradually decreased to 0.42 ng/ml at 4 years and 0.19 ng/ml at 5 years after PPB. These data indicate that PPB is a successful treatment option in men with clinically localized prostate cancer. Previous studies have shown that PPB is effective especially for clinically localized prostate cancer in low risk patients. Kollmeier et al[14] showed that low-risk patients who receive an optimal dose have a 94% BFR at 8 years, demonstrating the importance of patient selection and implant quality.

Since a primary Gleason grade 4 was reported as a predictive factor for biochemical recurrence[28], BFR was evaluated based on the Gleason score (Fig. 2a). The 5-year BFR in patients with Gleason score 7 (3+4) or lower was significantly better than that in those with Gleason score 7 (4+3) or higher. These results are in accord with those of previous studies.

The 5-year BFRs based on D'Amico risk classification in the current series were 100%, 94.7% and 88.5% at low, intermediate and high risk, respectively (Fig. 2b). There was no statistically significant difference between the BFR of these patients because of the short follow-up period. However, no low risk patient has relapsed, suggesting that the outcome for low risk patients is consistent with the results of previous studies.

The efficacy of EBRT combined with PPB has been controversial. Some previous studies have shown the benefit of EBRT combined with PPB even for patients with intermediate or high risk prostate cancer[15,16,23]. Sylvester et al[24,25] showed that the long-term follow-up data demonstrated an improvement of biochemical control by combined EBRT after PPB. On the other hand, Blasko et al[1] reported that there was no significant improvement in the BER between monotherapy and EBRT combined therapy in each of the risk groups. Furthermore, Kalakota et al[13] demonstrated a decline of the threshold of late rectal toxicity with combined EBRT. The current data (Fig. 3) showed that the 5-year BFR in patients treated with monotherapy was significantly higher than in those treated with EBRT combined therapy. Furthermore, 5 of 6 (83.3%) relapsed cases were cases treated with combined EBRT. Kollmeier et al[14] demonstrated that monotherapy with high implant quality in low risk prostate cancer patients achieves optimal outcomes. Stock et al[22] and D'Amico et al[5] demonstrated the effectiveness of PPB combined with both ADT and EBRT for high risk patients. On the other hand, several studies reported that supplemental ADT was significantly associated with the risk of all-cause mortality and the risk of myocardial infarction[6,8,18]. Age and a past history of cardiovascular disease should be considered in cases with ADT for decreasing prostate. Although the indications for PPB without additional treatment are important, it is still inconstant between institutes. Munro et al[17] demonstrated that PPB monotherapy achieves good biochemical control over 10 years after implant for clinically localized prostate cancer in patients with Gleason score 7 that are at intermediate risk. Taira et al[27] reported that most intermediate risk patients with more than two risk factors received combined EBRT, and that patients with more than two risk factors had a slightly greater risk of prostate cancer-specific mortality. These reports suggest that most patients in the current series who underwent PPB were those with low risk or with intermediate risk with only one risk factor. Physicians must select the optimal treatment for cases with many risk factors because there are several options besides PPB for treating clinically localized prostate cancer, including radical prostatectomy and other radiation therapy. It is necessary to define carefully the indications for PPB to achieve optimal outcomes.

In addition, it is important to consider other malignancies in the adjacent ogans after PPB. Liauw et al[15] reported the possibility of a minor risk of developing bladder cancer and colorectal cancer. Cystourethroscopy and colon fiberscopy are conducted for all patients before PPB and for those who show hematuria or rectal bleeding after PPB. There was one patient who developed bladder cancer and another with colorectal cancer after PPB and both were curable.

In summary, our 6-year experience suggests that PPB is an effective option for localized prostate cancer, especially for patients classified as low risk. Patients with prostate cancer that do not require combined EBRT have the best chance of response. Further follow-up is needed to evaluate the long-term outcome.

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