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Abstract

From January 2004 to March 2007, 308 patients with clinically localized prostate cancer were treated using iodine-125 (¹²⁵I) seed implantation (permanent brachytherapy) at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. We evaluated the treatment's efficacy and morbidity in 300 prostate cancer patients who were followed up for more than 1 month after brachytherapy. Based on the National Comprehensive Cancer Network (NCCN) guidelines, patients with a prostate volume of less than 40 ml in transrectal ultrasound imaging were classified as low or intermediate risk. The median patient age was 67 years (range 50 to 79 years), the median prostate-specific antigen (PSA) value before biopsy was 6.95 ng/ml (range 1.13 to 24.7 ng/ml), and the median prostate volume was 24.33 ml (range 9.3 to 41.76 ml). The median follow-up was 18 months (range 1 to 36 months) and the PSA levels decreased in almost all patients after brachytherapy. Although 194 of 300 patients (64.7%) complained of difficulty in urination, pollakisuria/urgency, miction pain, and/or urinary incontinence, all of which might be associated with radiation prostatitis during the first month after brachytherapy, these symptoms gradually improved. ¹²⁵I seed implantation brachytherapy is safe and effective for localized prostate cancer within short-term follow up.

KEYWORDS: localized prostate cancer, brachytherapy, prostate specific antigen, urinary morbidity

Original Article

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From January 2004 to March 2007, 308 patients with clinically localized prostate cancer were treated using iodine-125 (¹²⁵I) seed implantation (permanent brachytherapy) at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. We evaluated the treatment's efficacy and morbidity in 300 prostate cancer patients who were followed up for more than 1 month after brachytherapy. Based on the National Comprehensive Cancer Network (NCCN) guidelines, patients with a prostate volume of less than 40 ml in transrectal ultrasound imaging were classified as low or intermediate risk. The median patient age was 67 years (range 50 to 79 years), the median prostate-specific antigen (PSA) value before biopsy was 6.95 ng/ml (range 1.13 to 24.7 ng/ml), and the median prostate volume was 24.33 ml (range 9.3 to 41.76 ml). The median follow-up was 18 months (range 1 to 36 months) and the PSA levels decreased in almost all patients after brachytherapy. Although 194 of 300 patients (64.7%) complained of difficulty in urination, pollakisuria/urgency, miction pain, and/or urinary incontinence, all of which might be associated with radiation prostatitis during the first month after brachytherapy, these symptoms gradually improved. ¹²⁵I seed implantation brachytherapy is safe and effective for localized prostate cancer within short-term follow up.

Key words: localized prostate cancer, brachytherapy, prostate specific antigen, urinary morbidity

In the past decade, brachytherapy has been added to the armamentarium for the treatment of localized prostate cancer by the technical development of transrectal ultrasound-guided transperineal seed implantation. In July 2003, the Japanese government legalized the use of iodine-125 (¹²⁵I) seed source. From January 2004 through February 2007, 300

patients with clinically localized prostate cancer were treated with permanent brachytherapy by using ¹²⁵I seed at our institution. In this study, we evaluated the efficacy and morbidity of 300 localized prostate cancer patients who were followed up for more than 1 month after ¹²⁵I seed implantation brachytherapy.

Materials and Methods

Treatment criteria. From January 2004 through February 2007, 300 patients with clinically

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localized prostate cancer were treated using ^{125}I Seed implantation (permanent brachytherapy) at Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. Based on the National Comprehensive Cancer Network (NCCN) guidelines, we defined the indications for brachytherapy as low-risk group (PSA < 10 ng/ml and Gleason score ≤ 6 and $\leq \text{T2a}$) or intermediate-risk group (PSA: 10–20 and/or Gleason score 7 and/or T2b–T2c).

Pre-planning. Pre-planning is an outpatient procedure usually performed 1 month before seed implantation. During the pre-planning, transrectal ultrasound (TRUS), a volumetric study of the prostate gland was performed with the patients in the dorsal lithotomy position; the prostate gland was scanned at 5-mm intervals from the proximal seminal vesicles/base of the prostate gland to the apex using a biplanar ultrasound probe (ProSound SSD-5500, Aloka, Tokyo, Japan). The captured images were digitized with a planning computer (Fig. 1). The treatment planning was performed using the brachytherapy planning system VariSeed 7.1 (Varian Medical Systems, Palo Alto, CA, USA) to calculate the well-designed dose volume histogram (DVH). The gross target volume (GTV) was defined as the prostate itself visualized on the TRUS images. The planning target volume (PTV) was determined from the GTV plus a treatment margin of 3 mm in the lateral direction. We set the treated volume to include the PTV

within the prescribed isodose (145 Gy), using a modified peripheral loading technique.

Neoadjuvant hormonal therapy. In cases where prostate volume was over 40 ml or where adequate dose volume histogram could not be calculated in pre-planning, luteinizing hormone-releasing hormone (LH-RH) agonist was administered for periods of 3–6 months to reduce prostate volume.

Seed implantation. The seed implantation was performed under spinal anesthesia, with the patient in the extended lithotomy position, similar to the position in pre-planning. A Mick applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY, USA) was used to deposit the seeds. The activity of the ^{125}I seed source was 0.33 mCi/seed.

PSA evaluation and morbidity. All patients were followed up at 1 month and every 3 months in the first year after brachytherapy and every 6 months thereafter. Clinical follow-up was started from the day of brachytherapy. PSA was evaluated and urinary morbidity (difficulty in urination, pollakisuria/urgency, miction pain, and urinary incontinence) was recorded at each visit, according to the National Cancer Institute common terminology criteria for adverse events version 3.0 (NCI-CTCAE v3.0).

Statistical analysis. Statistical analysis for differences in prostate volume reduction after LH-RH agonist was performed using Fisher's test using StatView J5.0 (SAS Institute, Cary, NC, USA).

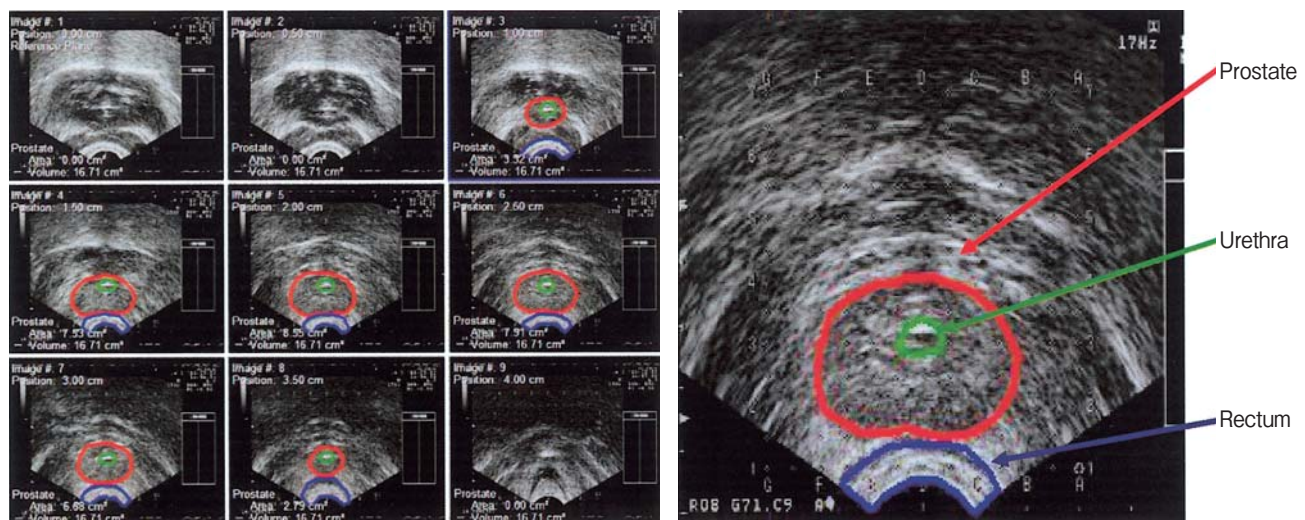


Fig. 1 Transrectal ultrasound images in pre-planning study.

Differences were regarded as statistically significant at p values less than 0.05.

Results

The patients' clinical characteristics are shown in Table 1. Of the 300 patients, 155 were placed into the low-risk group and 127 into the intermediate-risk group. The median age was 67 years (range 50 to 79 years), the median PSA value before biopsy was 6.95 ng/ml (range 1.13 to 24.7 ng/ml), and the median prostate volume was 24.33 ml (range 9.3 to 41.76 ml). Of the 129 patients receiving hormonal therapy, 56 received LH-RH agonist to reduce volume and subsequently experienced a 31.2% reduction (Fig. 2; reduction from 37.0 ± 6.67 to 25.59 ± 5.41 ml, $p < 0.0001$). The median follow-up was 18 months (range 1 to 36 months), and the PSA levels gradually decreased after brachytherapy (Fig. 3). The average PSA level was 0.57 ± 0.38 ng/ml in the low-risk group and 0.78 ± 0.41 ng/ml in the intermediate-risk group at 30 months after brachytherapy. Although 194 of the 300 patients (64.7%) complained of difficulty in urination, pollakisuria/urgency, miction pain, and/or urinary incontinence, all of which might be associated with radiation prostatitis during the first month after brachytherapy (Fig. 4). Most urinary symptoms were generally grade 1 according to NCI-CTCAE version 3.0, and the degree of these symptoms gradually improved. During the follow-up, 2 patients developed

urinary obstruction requiring catheterization. One patient improved gradually after receiving medication with an alpha-blocker, the other still required catheterization 11 months after brachytherapy.

Discussion

Prostate brachytherapy has been increasingly utilized as the definitive treatment for clinically localized prostate cancer. The results of prostate brachytherapy have been reported to be as favorable as the those

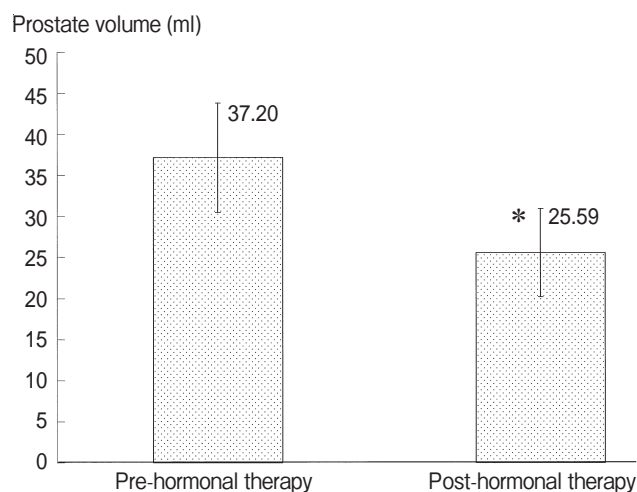


Fig. 2 Comparison of prostate volume pre and post hormonal therapy ($p < 0.0001$).

Table 1 Classification of patients

Age	: 50–79 y.o	(median: 67 y.o)
PSA (diagnosed)	: 1.13–24.7 ng/ml	(median: 6.95 ng/ml)
Prostate volume	: 9.3–41.76 ml	(median: 24.33 ml)
Follow-up	: 1–36 month	(median: 18 month)
Hormonal Tx No	: 171 pts	
Yes	: 129 pts	
PSA		
≤ 10 ng/ml	: 235 pts	
10–20 ng/ml	: 59 pts	
≥ 20 ng/ml	: 6 pts	
Gleason score		
≤ 6	: 188 pts	
= 7	: 100 pts	
≥ 8	: 12 pts	

pts: patients

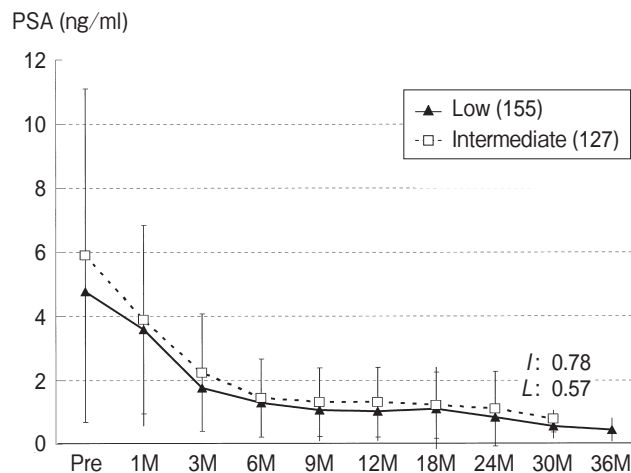


Fig. 3 PSA response after brachytherapy.

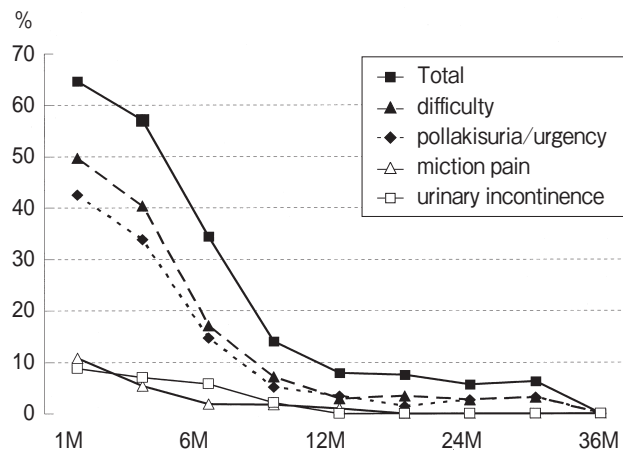


Fig. 4 Morbidity after brachytherapy.

for the most positive radical prostatectomy series, with lower incidences of urinary incontinence and sexual dysfunction [1-4]. Based on NCCN guidelines, localized prostate cancer was classified into 3 groups: 1) Low-risk group (PSA < 10 ng/ml and Gleason score ≤ 6 and $\leq T2a$); 2) Intermediate-risk group (PSA: 10-20 and/or Gleason score = 7 and/or T2b-T2c); 3) High-risk group (PSA: > 20 ng/ml and/or Gleason score ≥ 8 and/or $\geq T3a$). The guidelines recommend that seed implantation monotherapy is indicated for the low-risk group. On the other hand, the high-risk group should be treated with a combination of brachytherapy and external beam radiation therapy. Either brachytherapy alone or in combination with external beam radiation therapy is indicated for the intermediate-risk group, according to percentage of positive cores in the prostate biopsy cancer.

In Japan, the use of ^{125}I seed source was legalized in July 2003. Japanese guidelines for the safe administration of I-125 brachytherapy demonstrated that the radioactivity in the prostate gland after brachytherapy might be within 1,300 MBq, which would indicate that a large prostate volume (over 40 ml) might contraindicate brachytherapy as a monotherapy, and that an administration of neoadjuvant ADT should be considered. Wilson *et al.* reported that neoadjuvant ADT is useful in decreasing the size of prostates greater than 50 to 60 ml in volume and in improving the dosimetry and technical feasibility of brachytherapy [5]. In our study, the administration of LH-RH agonist mono-

therapy reduced prostate volume by 31.2%.

Stone *et al.* reported a significant increase in urinary symptoms and bother scores, which peaked at 6 months and persisted for 2 to 3 years after brachytherapy [6]. These urinary symptoms might be associated with radiation prostatitis, and our data also demonstrated that short-term urinary morbidity, including difficulty in urination, pollakisuria/urgency, miction pain, and/or urinary incontinence, peaked at 1 month after brachytherapy. Most urinary symptoms were generally grade 1 according to NCI-CTCAE version 3.0, except for 2 patients who developed urinary retention (grade 3 morbidity). One patient still requires catheterization, and medications (alpha-blockers and nonsteroidal anti-inflammatory drugs) have not relieved this patient's urinary retention. In this case, trans-urethral resection of the prostate (TUR-p) may be required in the future.

Based on these recommendations and results, our current criteria for brachytherapy are shown in Fig. 5. Although patients hope brachytherapy will reduce morbidity and shorten the hospital stay, we must consider their clinical factors, including PSA, Gleason score, age, and complications. Our indications for this procedure are low or intermediate risk and prostate volume less than 30 ml by trans-abdominal ultrasound imaging. If these factors are present, pre-planning is performed. If adequate DVH is found, brachytherapy alone is chosen. If prostate volume is over 40 ml or the adequacy of DVH cannot be evaluated, LH-RH agonist is administered for 3 to 6 months.

Serum PSA values have been reported to gradually decline after brachytherapy [7]. Previous studies have established that median PSA nadir levels were 0.2-0.5 ng/ml [7, 8] and continue to decrease for at least 4-5 years after brachytherapy [9, 10]. Our data indicated that median PSA levels were 0.57 ng/ml in the low-risk group and 0.78 ng/ml in the intermediate-risk group at 30 months after brachytherapy. Though the PSA levels gradually and satisfactorily decreased, it might be too early to evaluate the PSA nadir and efficacy of brachytherapy.

Conclusion. ^{125}I seed implantation brachytherapy is safe and effective for examining short-term outcomes of localized prostate cancer. LH-RH agonist administration reduced prostate volume. Further follow-up is needed to evaluate the efficacy and late-term morbidity of brachytherapy.

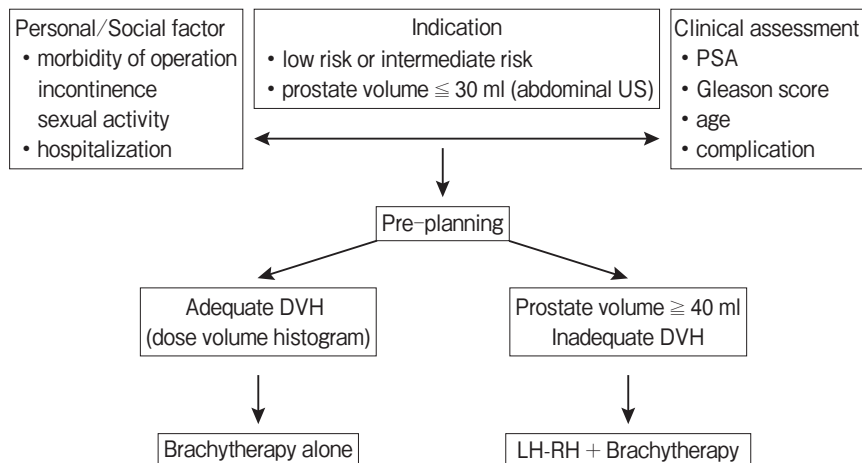


Fig. 5 Current patient selection criteria (Okayama Univ.)

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