Acta Medica Okayama

Volume 61, *Issue* 6 2007 *Article* 4

DECEMBER 2007

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Shin Ebara, *Okayama University*
Daisuke Manabe, *Okayama University*
Yasuyuki Kobayashi, *Okayama University*
Ryuta Tanimoto, *Okayama University*
Takashi Saika, *Okayama University*
Yasutomo Nasu, *Okayama University*
Shirou Saito, *National Hospital Organization Tokyo Medical Center*
Takefumi Satoh, *Kitasato University School of Medicine*
Kenta Miki, *Jikei University School of Medicine*
Katsuyoshi Hashine, *National Hospital Organization Shikoku Cancer Center*
Hiromi Kumon, *Okayama University*

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Abstract

From September 2003 to December 2005, 188 patients who visited our hospital and allied institutions for the purpose of prostate brachytherapy were administrated hormonal therapy for volume reductions before brachytherapy. The pretreatment and posttreatment of prostate volume using a transrectal ultrasound volumetric study and the types and duration of hormonal therapy were analyzed. We administered 91 patients with Luteinizing hormone-releasing hormone (LH-RH) agonist, 49 patients with anti-androgen (bicaltamide/flutamide), and 48 patients with maximum androgen blockade (MAB). The duration of the hormonal therapy was 1-3 months for 49 patients, 4-6 months for 59 patients, 7-9 months for 40 patients, 10-12 months for 32 patients, and over 13 months for 8 patients. Before the initiation of hormonal therapy, the mean prostate volume was 35.12 ml (11.04-78.71 ml), and the average of prostate volume before and after hormonal therapy was 36.79 ml and 24.79 ml, respectively (a 32.4% reduction). The prostate volume reduction rate was 32.0% for the LH-RH agonist only, 18.1% for the anti-androgen only and 41.2% for the MAB. No statistically significant difference was observed for the duration of hormonal therapy between 3 groups. A three-month course of the neoadjuvant LH-RH agonist indicated a sufficient volume reduction effectiveness for a large prostate volume.

KEYWORDS: androgen deprivation therapy, brachytherapy, localized prostate cancer, prostate volume reduction

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*PMID: 18183078 [PubMed - in process]

Acta Med. Okayama, 2007
Vol. 61, No. 6, pp. 335–340

Acta Medica Okayama
http://www.lib.okayama-u.ac.jp/www/acta/

Original Article

The Efficacy of Neoadjuvant Androgen Deprivation Therapy as a Prostate Volume Reduction before Brachytherapy for Clinically Localized Prostate Cancer

Shin Ebara[a], Daisuke Manabe[a], Yasuyuki Kobayashi[a], Ryuta Tanimoto[a], Takashi Saika[a]*, Yasutomo Nasu[a], Shirou Saito[b], Takefumi Satoh[c], Kenta Miki[d], Katsuyoshi Hashine[e], and Hiromi Kumon[a]

[a]Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan,
[b]Department of Urology, National Hospital Organization Tokyo Medical Center, Tokyo 152–8902, Japan,
[c]Department of Urology, Kitasato University School of Medicine, Sagamihara, Kanagawa 228–8555, Japan,
[d]Department of Urology, Jikei University School of Medicine, Tokyo 145–8051, Japan, and
[e]Department of Urology, National Hospital Organization Shikoku Cancer Center, Matsuyama 791–0280, Japan

From September 2003 to December 2005, 188 patients who visited our hospital and allied institutions for the purpose of prostate brachytherapy were administrated hormonal therapy for volume reductions before brachytherapy. The pretreatment and posttreatment of prostate volume using a transrectal ultrasound volumetric study and the types and duration of hormonal therapy were analyzed. We administered 91 patients with Luteinizing hormone-releasing hormone (LH-RH) agonis, 49 patients with anti-androgen (bicaltamide/flutamide), and 48 patients with maximum androgen blockade (MAB). The duration of the hormonal therapy was 1–3 months for 49 patients, 4–6 months for 59 patients, 7–9 months for 40 patients, 10–12 months for 32 patients, and over 13 months for 8 patients. Before the initiation of hormonal therapy, the mean prostate volume was 35.12 ml (11.04–78.71 ml), and the average of prostate volume before and after hormonal therapy was 36.79 ml and 24.79 ml, respectively (a 32.4% reduction). The prostate volume reduction rate was 32.0% for the LH-RH agonist only, 18.1% for the anti-androgen only and 41.2% for the MAB. No statistically significant difference was observed for the duration of hormonal therapy between 3 groups. A three-month course of the neoadjuvant LH-RH agonist indicated a sufficient volume reduction effectiveness for a large prostate volume.

Key words: androgen deprivation therapy, brachytherapy, localized prostate cancer, prostate volume reduction

In the past decade, the results of clinical trials in men treated with a combination of androgen deprivation therapy (ADT) and external-beam radiotherapy (EBRT) have demonstrated a significant benefit [1–3]. As a result, ADT is increasingly used in combination with prostate brachytherapy. In Japan, the use of an iodine-125 (I-125) seed source was approved legally in July 2003, and over 1,000

Received June 18, 2007; accepted August 2, 2007.
*Corresponding author. Phone: +81–86–235–7287; Fax: +81–86–231–3986
E-mail: saika@cc.okayama-u.ac.jp (T. Saika)

patients with clinically localized prostate cancer have been treated with I-125 prostate brachytherapy alone or brachytherapy with external-beam radiotherapy (EBRT) at our hospital and allied institutions. Acute urinary morbidity following brachytherapy has been already reported [4]. Neoadjuvant ADT is often used before prostate brachytherapy for unfavorable geometry, urinary obstructive symptoms and higher risk pathologic features [5, 6]. Especially unfavorable geometries including pubic arch interference are due to the fact that the body structure of Japanese males may be small and the pelvic bone may be narrow compared with Western-European males. Moreover, Japanese guidelines for the safe administration of I-125 brachytherapy has specified that the radioactivity in the prostate gland after brachytherapy should be within 1,300 MBq, which indicates that a large prostate volume over 40 ml may be a contra-indication for brachytherapy as a monotherapy and that the administration of neoadjuvant ADT should be considered. However ADT as a prostate volume reduction has not been well documented, and no definitive indications have been established. The purpose of the present study was to evaluate the efficacy of neoadjuvant ADT as a prostate volume reduction before brachytherapy for clinically localized prostate cancer.

Materials and Methods

From September 2003 to December 2005, 188 patients who visited our hospital and allied institutions for the purpose of prostate brachytherapy were administrated neoadjuvant ADT. The reason for the neoadjuvant ADT included a suboptimal geometry, a large prostate volume, pubic arch interference, urinary symptoms and the need to waiting until I-125 permanent prostate brachytherapy alone or in combination with external-beam radiotherapy could be performed.

Before and after the administration of neoadjuvant ADT, all patients underwent a transrectal ultrasound volumetric study of the prostate gland. All ultrasound studies were obtained with the patients in the dorsal lithotomy position using a biplanar ultrasound probe. For the volumetric study, the prostate gland was scanned at 5-mm intervals from the proximal seminal vesicles/base of the prostate gland to the apex using the brachytherapy planning system VariSeed 7.1 (Varian Medical Systems, Palo Alto, CA, USA) or Interplant 3.3 (CMS, St. Louis, MO, USA).

The relationship between the volume reduction of the prostate gland and the method and durations of ADT were examined in a multivariate analysis. Statistical analysis for the differences in the prostate volume reduction rate between each ADT was performed using the Fisher's Exact test using Statview J5.0 (SAS, Cary, NC, USA). Differences were regarded as statistically significant at p values less than 0.05.

Results

The clinical characteristics of 188 patients are shown in Table 1. The median patient age was 68 years. Patients presented with median pretreatment PSA levels of 7.88 ng/ml, a median Gleason score of 6 and a median pretreatment prostate volume of 35.12 ml. Table 2 presents the type and the duration of androgen deprivation therapy. We administrated 91 patients with Luteinizing hormone-releasing hormone (LH-RH; Leuprolide 3.75 mg or Goserelin 3.6 mg) agonist, 49 patients with anti-androgen (bicaltamide 80 mg or flutamide 375 mg), and 48 patients with maximum androgen blockade (MAB) that was achieved by the deprivation of testicular and adrenal androgen by simultaneous administration of LH-RH and anti-androgen. The duration of the hormonal therapy was 1–3 months for 49 patients, 4–6 months for 59 patients, 7–9 months for 40 patients, 10–12

Table 1 Clinical and pathological characteristics of the patients

Median (range)			
Age (years)		68	(51–85)
Pretreatment PSA (ng/ml)		7.88	(0.7–29.0)
Gleason score		6	(4–9)
Pretreatment prostate volume (ml)		35.12	(11.04–78.71)
Number of patients (%)			
Pretreatment PSA (ng/ml)	< 10	126	(67.0%)
	10–20	57	(30.3%)
	> 20	5	(2.7%)
Gleason score	≤ 6	120	(63.8%)
	3 + 4	36	(19.1%)
	4 + 3	29	(15.4%)
	≥ 8	3	(1.6%)

months for 32 patients, and over 13 months for 8 patients. Every patient underwent the prostate brachytherapy after the neoadjuvant ADT. Table 3 presents the difference in the prostate volume before and after androgen deprivation therapy. The average of prostate volume before and after hormonal therapy was 36.79 ml and 24.79 ml, respectively (a 32.4% reduction, $p < 0.0001$). The prostate volume reduction rate was 32.0% in LH-RH agonist only, 18.1% in anti-androgen only and 41.2% in MAB ($p < 0.0001$). There were no differences between each LHRA agents or antiandrogen agent. We also evaluated the relationship between the prostate volume reduction rate and the duration of hormonal therapy (Fig. 1). Fig. 1A shows that 38 patients (41.8%) who received LH-RH for 1–3 months had only a 27.7% prostate volume reduction, 22 patients (24.1%) who received it for a 4–6 months duration had a 37.4% reduction, and 31 patients (34.1%) who received it for over 7 months had a 34.7% reduction. Fig. 1B shows the differences in the prostate volume after each duration of the anti-androgen drug only: 5 patients (10.2%) who received it for a 1–3 months duration had a 12.5% prostate volume reduction, 19 (38.8%) who received it for a 4–6 months duration had a 22.4% reduction and 25 (51.0%) who received it for over 7 months had a 16.2% reduction. Fig. 1C shows the differences in prostate volume after each duration of MAB. Six patients (12.5%) who received it for a 1–3 months duration had a 33.9% prostate volume reduction, 18 patients (37.5%) who received it for a 4–6 months duration had a 38.5% reduction, and 24 patients (50.0%) who received it for over 7 months had a 45.1% prostate volume reduction. No statistically significant difference was observed between the different durations of androgen deprivation therapy.

Table 2 Type and duration of androgen deprivation therapy (ADT)

		Number of patients (%)	
Type of ADT	LH-RH agonist only	91	(48.4%)
	Anti-androgen only	49	(26.1%)
	MAB	48	(25.5%)
Duration of ADT	1– 3 months	49	(26.1%)
	4– 6 months	59	(31.4%)
	7– 9 months	40	(21.3%)
	10–12 months	32	(17.0%)
	13– months	8	(4.2%)

LH-RH, luteinizing hormone-releasing hormone; MAB, maximum androgen blockade.

Discussion

Over the past decade, prostate brachytherapy has been increasingly utilized as a definitive management for clinically localized prostate cancer. Its results have been reported to be as favorable as those in the most positive radical prostatectomy series, with a decreased incidence of urinary incontinence and sexual dysfunction [7–10].

Neoadjuvant ADT is often used before prostate brachytherapy for unfavorable geometry, urinary obstructive symptoms and higher risk pathologic features [5, 6]. Wilson reported that neoadjuvant ADT is useful in decreasing the size of prostates greater than 50 to 60 ml in volume and improving the dosimetry and technical feasibility of brachytherapy [11]. Several studies reported that a 3 to 8 month duration of neoadjuvant ADT, including an LH-RH agonist with or without an anti-androgen, results in a prostate volume reduction of 21%–54% [12–18]. However, it is still unclear what kind of ADT is most effective and how long the ADT must be administrated for the volume reduction of the prostate.

In the present study, 3 methods of ADT were com-

Table 3 The difference of prostate volume before and after ADT

Type of ADT	before ADT	after ADT	reduction (%)	*P* value
Overall	36.79 ± 15.11	24.79 ± 9.77	32.4	< 0.0001
LH-RH only	35.58 ± 12.80	24.18 ± 10.12	32.0	< 0.0001
Anti-androgen only	26.38 ± 7.79	21.60 ± 6.95	18.1	< 0.0001
MAB	49.70 ± 15.69	29.21 ± 10.15	41.2	< 0.0001

ADT, androgen deprivation therapy; LH-RH, luteinizing hormone-releasing hormone; MAB, maximum androgen blockade.

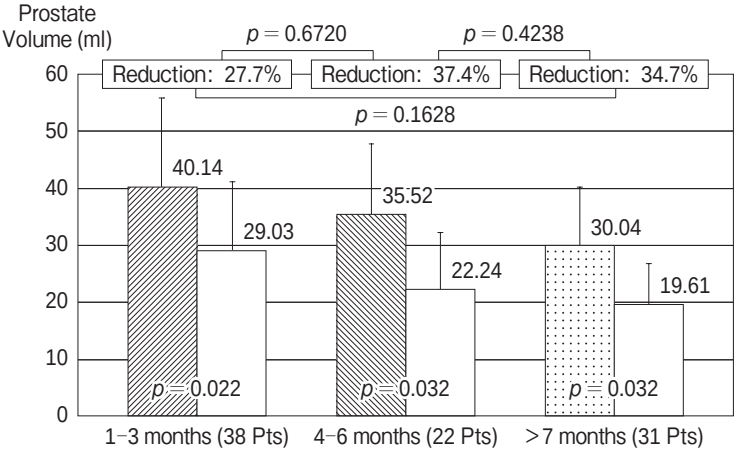

Fig. 1A The difference of prostate volume after each duration of LH-RH only. PTS, Patients.

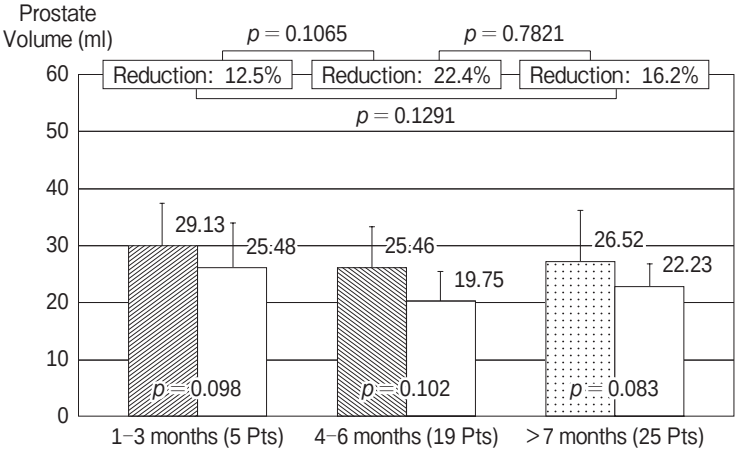

Fig. 1B The difference of prostate volume after each duration of Anti-androgen only.

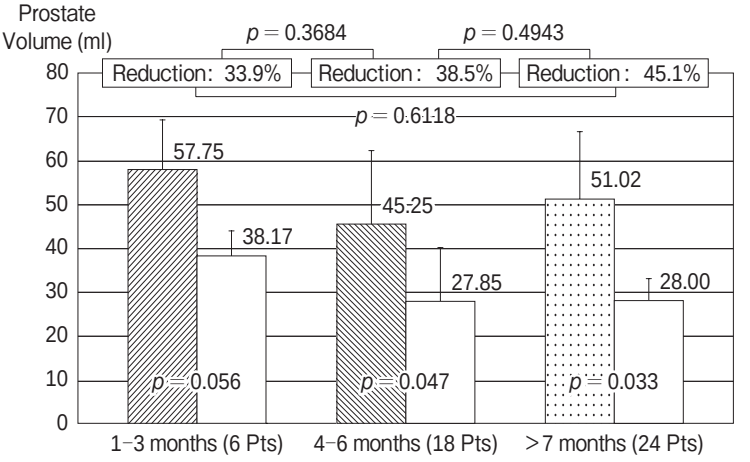

Fig. 1C The difference of prostate volume after each duration of MAB.

pared as to the prostate volume reduction. The overall result of average prostate volume reduction was 32.4%, which compares favorably with the results of previous studies using an LH-RH agonist with or without an anti-androgen. The volume reduction rate was 32.0% for the LH-RH agonist only, 18.1% for the anti-androgen only and 41.2% for the MAB, results which indicate no statistically significant difference. The over 6-month duration of MAB showed the greatest degree of volume reduction (reduction rate 45.1%), but there is no statistically significant difference between each duration of MAB therapy. Therefore, our data may suggest that a prostate volume of less than 60 ml may be low enough for the administration of a 3-month course of LH-RH only, considering the cost and side effects of MAB, which can include hot flashes, loss of potency and fatigue [19]. Cases of prostate volume greater than 60 ml may be contra-indications for brachytherapy with neoadjuvant ADT. If the prostate volume is less than 50 ml and the patient hopes to maintain erectile function during the hormonal therapy, anti-androgen might be selected for the volume reduction.

We did not consider the overall results of the quality of life (QOL) after the brachytherapy with or without ADT. Some studies have been reported regarding a possible correlation between ADT and urinary dysfunction following brachytherapy [20–23]. Some of these have indicated an increased risk of urinary retention with ADT [21, 22], and others have indicated that overall QOL and urinary functions do not appear to be significantly related to pre-implant prostate volume and hormonal therapy [20, 23]. Since the indication of prostate volume for brachytherapy in Japan is smaller than that for Western European males, further investigation is needed to confirm such a relationship between brachytherapy with or without neoadjuvant ADT and QOL.

Conclusions. Since the prostate volume is an important factor for an adequate dose volume histogram in radiation therapy, neoadjuvant androgen deprivation therapy is often used before radiation therapy, especially before brachytherapy in cases of unfavorable geometry. In our study, a 3-month course of neoadjuvant LH-RH agonist monotherapy indicated a sufficient volume reduction effectiveness for large prostate volumes less than 60 ml. Anti-androgen monotherapy might be selected according to the prostate volume, urinary symptoms and sexual activity of the patient.

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