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CLINICAL INVESTIGATION **Prostate**

HIGH-DOSE-RATE BRACHYTHERAPY OF A SINGLE IMPLANT WITH TWO FRACTIONS COMBINED WITH EXTERNAL BEAM RADIOTHERAPY FOR HORMONE-NAIVE PROSTATE CANCER

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Purpose: To evaluate the preliminary outcomes of high-dose-rate (HDR) brachytherapy of a single implant with two fractions and external beam radiotherapy (EBRT) for hormone-naive prostate cancer.
Methods and Materials: Between March 2000 and Sept 2003, a total of 53 patients with tumor Stage T1c–T3b N0 M0 prostate cancer were treated with HDR brachytherapy boost doses (7.5 Gy/fraction) and 50-Gy EBRT during a 5.5-week period. Median follow-up was 61 months. Patients were divided into groups with localized (T1c–T2b) and advanced disease (T3a–T3b). We used the American Society for Therapeutic Radiology and Oncology (ASTRO) definition for biochemical failure. According to recommendations of the Radiation Therapy Oncology Group–ASTRO Phoenix Consensus Conference, biochemical failure-free control rates (BF-FCRs) at 3 years were investigated as 2 years short of the median follow-up.
Results: Between April 2000 and Sept 2007, Common Terminology Criteria for Adverse Events Version 2.0 late Grade 2 genitourinary and gastrointestinal toxicity rates were 0% and 3.8%, respectively. Erectile preservation was 25% at 5 years. Overall survival was 88.1% and cause-specific survival was 100%. At 3 years, ASTRO BF-FCRs of the localized and advanced groups were 100% and 42%, respectively ($p = 0.001$).
Conclusions: The HDR brachytherapy of a single implant with two fractions plus EBRT is effective in treating patients with localized hormone-naive prostate cancer, with the least genitourinary and gastrointestinal toxicities; however, longer median BF-FCR follow-up is required to assess these findings.

Prostate cancer, Brachytherapy, Radiation therapy, High-dose-rate, Radiation toxicity.

INTRODUCTION

Treatment options for men with clinically localized prostate cancer include radical prostatectomy, external beam radiation therapy (EBRT), interstitial brachytherapy, hormonal therapy, and watchful waiting. If EBRT is used, high doses of more than 70 Gy must be delivered to achieve local control; however, this may increase the risk of rectal complications. We provided high-dose-rate (HDR) brachytherapy combined with EBRT for prostate cancer since 2000. A benefit of HDR brachytherapy is that it enables the prescription of dose escalation while suppressing the dose to surrounding normal structures by using optimization methods.

Multiple implants with a single fraction or a single implant with multiple fractions are available according to the HDR brachytherapy administration pattern. In combination with EBRT, Stromberg *et al.* (1) initiated three implants with a single fraction of 5.5 Gy each, whereas Martinez *et al.* (2) reported promising results by using two to three implants with a single fraction of 5.5–11.5 Gy each, and Mate *et al.* (3) used a single implant with four HDR fractions of 3–4 Gy each. The strength of multiple implants with a single fraction is that it delivers almost the same physical burden per implant as ^{125}I permanent brachytherapy. Its weakness is the repeated lumbar anesthesia and treatment planning. Conversely, the strength of a single implant with multiple fractions is the single anesthesia and treatment planning; its weakness is the heavy physical burden. In a single implant with multiple fractions, the applicators remain in place for all fractions.

In Japan, use of a single implant with multiple fractions has prevailed because of the limited number of anesthesiologists available and the iatrogenic risk of multiple lumbar anesthesia. Yoshioka *et al.* (4) reported a single implant with eight fractions of 5.5 Gy each for 5 days as monotherapy. Hiratsuka *et al.* (5) reported promising long-term biochemical control rates by using a single implant with four fractions of 5.5 Gy each for 2 days. Akimoto *et al.* (6) also reported a single implant with five fractions of 5 Gy each for 3 days, three fractions of 7 Gy each for 2 days, and two fractions of 9 Gy each

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Table 1. Combination of HDR brachytherapy and EBRT

	T1c–T2b	T3a–T3b	
EBRT field	Prostate, Seminal vesicles	Whole pelvis	Prostate, Seminal vesicles
Total dose/fractions	50/25	40/20	10/5
HDR brachytherapy		T1c–T3b	
Total dose (Gy) / fractions		15/2	
Total treatment period (wk)		5.5	
α/β = 2 (Gy)		85.6	
α/β = 5 (Gy)		76.8	

Abbreviations: EBRT = external beam radiation therapy; HDR = high dose rate; Gy = Gray; wk = weeks.

for 1 day, with the concurrent use of hormone therapy in all three series. On the basis of the trend toward emphasizing quality of life during treatment, we used a single implant with two fractions of 7.5 Gy each as a boost to EBRT of 50 Gy. The currently accepted low α/β ratios make hypofractionated HDR brachytherapy ideal (7). For α/β values as low as 2 and 5 for tumor control probability, biologic effective doses using the present brachytherapy with EBRT were 85.6 and 76.8 Gy, respectively (Table 1).

This study reports on the preliminary survival and radiation toxicity of hormone-naive patients treated with HDR brachytherapy of a single implant with two fractions combined with EBRT for hormone-naive prostate cancer.

METHODS AND MATERIALS

Patient selection

All patients were examined by the referring urologist, who conducted an initial evaluation that included medical history, physical examination, serum prostate-specific antigen (PSA) measurement, and histologic diagnosis. Tumor (T) stage was determined strictly by means of digital rectal examination. Urologists at our hospital do not use hormone therapy as the first option of treatment before radical prostatectomy because of its side effects and to reserve this treatment as the final option after relapse. The consensus between urologists and radiation oncologists is that hormone therapy is not used before radiation treatment (RT) and is initiated only in the case of biochemical failure after RT. This clinical investigation was approved by the ethics committee of our institute, and informed consent was obtained from all patients.

Pretreatment diagnosis evaluations were performed according to the tumor, node, metastasis classification system of the International Union Against Cancer 1997. Criteria for inclusion in the study were as follows: good performance status, life expectancy longer than 5 years, and unwilling or unsuitable for radical prostatectomy. Exclusion criteria were any of the following: Stage higher than T4a, PSA level greater than 100 ng/mL, and prostate gland larger than 40 mL. These criteria were adopted because prostate cancer with higher than Stage T4a and/or PSA level greater than 100 ng/mL is uncontrollable, with a high incidence of distant metastases, and prostate gland larger than 40 mL is irradiated unevenly with brachytherapy. Patients with a history of transurethral resection also were excluded. Only patients with Stage T1c–3b, PSA level less than 100 ng/mL, prostate gland smaller than 40 mL, and no history of transurethral resection were eligible for the study.

All patients underwent RT as initial treatment for prostate cancer and had negative bone scan and negative lymph node results by means of magnetic resonance imaging or computed tomography (CT) before treatment. All 53 consecutive patients who underwent combined HDR brachytherapy and EBRT between April 2000 and Sept 2003 were enrolled prospectively. Median follow-up was 61 months (range, 48–89 months). Clinical characteristics are listed in Table 2. Median age was 76 years (range, 50–87 years). Median initial PSA level was 14 ng/mL (range, 5–85 ng/mL), and median prostate gland volume was 20 mL (range, 10–38 mL).

Previous studies of radical prostatectomy focused mainly on prostate cancer contained within the capsule, but not on that extending beyond the capsule. It is important to know whether the schedule in the present study can be used to treat patients with prostate cancer that extends beyond the capsule. Patients first were divided into groups with localized (T1c–T2b) and advanced disease (T3a–T3b) according to T stage. It also is important to know whether the schedule in the present study can be compatible with localized prostate cancer with radical prostatectomy. Patients in the localized group then were assigned into risk subgroups based on standard risk

Table 2. Patients characteristics and risk classification

T stage	T1c	10
	T2a	15
	T2b	10
	T3a	8
	T3b	10
Age	median (range)	76 (50–87) years old
PSA	median (range)	14 (5–85) ng/mL
≦10		6
>10		47
Gleason score		
<7		25
=7		19
>7		9
Volume	median (range)	21 (10–44) ml
Localized (T1c–T2b)	low	4 T1c/T2a & PSA≦10 & GS<7
	intermediate	18 one unfavorable parameter
	high	13 Two or more unfavorable parameters
Advanced (T3a/T3b)		18

Abbreviations: PSA = prostate-specific antigen.