Delayed Radiotherapy for Patients with Localized Prostate Cancer: Validation by Propensity Score Matching

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Abstract. *Aim: To retrospectively investigate the biochemical outcome following delayed radiotherapy in patients with prostate cancer. Patients and Methods: From July 2000 to November 2008, 144 consecutive patients with localized prostate cancer underwent radiotherapy and androgen-deprivation therapy. Biochemical progression-free survival was compared in patients who began radiotherapy >6 months (delayed group) with these who began ≤6 months (non-delayed group) from diagnosis by biopsy. Treatment selection bias was adjusted by the propensity score method. Results: After a median follow-up of 64 months, the 5-year biochemical progression-free survival of the delayed and non-delayed groups was 87.4% (95% confidence interval, CI=69.7-95.1%) and 96.6% (95% CI=89.6-98.9%), respectively (p=0.03). Delayed radiotherapy was the only independent risk factor for biochemical progression (hazard ratio=3.97, 95% CI 1.07-14.7, p=0.04). The results were validated by propensity score analysis. Conclusion: Delaying radiotherapy by >6 months increases the risk of biochemical progression in patients with localized prostate cancer.*

A delay in cancer therapy usually results in an unfavorable outcome. The impact of delayed surgery for prostate cancer after diagnosis has been the subject of much discussion. Nam *et al*. stated that delayed prostatectomy to treat localized prostate cancer, was associated with increased biochemical progression (1). For radiotherapy, the consequences of delayed treatment have not been fully-investigated. In a meta-analysis of 46 studies, Huang *et al*. reported that a delay in radiotherapy decreased local control rates in breast and head and neck cancer (2). To the best of our knowledge, there is only one report available regarding delayed radiotherapy for prostate cancer (3).

Selection of the appropriate treatment is essential for patients with an initial diagnosis. Treatment options for prostate cancer are increasing, which can be a cause of delayed therapy. In addition, many patients with prostate cancer in Japan first undergo androgen-deprivation therapy (ADT) before they consult a radiation oncologist (4), and some patients undergo prolonged ADT before radiotherapy. Therefore, to evaluate the impact of radiotherapy delay after diagnosis based on prostate biopsy, we investigated the biochemical outcomes for all patients with localized prostate cancer.

Patients and Methods

Patients. Patients with localized prostate cancer who underwent radiotherapy and ADT were enrolled in this study. From July 2000 to November 2008, 144 consecutive patients were identified. Patients were referred by six neighbouring hospitals to the Tsukuba Medical Center Hospital, to receive radiotherapy. The median patient age was 71 years, range 52-91 years. The patients' characteristics are shown in Table I. Patients were classified into two groups according to the duration of delay from initial diagnosis by prostate biopsy until the initiation of radiotherapy. Patients for whom radiotherapy was delayed by >6 months were assigned to the delayed group. The other patients were assigned to the non-delayed group. Patients' characteristics between these two groups were well balanced with regard to T-stage, pretreatment prostate specific antigen (PSA) levels, Gleason scores, risk classification, and age.

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Table I. *Patients' characteristics*.

Characteristic	Delay in radiotherapy after diagnosis		*p*-Value
	≤6 Months (n=110)	>6 Months (n=34)	
Age (years)			0.10
≤65	50	10	
>65	60	24	
T stage			0.85
T1	15	7	
1b	0	1	
1c	15	6	
T2	32	14	
2a	2	8	
2b	13	4	
2c	17	2	
T3	53	13	
3a	28	6	
3b	25	7	
PSA level at diagnosis (ng/ml)			0.24
≤10	57	16	
10-20	21	11	
>20	32	7	
Gleason score			0.26
2-6	52	11	
7	14	7	
>7	44	16	
Risk classification+			0.58
Intermediate	30	12	
High	80	22	

+According to the report of Kuban *et al*. (7).

Pre-treatment evaluations. Pre-treatment evaluations included medical history, performance status, digital examination of the prostate, complete blood count (CBC), hepatic function tests, PSA values, chest X-rays, bone scintigrams, and histological examination of the prostate. Lymph node metastasis was evaluated by abdominal and pelvic computed tomography (CT) and magnetic resonance imaging (MRI). These examinations were performed prior to radiotherapy and ADT. All patients were histologically-diagnosed with adenocarcinoma, with no metastatic abdominal or pelvic lymph nodes, such as the obturator, internal, external, common iliac, or paraaortic lymph nodes. A core biopsy was performed on at least three points in each lobe. T-Stage was diagnosed by MRI and digital rectal examination performed by urologists. Clinical stages were defined based on the 2010 American Joint Committee on Cancer Seventh Edition (5).

After completion of radiotherapy, follow-up was performed every three months for five years, and every 3-6 months thereafter. At each visit, the patients underwent physical examinations and PSA values were assessed.

Radiotherapy. The treatment system included a treatment planning CT (CTS20SPS; Shimadzu Co., Kyoto, Japan), a treatment planning system (RTP; Mitsubishi Electric Co., Tokyo, Japan or Pinnacle3, Philips, Eindhoven, the Netherlands), and a linear accelerator (EXL 20DP; Mitsubishi Electric Co., Tokyo, Japan). All patients received external beam radiotherapy to the whole pelvis, followed by boosted radiotherapy to the prostate using 10-MV photons. Patients were treated five times per week. Between July 2000 and February 2004, the patients were irradiated with up to 46 Gy at 2-Gy daily doses to the whole pelvis, including the prostate, seminal vesicles, and internal iliac lymph nodes, using four-field, three-dimensional, conformal radiotherapy (3DCRT) techniques. Total doses of 70 Gy and 54 Gy were prescribed for the prostate and the seminal vesicles, respectively. After March 2004, the daily dose was reduced to 1.8 Gy, and the total prescribed dose was changed to 46.8 Gy to the whole pelvis, an additional 11.2 Gy to the prostate and the proximal site of the seminal vesicles, and a boosted dose of 14.2-17.6 Gy to the prostate using a seven-field 3DCRT technique. Thus, patients received a total dose of 72.0-75.6 Gy to the prostate. The median dose was 72 Gy given in 40 fractions. The dose-escalating scheme and the number of patients treated are shown in Table II.

Hormone therapy. ADT consisted of a combination of a luteinizing hormone–releasing hormone agonist (LH-RH) and a non-steroidal anti-androgen (flutamide or bicalutamide), or orchiectomy combined with bicalutamide in order to achieve maximal androgen blockade. A long-acting LH-RH was delivered subcutaneously combined with a flutamide dose of 375 mg or a bicalutamide dose of 80 mg orally, daily for six and 119 patients, respectively. Five patients underwent orchiectomy in conjunction with bicalutamide. Four patients received bicalutamide-only. The remaining 10 patients received LH-RH only as hormonal therapy.

End-point definition. The primary end-point for this study was the biochemical progression-free survival. The event of failed progression-free survival was defined as biochemical (PSA) progression. The definition of biochemical progression used in this study was developed by the American Society for Therapeutic Radiology and Oncology in 2005 in Phoenix (6); biochemical progression was defined as an increase of at least 2 ng/ml in nadir PSA level.

Statistical analysis. The χ^2 test and Fisher's exact test were used to detect differences between the two groups. Student's *t*-test was used to assess differences in mean values. A *p*-value of ≤0.05 was considered significant. Biochemical progression-free survival was calculated from the date of diagnosis by prostate biopsy to the date of biochemical progression or last follow-up. Cox proportional hazard regression analysis and univariate analysis were used to identify the most significant independent prognostic factors, using variables such as age, risk classification according to the report of Kuban *et al*. (7), irradiation dose, and delay in radiotherapy. Survival was calculated by the Kaplan-Meier method, and differences were analyzed with the log-rank test. To validate the results, a propensity score (8) for the delay in radiotherapy was calculated from the coefficients of parameters from a logistic-regression model analysis. The coefficient of parameters included age, irradiated dose, Gleason score, serum PSA levels, and T-stage. After matching patients by their propensity score, biochemical progression-free survival was compared. Statistical analysis between the two groups was performed with STATA 12 (Stata Corp., College Station, TX, USA).

Table II. *Schedule of dose escalation*.

Time period	Dose (Gy)				No. of patients
	Whole pelvis	SV+prostate	Prostate-only	Total dose	
Jul. 2000 to Feb. 2004	46.0	8.0	16.0	70.0	44
Mar. 2004 to Oct. 2005	46.8	16.2	9.0	72.0	34
Nov. 2005 to Aug. 2006	46.8	16.2	10.8	73.8	17
Sep. 2006 to Nov. 2008	46.8	16.2	12.6	75.6	49

SV, Seminal vesicles.

Results

The median follow-up period for all patients was 64.0 months. The difference in biochemical progression-free survival between the two groups is shown in Figure 1. The 5-year biochemical progression-free survival in the delayed and non-delayed groups were 87.4% [95% confidence interval (CI)=69.7-95.1%] and 96.6% (95% CI=89.6-98.9%), respectively (p=0.03). Delayed radiotherapy was the only independent risk factor for progression (hazard ratio=3.97, 95% CI=1.07-14.7, p=0.04; Table III). According to risk classification based on the report of Kuban *et al*., age and irradiated dose were not associated with increased risks with regard to biochemical progression-free survival.

Twenty-five patients from the delayed radiotherapy group were matched with 50 patients from the non-delayed group by propensity scores. The 5-year biochemical progression-free survival in the delayed and non-delayed radiotherapy groups were 82.3% (95% CI=59.3-93.0%) and 97.2% (95% CI=82.1-99.6%), respectively. The delayed group had a significantly worse 5-year biochemical progression-free survival compared to the non-delayed group (p=0.03). Delayed radiotherapy was also an independent risk factor for progression (hazard ratio=8.34, 95% CI=1.51-46.2, p=0.03). Age was a marginal risk factor for progression (hazard ratio=0.15, 95% CI=0.02-0.97, p=0.05).

Table III. *Prognostic factors for biochemical progression analyzed by multivariate analysis*.

Prognostic factor	Hazard ratio	95% CI	p-Value
Risk classification (intermediate *vs*. high)	0.83	0.24-2.79	0.76
Dose (≤72 Gy *vs*. >72 Gy)	0.59	0.15-2.35	0.45
Age (≤65 years *vs*. >65 years)	0.82	0.15-4.33	0.81
Delay in radiotherapy (≤6 months *vs*. >6 months)	3.97	1.07-14.7	0.04

CI: Confidence interval.

Discussion

Delayed radiotherapy treatment theoretically provides an opportunity for enhanced tumor cell growth and subsequent metastasis. The results of our study suggest that a delay in radiotherapy is associated with unfavorable biochemical progression. In their study of surgery to treat prostate cancer, Nam *et al*. first described how delaying treatment after diagnosis carried a risk of biochemical progression (1). Biochemical progression in patients who underwent surgery ≥3 months after diagnosis was greater than in these who underwent surgery <3 months after diagnosis. Later, Freedland *et al*. found that patients had a worse outcome if surgery was delayed by over 180 days (9). Moul *et al*. reported that unfavorable outcome was observed in high-risk patients (10). However some results have been controversial (11), O'Brien *et al*. reported that patients with low-risk had also greater risk of biochimerical progression (12). In our study, 70% of the patients were at high risk; this percentage of patients with a greater propensity for recurrence was greater than in the previously reported surgical series.

There is little available literature regarding the effect of delayed radiotherapy on biochemical progression. Nguyen *et al*. reported that a delay in radiotherapy increased biochemical progression (3). Two-hundred and twenty low-risk patients and 240 high-risk patients (clinical stages T1c to T2c) from multiple institutions were analyzed in their study. The median radiation dose was 70.4 Gy, and ADT was not administered. The biochemical progression-free survival at five years in high-risk patients who underwent radiotherapy ≥2.5 months or <2.5 months after diagnosis were 45% and 61%, respectively; this difference was statistically significant (p=0.014). The delay in radiotherapy increased the hazard ratio by a rate of 8% per month of delay. To increase reliability, in our study, one radiation oncologist performed delineation of the prostate cancer. An additional analysis with the propensity score was then performed; this resulted

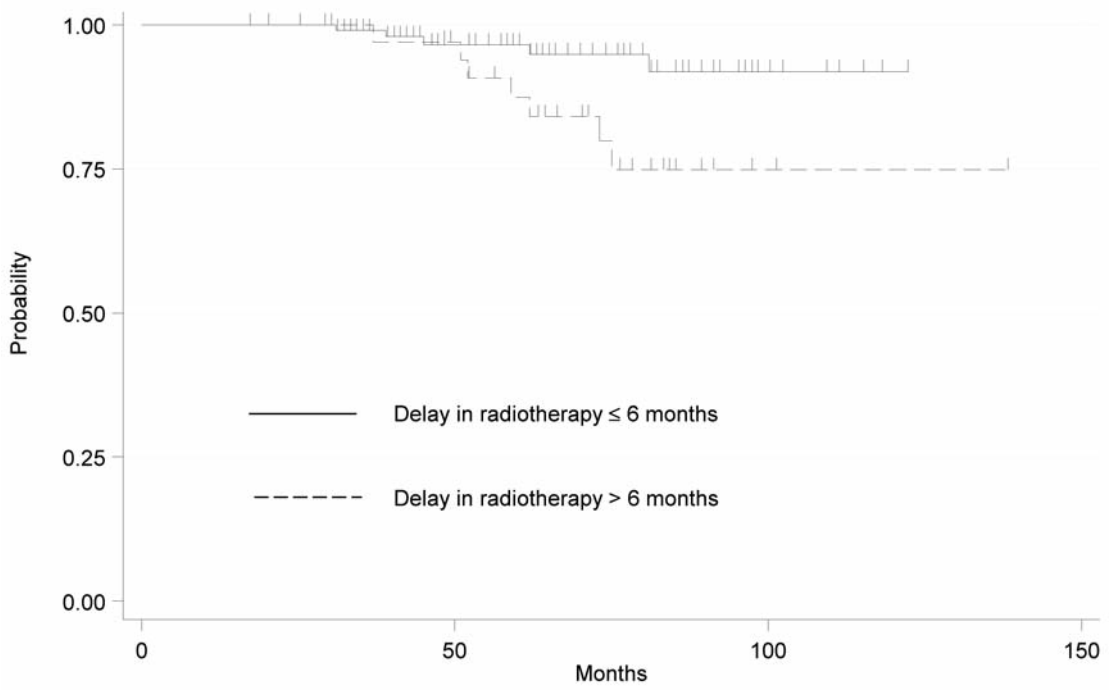

Figure 1. *Biochemical progression-free survival estimated by the Kaplan–Meier method. Five-year biochemical progression-free survival in delayed and non-delayed groups were 87.4% (95% confidence interval, CI=69.7-95.1%) and 96.6% (95% CI=89.6-98.9%), respectively. Patients in the delayed group had significantly shorter biochemical progression-free survival compared to the non-delayed group (p=0.03).*

in outcomes similar to those obtained by conventional methods. Rosenbaum and Rubin first described the use of a propensity score to reduce bias; this method was found to be useful for observational studies (8). Accordingly, there was little difference in the irradiated field compared to patients in Nguyen *et al*.'s multi-institutional study. In our study, 46% of the patients had stage T3 disease; this represents more high-risk patients with a greater likelihood of biochemical progression than those included in Nguyen *et al*.'s study. Nguyen *et al*. mentioned that ADT remained to be seen, whether it reduce biochemical progression (3). However, according to our results, ADT did not reduce biochemical progression.

Radiotherapy was delayed due to prolonged administration of neoadjuvant ADT. According to two previous studies, neoadjuvant ADT before prostatectomy does not improve biochemical progression-free survival (13, 14). Three randomized trials have investigated the optimal duration of neoadjuvant ADT before radiotherapy (15-17). Laverdiere *et al*. compared 3 months of neoadjuvant ADT with 10 months of neoadjuvant and concurrent ADT with a radiation dose of 64 Gy given in 37 fractions in stage T2 to T3 patients (17). There were no significant differences in the outcomes of those who received three months of ADT compared to those who received 10 months of ADT. The TROG 96-01 trial reported that patients who received six months of neoadjuvant and concurrent ADT had better overall survival and cause-specific survival compared to those who received three months of neoadjuvant and concurrent ADT (16). In the TROG 96-01 study, 802 patients who had stage T2b to T4 prostate cancer and any PSA level and Gleason score underwent radiotherapy at a dose of 66 Gy administered in 33 fractions to the prostate and seminal vesicles; >80% of the patients were at high risk. Crook *et al*. reported a Canadian trial of 378 patients with stage T1c to T4 disease; this study compared three months and eight months of neoadjuvant ADT (15). The radiation dose was 66 Gy to the pelvis if the risk of pelvis lymph node involvement was >10-15%. Neoadjuvant ADT for eight months did not improve biochemical control rates compared to neoadjuvant ADT for three months, but only for high-risk patients. All of these results indicate that the optimal combination of radiotherapy and ADT has not yet been determined. Differences between our study and previous clinical studies include a higher radiation dose in our study and others undergoing adjuvant ADT after radiotherapy. The median time of 11 months in the delayed group was a longer duration of neoadjuvant ADT compared to previous studies, and it confirmed that a delay in radiotherapy may be associated with biochemical progression even if ADT is employed.

Limitations of this study were its retrospective design and the relatively small total number of patients that were included. Further studies are needed before definitive conclusions can be drawn, but our findings suggest that delaying radiotherapy by more than six months increases the risk of biochemical progression in patients with localized prostate cancer, even if ADT is administered. Thus, in our institution, we consider initiating radiotherapy within six months of diagnosis of prostate cancer, since it appears that delayed radiotherapy may lead to increased biochemical progression.

Conflicts of Interest

The Authors have no conflicts of interest.

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