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Does Treatment Duration Affect Outcome after Radiotherapy for Prostate Cancer?

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Abstract

Purpose—The protraction of external beam radiotherapy (RT) time is detrimental in several disease sites. In prostate cancer, the overall treatment time can be considerable, as can the potential for treatment breaks. We evaluated the effect of elapsed treatment time on outcome after RT for prostate cancer.

Methods and Materials—Between April 1989 and November 2004, 1,796 men with prostate cancer were treated with RT alone. The nontreatment day ratio (NTDR) was defined as the number of nontreatment days divided by the total elapsed days of RT. This ratio was used to account for the relationship between treatment duration and total RT dose. Men were stratified into low risk ($n = 789$), intermediate risk ($n = 798$), and high risk ($n = 209$) using a single-factor model.

Results—The 10-year freedom from biochemical failure (FFBF) rate was 68% for a NTDR <33% vs. 58% for NTDR $\geq$ 33% ($p = 0.02$; BF was defined as a prostate-specific antigen nadir + 2 ng/mL). In the low-risk group, the 10-year FFBF rate was 82% for NTDR <33% vs. 57% for NTDR $\geq$ 33% ($p = 0.0019$). The NTDR was independently predictive for FFBF ($p = 0.03$), in addition to T stage ($p = 0.005$) and initial prostate-specific antigen level ($p < 0.0001$) on multivariate analysis, including Gleason score and radiation dose. The NTDR was not a significant predictor of FFBF when examined in the intermediate-risk group, high-risk group, or all risk groups combined.

Conclusions—A proportionally longer treatment duration was identified as an adverse factor in low-risk patients. Treatment breaks resulting in a NTDR of $\geq$ 33% (e.g., four or more breaks during a 40-fraction treatment, 5 d/wk) should be avoided.

Keywords

Treatment break; Prostate; Biochemical failure; Radiotherapy; Prostate-specific antigen

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Introduction

Protraction of radiotherapy (RT) has been shown to be detrimental in several treatment sites (1–4). This has been particularly true in head-and-neck subsites, such as oropharynx and oral cavity cancers (1,4). Treatment prolongation is believed to be detrimental owing to the accelerated repopulation of tumor clonogens. Although the results of studies in prostate cancer have been mixed, an extended treatment time is thought to affect the outcome minimally, if at all.

In 1990, data from the Mallinckrodt Institute of Radiology showed no effect of overall treatment time on outcome (5). They examined their series of 542 men treated between 1966 and 1985. The median dose in their group was 63 Gy, a dose that would be considered insufficient today (6,7). The patients were divided into four groups according to the number of treatment days (8, 9, 10, and >10 weeks). No difference was found among these groups in pelvic control, progression-free survival, or overall survival. This was later confirmed by an effort from the Radiation Therapy Oncology Group, which pooled the data sets from Radiation Therapy Oncology Group trials 75-06 and 77-06 and found similar results (8). These patients were divided into groups according to the total elapsed days of ≤ 7 , 8–9, and >9 weeks. Again, no differences were found in local control, disease-free survival, or overall survival.

However, the results from the University of Florida demonstrated that when the overall treatment time was >8 weeks, local failure increased (9). This group of patients, treated between 1964 and 1982, had received a dose range of 65–70 Gy, and 45% were diagnosed by transurethral resection of the prostate (TURP). The present study examined the potential effect of overall treatment time in a more contemporary group of patients, treated in the prostate-specific antigen (PSA) era (*i.e.*, 1989–2004). In contrast to the previous studies, which contained patients from >20 years ago treated with lower doses, the median dose in the present study was 76 Gy.

Methods and Materials

Between April 1, 1989 and November 31, 2004, 1,796 men were treated with definitive RT alone (no androgen deprivation therapy) in the Department of Radiation Oncology at Fox Chase Cancer Center (Philadelphia, PA). Of the 1,796 patients, 209 (12%) were considered to have high-risk prostate cancer, defined as Stage T3 or Gleason score 8–10, or pretreatment PSA level of ≥ 20 ng/mL, and 789 (44%) were considered to have low-risk disease, defined as less than Stage T3, Gleason score <7, and PSA level <10 ng/mL. The remaining 798 patients were considered to have intermediate risk. The T stage was determined solely from the palpation findings on digital rectal examination (no upstaging done using prostate biopsy results or radiographic imaging findings) using the 2002 American Joint Committee on Cancer staging guidelines (10). The proportion of patients undergoing staging abdominopelvic computed tomography and bone scan was 65% and 80% in the low-risk group, 71% and 89% in the intermediate-risk group, and 80% and 94% in the high-risk group, respectively.

All men had pathologic confirmation of prostate cancer before definitive treatment. All slides for patients diagnosed at referring institutions (86% in this study) were reviewed at the Fox Chase Cancer Center. Most cases were examined by an oncologic pathologist with special experience in urologic pathology. Cases with a discrepancy in diagnosis or grade with the outside institution were examined by a panel of oncologic pathologists until a consensus diagnosis was reached. The median number of biopsy cores taken was 7 (range, 1–36).

Three-dimensional conformal ($n = 1,362$) and intensity-modulated ($n = 434$) RT techniques were used. Some intermediate-risk or high-risk patients did not receive androgen deprivation

therapy because of physician preference, patient preference, and year of treatment, as it relates to the publication of clinical trials supporting its use.

To account for the effect of radiation dose on overall treatment time, a nontreatment day ratio (NTDR) was defined. This was calculated as the number of non-RT days during a treatment course divided by the total elapsed days. For example, when 40 fractions are delivered, 5 d/wk, beginning on a Monday with seven weekends and no holidays or treatment breaks, the NTDR would equal 25.9% $\{[(14 \text{ weekend days}) \div 54 \text{ elapsed days}] \times 100\}$. In contrast, the NTDR when four treatment breaks are required, the NTDR will equal 33.3% $\{[(16 \text{ weekend days} + 4 \text{ break days}) \div 60 \text{ elapsed days}] \times 100\}$. The median NTDR was 30% (range, 23–79%). Analysis was also done using the absolute number of nontreatment days during the RT course.

Treatment and follow-up

Our three-dimensional conformal RT and intensity-modulated RT techniques have been previously reported (11,12). The patients were treated in the supine position in a custom-made thermoplastic cast for immobilization. The radiation dose has been reported as the International Commission of Radiation Units and Measurements reference dose (13). For intensity-modulated RT, the dose was prescribed to the 95% isodose of the beam arrangements and normalized so that the planning target volume was included within the 95% isodose line. All patients were treated with 10–18-MV photons. The radiation dose escalated over time. The median total dose for all patients was 76 Gy (range, 65–82). The median dose for low-, intermediate-, and high-risk prostate cancer was 74 Gy (range, 65–82), 76 Gy (range, 66–82), and 76 Gy (range, 68–82), respectively.

Statistical analysis

The distributions of freedom from biochemical failure (BF) were calculated using the Kaplan-Meier product limit method. Cox proportional hazards regression analysis was used for univariate and multivariate analyses (14). BF was defined as the PSA nadir + 2 ng/mL (15). The variables also analyzed included the absolute number of non-RT days, Gleason score, pretreatment PSA level, T stage, and radiation dose. A *p* value of ≤ 0.05 was considered statistically significant; all analyses were done using Statistical Analysis Systems statistical software.

Results

Various patient- and treatment-related characteristics are summarized in Table 1. Using the single-factor, risk stratification model (16), the proportion of men with low-risk disease (Gleason score <7, PSA level of ≤ 10 ng/mL, and Stage T1-T2), high-risk disease (Gleason score ≥ 8 or PSA level >20 ng/mL or Stage T3), and intermediate-risk disease (Gleason score 7 or PSA level >10 but <20 ng/mL and no high-risk features) was 44% (*n* = 795), 12% (*n* = 209), and 44% (*n* = 799), respectively. The median follow-up was 62 months (range, 1–210). The median total dose for all patients was a dose of 76 Gy (range, 65–82).

Figure 1 shows the Kaplan-Meier freedom from BF (FFBF) estimates according to quartiles of NTDR. The upper quartile appeared to be associated with a greater risk of BF and was chosen as the cutpoint for subsequent analysis. Given the median radiation dose of 76 Gy in 38 fractions 5 d/wk, three or more treatment breaks (including holidays) was associated with an increased risk of BF. Figure 2 illustrates the FFBF for the entire cohort using an NTDR of 33% as the cutpoint. When examining the entire cohort of patients, the 10-year FFBF rate was 68% for an NTDR of <33% and 58% for an NTDR of $\geq 33\%$ (*p* = 0.02). Figures 3–5 illustrate the FFBF according to an NTDR of $\geq 33\%$ for low-, intermediate-, and high-risk patients, respectively.

An NTDR of $\geq 33\%$ was a statistically significant predictor of FFBF for the low-risk group but not for the intermediate- or high-risk group. The 10-year FFBF rate for the low-risk group was 82% for an NTDR of $< 33\%$ and 57% for an NTDR of $\geq 33\%$ ($p = 0.0019$). The 10-year overall survival rate for the low-risk group was 76% and 85% for an NTDR of $< 33\%$ and $\geq 33\%$, respectively ($p = 0.50$). Table 2 lists the 5- and 10-year rates of FFBF by risk group, with the corresponding confidence intervals.

Salvage therapy for patients with BF consisted of salvage androgen deprivation therapy or cryosurgery. Salvage androgen deprivation therapy was used in 19%, 9%, and 3% of the high-, intermediate-, and low-risk groups, respectively. Cryosurgery was used in 3% of low-risk patients, 1% of intermediate-risk patients, and 0% of high-risk patients. Salvage prostatectomy or brachytherapy was not used.

The multivariate analysis results are listed in Table 3. Overall, a trend ($p = 0.08$) was noted for significance of NTDR in a model including T stage ($p < 0.0001$), Gleason score ($p < 0.0001$), pretreatment PSA level ($p < 0.0001$), and radiation dose. In the low-risk group, NTDR retained its statistical significance ($p = 0.03$), as did T stage ($p = 0.005$) and pretreatment PSA level ($p < 0.0001$) in a model that also contained the Gleason score and radiation dose. In a similar model with radiation dose analyzed categorically (< 70 , 70–72, 72–76, and > 76 Gy), the NTDR retained its statistical significance ($p = 0.007$). In an identical model testing for overall survival, the NTDR was not significant. For the intermediate-risk group, Gleason score ($p = 0.01$) and initial PSA level ($p = 0.01$) were the only predictors in the same model. For the high-risk group, only the Gleason score ($p = 0.002$) retained statistical significance. These results were not altered when the absolute number of non-treatment days was used in place of the NTDR (data not shown).

Discussion

Prolonging the treatment time is generally not advisable in radiation oncology, because of the theoretical risk of accelerated tumor cell repopulation. For squamous cell carcinoma of the head and neck, this has been a well-documented paradigm. For prostate adenocarcinoma, the results have been less clear, with conflicting studies. The University of Florida analyzed local control using time–dose scatter distributions, as well as absolute treatment time divided by stage (Stage A–C) (9). The cohort analyzed was in the pre-PSA era using non-Gleason score grading and 45% of patients were diagnosed by transurethral resection of the prostate. In addition, some patients were treated with split-course RT. Although this group is clearly not comparable to the patient in the present report, they did show worse local control for Stage B2 patients whose total treatment time was > 8 weeks instead of ≤ 8 weeks. Stage B2 was defined as palpable tumor confined to the prostate and involving at least an entire lobe. Of these Stage B2 patients, 77% had their tumor graded as well or moderately differentiated, which might have been comparable to some of the low-risk cohort in the present report. In the Florida series, when the radiation dose was limited to ≥ 65 Gy, the overall treatment time was significant for well, moderate, and poorly differentiated grades.

Lai *et al.* (8) analyzed overall treatment time on prostate cancer outcome using patients enrolled in two prospective Radiation Therapy Oncology Group studies (17,18). The patients were required to have received a minimal dose of 65 Gy and no androgen deprivation therapy. The patients were stratified into three total treatment time groups: ≤ 7 , 8–9, and > 9 weeks. No differences were found in local control, disease-free survival, or overall survival according to treatment time for this cohort, even when stratified by Gleason score or T stage. Another retrospective, single-institution experience likewise showed no difference in outcome according to overall treatment time (5).

These previous studies described the results of a much different group of patients than in the present study. To our knowledge, the only other series addressing overall treatment time in the PSA era was from William Beaumont Hospital (19). This series addressed the effect of clinical- and treatment-related prognostic factors on biochemical outcome. Treatment time was not predictive of the FFBB on univariate or multivariate analysis, including pretreatment PSA level, T stage, or Gleason score. The additional strengths of the present study include higher radiation doses and longer follow-up. Dose-escalated RT has been shown to improve FFBB through better local control (20–22). This benefit with higher doses might allow differences in local control related to secondary factors, such as the NTDR, to be more apparent. Also, extended follow-up enables better detection of late BF resulting from a slowly increasing PSA level, a pattern consistent with local disease persistence (23).

The present study is the largest reported to address this question and the first to stratify by contemporary risk groups. To account for the varying radiation doses, which corresponded to the varying durations of treatment, using conventional fractionation, we analyzed the treatment time using a ratio (NTDR) of the nontreatment days to the total number of elapsed days. The NTDR analyzes nontreatment days as a percentage of the total treatment duration. An NTDR of <33% corresponds to ≤ 3 nontreatment days (including holidays) during a prostate RT regimen totaling 40 fractions delivered 5 d/wk. With a greater NTDR, a statistically significant detriment in FFBB was found in the low-risk group.

The relationship of NTDR to BF was only seen in the low-risk group. We postulated that the importance of treatment time for local RT is inversely related to the risk of metastatic disease. Patients most likely to be affected by differences in local treatment are those most likely to have local-only disease (*i.e.*, low risk). Conversely, one would expect intermediate- and high-risk groups to be more likely to present with subclinical metastatic disease that was untreated in this study of RT alone (no androgen deprivation therapy). Subsequent progression of metastatic disease contributes to BF and might have diluted the effect of an increasing NTDR in the intermediate- and high-risk patients (23). These intermediate- and high-risk patients might require radiation doses greater than those used in our study and/or adjuvant androgen deprivation therapy to see an effect of prolonged treatment time.

This study was a retrospective, single-institution study and was therefore subject to biases. These included patient selection for allowing treatment breaks, patient selection for RT alone, preference for the day of the week patients began treatment, and the use of a 2-Gy fraction size. However, these data are thought provoking and should be investigated in other data sets, as well as prospectively. This study supports minimizing treatment breaks to <3 days when 38 fractions (2-Gy fractions, 5 d/wk beginning on a Monday, 76 Gy total) are used and to <4 days for 40 fractions (total dose 80 Gy). Individual institutions are encouraged to calculate the NTDR for a more precise evaluation of treatment protraction according to the RT regimen used.

Conclusions

The results of our study have shown that low-risk prostate cancer patients have a statistically significant detriment in FFBB with a prolonged treatment duration. All patients should be encouraged to avoid treatment breaks when possible and to limit breaks and holidays to less than four during the course of 40 treatment sessions. Broader conclusions regarding the relative importance of repopulation for prostate cancer requires additional study and validation.

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Fig. 1. Kaplan-Meier freedom from biochemical failure estimates for all patients according to nontreatment day ratio (NTDR) quartile ($n = 1,796$).

Fig. 2. Kaplan-Meier freedom from biochemical failure estimates by nontreatment day ratio (NTDR) of <33% vs. ≥33% for all patients ($n = 1,796$).

Fig. 3. Kaplan-Meier freedom from biochemical failure estimates by nontreatment day ratio (NTDR) of <33% vs. ≥33% for low-risk patients ($n = 789$).

Fig. 4. Kaplan-Meier freedom from biochemical failure estimates by nontreatment day ratio (NTDR) of <33% vs. ≥33% for intermediate-risk patients ($n = 798$).

Fig. 5. Kaplan-Meier freedom from biochemical failure estimates by nontreatment day ratio (NTDR) of $<33\%$ vs. $\geq 33\%$ for high-risk patients ($n = 209$).

Table 1Patient characteristics ($n = 1,796$)

Characteristic	Value
Patients	1,796 (100)
Age (y)	
Median	69
Range	27–87
Gleason score	
2–6	1,365 (76)
7	386 (21)
8–10	45 (3)
Pretreatment PSA	
Median (ng/mL)	7.4
Range (ng/mL)	0.4–135
≤10 ng/mL	1,247 (70)
>10–19.99 ng/mL	417 (23)
≥20 ng/mL	132 (7)
T stage	
T1	990 (55)
T2	755 (42)
T3	51 (3)
Risk group	
Low	789 (44)
Intermediate	798 (44)
High	209 (12)

Abbreviation: PSA = prostate-specific antigen.

Data presented as number of patients, with percentages in parentheses, unless otherwise noted.

Table 2

FFBF rate at 5 and 10 years stratified by risk group and NTDR

Risk group	FFBF rate (%)		<i>p</i> [*]
	5 y	10 y	
All combined			0.02
NTDR <33%	88 (85–90)	68 (63–73)	
NTDR ≥33%	84 (80–88)	58 (48–67)	
High risk			1.0
NTDR <33%	71 (62–78)	43 (31–56)	
NTDR ≥33%	65 (46–76)	60 (40–73)	
Intermediate risk			0.32
NTDR <33%	84 (80–87)	64 (55–71)	
NTDR ≥33%	84 (77–90)	58 (45–70)	
Low risk			0.0019
NTDR <33%	95 (93–97)	82 (74–87)	
NTDR ≥33%	90 (82–94)	57 (38–72)	

Abbreviations: FFBF = freedom from biochemical failure; NTDR = nontreatment day ratio.

Data in parentheses are 95% confidence intervals.

* Log-rank test.

Table 3
Cox proportional multivariate analyses for biochemical failure

Variable	Baseline	Hazard ratio	95% CI	p
All patients (n = 1,796)				
NTDR	<33%	1.3	0.97–1.6	0.08
Gleason score	≤7	2.2	1.2–4.1	<0.0001
T stage	T1-T2	2.5	1.5–4.2	<0.0001
Pretreatment PSA	<20 ng/mL	3.3	2.3–4.6	<0.0001
Radiation dose (Gy)	Lower	1.0	1.0–1.0	0.33
Low risk (n = 789)				
NTDR	<33%	1.8	1.1–3.1	0.03
Gleason score	≤7	1.2	0.86–1.8	0.26
T stage	T1-T2	2.1	1.3–3.6	0.005
Pretreatment PSA	<20 ng/mL	1.3	1.2–1.5	<0.0001
Radiation dose (Gy)	Lower	1.0	1.0–1.0	0.94
Intermediate risk (n = 798)				
NTDR	<33%	1.1	0.74–1.5	0.71
Gleason score	≤7	1.6	1.1–2.2	0.01
T Stage	T1-T2	1.3	0.9–1.8	0.16
Pretreatment PSA	<20 ng/mL	1.6	1.1–2.3	0.01
Radiation dose (Gy)	Lower	1.0	1.0–1.0	0.31
High risk (n = 209)				
NTDR	<33%	1.2	0.68–2.2	0.50
Gleason score	≤7	2.7	1.6–4.7	0.001
T stage	T1-T2	1.8	0.7–4.7	0.13
Pretreatment PSA	<20 ng/mL	1.6	0.63–4.2	0.60
Radiation dose (Gy)	Lower	1.0	1.0–1.0	0.10

Abbreviations: CI = confidence interval; NTDR = nontreatment day ratio; PSA = prostate-specific antigen.