Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, pp. 755–760, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.02.026

CLINICAL INVESTIGATION **Prostate**

EXTERNAL BEAM RADIOTHERAPY FOR PROSTATE CANCER PATIENTS ON ANTICOAGULATION THERAPY: HOW SIGNIFICANT IS THE BLEEDING TOXICITY?

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Purpose: To characterize the bleeding toxicity associated with external beam radiotherapy for prostate cancer patients receiving anticoagulation (AC) therapy.

Methods and Materials: The study cohort consisted of 568 patients with adenocarcinoma of the prostate who were treated with definitive external beam radiotherapy. Of these men, 79 were receiving AC therapy with either warfarin or clopidogrel. All patients were treated with three-dimensional conformal radiotherapy or intensity-modulated radiotherapy. Bleeding complications were recorded during treatment and subsequent follow-up visits.

Results: With a median follow-up of 48 months, the 4-year actuarial risk of Grade 3 or worse bleeding toxicity was 15.5% for those receiving AC therapy compared with 3.6% among those not receiving AC ($p < .0001$). On multivariate analysis, AC therapy was the only significant factor associated with Grade 3 or worse bleeding ($p < .0001$). For patients taking AC therapy, the crude rate of bleeding was 39.2%. Multivariate analysis within the AC group demonstrated that a higher radiotherapy dose ($p = .0408$), intensity-modulated radiotherapy ($p = 0.0136$), and previous transurethral resection of the prostate ($p = .0001$) were associated with Grade 2 or worse bleeding toxicity. Androgen deprivation therapy was protective against bleeding, with borderline significance ($p = 0.0599$). Dose–volume histogram analysis revealed that Grade 3 or worse bleeding was minimized if the percentage of the rectum receiving ≥70 Gy was <10% or the rectum receiving ≥50 Gy was <50%.

Conclusion: Patients taking AC therapy have a substantial risk of bleeding toxicity from external beam radiotherapy. In this setting, dose escalation or intensity-modulated radiotherapy should be used judiciously. With adherence to strict dose–volume histogram criteria and minimizing hotspots, the risk of severe bleeding might be reduced. © 2010 Elsevier Inc.

Prostate cancer, bleeding toxicity, anticoagulation therapy, warfarin, radiotherapy.

INTRODUCTION

Prostate cancer is the most common non–skin malignancy in men, and it is estimated that more than 180,000 new cases will have been diagnosed in 2008 (1). The incidence of prostate cancer increases as men age, to as much as 1 in 7 among those older than 70 years (1). External beam radiotherapy (EBRT) is one of the standard treatment options for localized prostate cancer, and it might be the preferred treatment option when treating men with significant comorbidities. Although EBRT is usually well tolerated, bleeding from radiation proctitis or cystitis is a common and potentially serious complication of EBRT.

In recent years, several studies have shown better biochemical outcomes after dose-escalated EBRT (2–4). The use of three-dimensional conformal RT and more recently, intensity-modulated RT (IMRT) has allowed the delivery of escalated radiation doses with more normal tissue sparing; however, rectal- and bladder-related toxicities remain a challenge (5–7). Several clinical and treatment factors have been associated with rectal and bladder bleeding, including a high radiation dose, mean rectal dose, whole pelvic RT (WPRT), previous transurethral resection of the prostate (TURP), and androgen deprivation therapy (ADT) (7–12). Although data are limited, it is logical to assume that anticoagulation (AC) therapy can also significantly influence the risk of bleeding. In one prospective study of 57 men undergoing EBRT for prostate cancer, 4 developed Grade 3 rectal bleeding toxicity, and all had been taking AC agents with either warfarin or high-dose aspirin (13).

Anticoagulation therapy is required for many patients with cardiovascular disorders, such as ischemic heart disease, atrial fibrillation, valvular disease, and venous thromboembolism. These disorders are much more prevalent in the

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Presented at the 49th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Los Angeles, CA, October 28 to November 1, 2007.

Conflict of interest: none.

Received Dec 23, 2008, and in revised form Feb 4, 2009. Accepted for publication Feb 12, 2009.

elderly population, similar to prostate cancer. Bleeding is a common complication of AC therapy, and for men undergoing EBRT for prostate cancer, the bleeding toxicity is expected to be greater. To investigate the risk of bleeding toxicity and to identify the potentially modifiable factors, we reviewed our experience of treating prostate cancer patients who were receiving AC therapy.

METHODS AND MATERIALS

The present study included patients with adenocarcinoma of the prostate, who had been treated with definitive EBRT at the University of Chicago Pritzker School of Medicine between 1988 and 2005. The other inclusion criteria were no evidence of metastatic disease, ≥2 years of potential follow-up, and no prostatectomy or brachytherapy as a component of treatment. Patients were excluded if they had no documented list of medications ($n = 54$). Patients were assigned to the AC group if they had listed either warfarin or clopidogrel on the medication list at their initial consultation or follow-up visits. A total of 568 patients were included, of whom 79 were in the AC group. A review of these patients was undertaken with approval from the hospital's institutional review board.

The patient and disease characteristics are listed in Table 1. The median age of the entire group was 69 years. The median prostate-specific antigen level was 9.2 ng/mL (range, 0.6–242.1). Patients were categorized as having low-, intermediate-, or high-risk disease according to the National Comprehensive Cancer Network classification (14). Most patients had low-risk (29.9%) or intermediate-risk (41.7%) disease; 159 patients (28.3%) had high-risk disease. Of the 568 patients, 317 (55.8%) had a pathologic Gleason score of ≤6, 195 (34.3%) had a Gleason score of 7, and 56 (9.9%) had a Gleason score of ≥8. Thirty-five (6.2%) patients had T3 or T4 disease. All patients were treated with three-dimensional conformal RT or IMRT. The median radiation dose was 72.0 Gy (range, 62.0–76.4), with a standard fractionation of 1.8 or 2.0 Gy per day. The radiation dose was prescribed to the minimal isodose line that encompassed the planning target volume. The planning target volume was established by expanding the prostate by 6–10 mm. The 45 patients (7.9%) thought to have a high risk of subclinical lymph node involvement were treated with WPRT. Dose–volume histogram (DVH) data for the rectum and bladder were available for 301 patients (55 of the 79 patients in the AC group). The rectum was defined as the outer wall of the rectum extending from the ischial tuberosities to the sigmoid flexure. The bladder was defined as the outer wall of the entire bladder. The prostate volume was calculated using images from the simulation computed tomography. The values were available for 298 patients (54 of 79 patients in the AC group). The use of ADT was at the discretion of the treating physicians during the study period. A total of 263 patients (46.3%) received ADT, and it typically consisted of a luteinizing hormone-releasing hormone analog and antiandrogen for a median of 4 months. Of the 247 patients with documented ADT duration, 206 (83.4%) received ≤6 months of ADT.

The evaluations were performed once weekly during treatment. After RT completion, the patients were generally followed at intervals of 3–9 months for 5 years and yearly thereafter. The median follow-up time, calculated from the date of RT initiation, was 48 months (range, 3.0–205.9). Bleeding toxicities were graded according to the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer Morbidity Scoring Scheme (15). In brief, microscopic hematuria or slight rectal bleeding was scored as Grade 1 toxicity. Macroscopic hematuria or intermittent rectal bleeding was considered Grade 2. Grade 3 or worse toxicity consisted of severe bleeding requiring invasive intervention, including cauterization, transfusion, or surgery. The use of endoscopy or cystoscopy for evaluation of bleeding was not strictly regulated, but was recommended for any patient with intermittent bleeding. Therefore, patients with Grade 2 or greater toxicity typically had confirmation of bleeding from a source thought to be consistent with radiation cystitis or proctitis. Bleeding toxicity observed during treatment was scored as acute toxicity and during follow-up as late toxicity.

Comparisons between the AC and control groups were made using the chi-square test. Univariate and multivariate analyses were

Table 1. Patient characteristics ($n = 568$)

Characteristic	No AC ($n = 489$)	AC ($n = 79$)	p
Age (y)			.5760
Median	69	70	
Range	42–83	49–82	
Race			.0670
White	188 (38.5)	42 (53.2)	
Black	282 (57.7)	35 (44.3)	
Other	16 (3.3)	1 (1.3)	
Unknown	3 (0.6)	1 (1.3)	
Risk category			.5481
High	140 (28.6)	19 (24.1)	
Intermediate	198 (40.5)	36 (45.6)	
Low	144 (29.4)	24 (30.4)	
Unknown	7 (1.4)	1 (1.3)	
Gleason score			.9378
2–6	273 (55.8)	44 (55.7)	
7	167 (34.2)	28 (35.4)	
8–10	49 (10.0)	7 (8.9)	
Initial PSA (ng/mL)			.1599
Median	9.17	9.48	
Range	0.6–242.1	1.74–89	
T stage			.3253
T1	264 (54.0)	49 (62.0)	
T2	193 (39.5)	23 (29.1)	
≥T3	29 (5.9)	6 (7.6)	
Unknown	3 (0.6)	1 (1.3)	
Follow-up (mo)			.4477
Median	48.2	47.4	
Range	3.0–205.9	3.5–132.8	
Pelvic RT	38 (7.8)	7 (8.9)	.7231
Radiation dose (Gy)			.0002
Median	72.0	74.0	
Range	62.0–76.4	68.0–76.4	
Mean rectal dose (Gy)*			.9574
Median	47.5	47.4	
Range	31.0–68.3	37.7–88.9	
Maximal rectal dose (Gy)*			.0900
Median	79.9	81.1	
Range	58.5–85.0	72.8–104.1	
IMRT	233 (47.7)	48 (60.8)	.0301
ADT	225 (46.0)	38 (48.1)	.7299
TURP	56 (11.5)	6 (7.6)	.2871

Abbreviations: AC = anticoagulation; PSA = prostate-specific antigen; RT = radiotherapy; IMRT = intensity-modulated radiotherapy; ADT = androgen deprivation therapy; TURP = transurethral resection of the prostate.

Data in parentheses are percentages.

* Of 301 patients for whom data were available (246 in no AC group and 55 in AC group).