

Clinical Correlations between Treatment with Anticoagulants/Antiaggregants and Late Rectal Toxicity after Radiotherapy for Prostate Cancer

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Abstract. *Aim: To assess variables related to grade 2 or higher late rectal toxicity (LRT) in prostate cancer treated with external radiotherapy. Patients and Methods: A retrospective analysis was carried out of 232 patients with T1–T3 prostate cancer treated with 3-dimensional conformal radiotherapy (3DCRT) (106 patients) or intensity modulated radiotherapy (IMRT) (126 patients) between June 2000 and May 2007. One hundred and seventy-seven patients received androgen deprivation therapy (ADT); fifty patients used anticoagulants/antiaggregants for vascular disease. Results: The median follow-up was 31 months (range, 6-79). At 5 years, the cumulative incidence of grade 2 or 3 LRT was 5.6%. On multivariate analysis, medication with anticoagulants/antiaggregants was correlated with grade 2 or 3 LRT ($p=0.027$), whereas age, National Comprehensive Cancer Network risk group classification, use of ADT, radiotherapy technique (3DCRT vs. IMRT) and total irradiated dose were not. Conclusion: Treatment with anticoagulants/antiaggregants appears to be a factor in grade 2 or 3 LRT.*

The essential dose-limiting organs in external radiotherapy (EXRT) for prostate cancer are the rectum and bladder, and one of the most relevant side-effects is chronic rectal bleeding. Several publications have described the clinical factors related to late rectal toxicity (LRT) (1-8). However, to our knowledge, few studies have reported correlations between the use of anticoagulants/antiaggregants and late gastrointestinal (GI) toxicity (9-11).

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Key Words: Prostate cancer, radiotherapy, late toxicity, rectal toxicity.

In this study, clinical variables, including treatment with anticoagulants/antiaggregants, were assessed in relation to LRT in prostate cancer patients who underwent curative EXRT.

Patients and Methods

Between June 2000 and May 2007, a total of 232 patients with clinically localized prostate cancer were treated with three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT). Their median age was 72 years (range, 50–83). Patient characteristics are shown in Table I. Patients were classified into low-, intermediate-, and high-risk groups based on the National Comprehensive Cancer Network (NCCN) risk group classification. AJCC clinical T stage according to RT technique were as follows: 3DCRT: 42 patients in T1, 41 in T2 and 23 in T3; IMRT: 35 in T1, 31 in T2 and 60 in T3. Fifty patients (22%) had received anticoagulants/antiaggregants before, during and after RT for cardiovascular or cerebrovascular disease. The Eastern Cooperative Oncology Group performance status (PS) during the RT period was as follows: PS=0 in 222 patients, PS=1 in 8 and PS=2 in 2. There was no PS 3 or 4 patients in this series. The consent of all patients was obtained before the study was carried out.

Radiotherapy. In planning both 3DCRT and IMRT, Eclipse (release 6.5; Varian Medical Systems, Palo Alto, CA, USA) was used for dose calculations. The daily dose was 2.0 Gy per fraction, and the prescribed total dose is shown in Table I. The techniques for treatment planning and delivery for 3DCRT and IMRT are described below.

3DCRT. All patients treated with 3DCRT were immobilized in the supine position with a vacuum bag system for their feet. CT scans were performed at 3- to 5-mm slice thickness using a multi-detector CT scanner (GE Light Speed QX/i, Milwaukee, WI, USA). Patients were instructed to urinate just before CT scanning and before every treatment fraction. The clinical target volume (CTV) was expanded in three dimensions with 0.7- to 1.0-cm margins to obtain the planning target volume (PTV), except at the prostate-rectum interface, where a 0.3-cm margin was adopted to decrease rectal involvement. The dose was specified according to the International Commission on Radiation Units and Measurements reference point and was delivered with 10-MV photons in fractions of 2.0 Gy.

Table I. Patient characteristics.

	(n=232) (%)
Median age (range)(years)	72 (50-83)
Presence of hypertension	56 (24)
Presence of diabetes mellitus	27 (12)
NCCN risk group	
Low	10 (4)
Intermediate	80 (35)
High	142 (61)
Clinical T stage	
T1	77 (33)
T2	72 (31)
T3	83 (36)
RT technique	
3DCRT	106 (46)
IMRT	126 (54)
Median of total dose (range) (Gy)	
3DCRT	74 (70-74)
IMRT	80 (72-80)
Use of ADT	
Yes	177 (76)
No	55 (24)
Anticoagulants/antiaggregants	
Yes	50 (22)
No	182 (78)

NCCN, National Comprehensive Cancer Network; RT, radiotherapy; 3DCRT, three dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; ADT, androgen deprivation therapy.

IMRT. Each patient was implanted with three gold markers in the prostate gland before the treatment planning CT scan was obtained. All patients treated with IMRT were immobilized in the supine position with a vacuum bag system for their whole body and CT scans were performed at a slice thickness of 2.5 mm. The CTV included the prostate and seminal vesicles. Based on our previous study (12), the CTV was expanded in three dimensions with a 0.5-cm margin to obtain the PTV, except at the prostate-rectum interface, where a 0.3-cm margin was adopted to decrease rectal involvement. A portion of rectal wall located at the level of the PTV and 0.5-cm outside of the PTV on the CT images was contoured. IMRT plans were created for 15-MV photons using standardized 5-7 coplanar fields. The prescribed dose to cover 95% of the target volume (D95) was 80 Gy. The maximum dose heterogeneity allowable in the PTV was 10%. Each treatment plan was optimized to ensure the following: no more than 65% of the rectal wall and urinary bladder received >35 Gy (V35 ≤65%); no more than 45% of the rectal wall and urinary bladder received >55 Gy (V55 ≤45%); no more than 25% of the rectal wall and urinary bladder received >75 Gy (V75 ≤25%); and the rectal wall and urethra received no more than 81 Gy as the maximal dose (Dmax). Thirty minutes before daily IMRT, each patient urinated. The patients were initially set up using laser marks on the skin and were repositioned based on the positions of the three gold markers, with Varian On-Board Imager, for every treatment fraction.

Table II. Statistical analysis results for grade 2 or 3 late rectal toxicities.

Factors	Univariate			Multivariate	
	P-value	RR (95% CI)	P-value		P-value
Age (years)	0.28	–			0.408
NCCN risk group	0.66	–			0.455
ADT	0.47	–			0.171
RT technique (3DCRT vs. IMRT)	0.78	–			0.251
Total dose (Gy)	0.55	–			0.252
Anticoagulants/antiaggregants	0.004	5.67 (1.22-26.23)			0.027
Hypertension	0.99	–			0.578
Diabetes mellitus	0.38	–			0.827

RR, relative risk; CI, confidence interval; NCCN, National Comprehensive Cancer Network; ADT, androgen deprivation therapy; RT, radiotherapy; 3DCRT, three dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

Follow-up. Follow-up evaluations after treatment were performed at intervals of 3-6 months for 5 years and every 6 months thereafter. The follow-up period ranged from 6 to 79 months (median, 31).

Toxicity scoring. LRT appeared no earlier than 90 days after the initiation of EXRT and was scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) morbidity scores (13-14). In brief, moderate diarrhea and colic, bowel movements of more than 5/day, excessive rectal mucus, or intermittent bleeding was considered grade 2 morbidity, and any laser cauterization or blood transfusion resulting from rectal bleeding was considered grade 3 toxicity.

Statistical analysis. The primary endpoint was grade 2 or higher LRT. The complication rates were determined using Kaplan–Meier estimates. The time to grade 2 or worse LRT was fit to a univariate proportional hazard regression model testing the clinical continuous variables such as patient age and total irradiated dose. The other clinical variables including presence of hypertension, presence of diabetes mellitus, NCCN risk group classification, use of androgen deprivation therapy (ADT), EXRT technique (3DCRT vs. IMRT), and treatment with anticoagulants/antiaggregants were tested by log-rank tests. Multivariate analysis was performed using Cox regression model to determine factors that correlated with grade 2 or higher LRT. The variables considered were patient age, NCCN risk group classification, use of ADT, total irradiated dose, EXRT technique (3DCRT vs. IMRT), and treatment with anticoagulants/ antiaggregants. Statistical analyses were performed using the Statistical Package for Social Sciences, version 11.0, for Windows. A $p < 0.05$ significance level (2-sided) was considered for all statistical tests.

Results

Six patients (2.6%) experienced grade 2 LRT. Two (0.9%) developed grade 3 LRT that required laser cauterization therapy. No patient developed grade 4 or higher LRT. The 5-year actuarial incidence of grade 2 or 3 LRT was 5.6%. The median time to developing grade 2 or 3 LRT was 13 months (range, 8-41). On univariate analysis, treatment with anticoagulants/antiaggregants was correlated with grade 2 or 3 LRT, whereas age, presence of hypertension, presence of diabetes mellitus, NCCN risk group, total irradiated dose, RT technique (3DCRT *vs.* IMRT), and use of ADT were not (Table II). On multivariate analysis, the use of anticoagulants/antiaggregants was related to grade 2 or 3 LRT (Table II). Among those patients who used anticoagulants/antiaggregants, the 5-year incidence of LRT was 10.1%, compared with 4.3% for those who did not receive anticoagulants/antiaggregants ($p=0.004$).

Discussion

A significant correlation between the medication of anticoagulants/antiaggregants and grade 2 or 3 LRT after definitive EXRT for localized prostate cancer was found, although the other clinical variables were not related statistically. However, it was difficult to ascertain whether these co-existing morbidities had any relationship to LRT or not, because our assessment was a retrospective study.

In contrast, some studies have reported that several clinical factors are related to LRT. Skwarchuk *et al.* (1) indicated that patient age is a continuous variable related to LRT. However, according to Schultheiss *et al.* (2), age <60 years was not correlated with late GI toxicity. Lawton *et al.* (3) found that age (≤ 70 *vs.* >70 years) was not significant for late grade 3 GI toxicity. Although it is difficult to directly compare their results and ours, we also found no significant difference in the development of grade 2 or 3 LRT in regard to age.

According to Liu *et al.* (4), coexisting GI disease increased the risk of late grade 2 or 3 GI toxicities. Skwarchuk *et al.* (1) and Herold *et al.* (5) have reported that diabetes was correlated with late GI toxicity. Several authors have identified the presence of acute GI toxicity as a significant factor for late GI toxicity (1, 2, 4, 6, 7) and some have also described an association between use of hormonal therapy (HT) and late GI toxicity (2, 4, 8). In contrast, like us, Zelefsky *et al.* (7) could not identify any relationship between HT and LRT.

To our knowledge, there are few reports about the relationship between the use of anticoagulants/antiaggregants and late GI toxicity. In the present study, treatment with anticoagulants/antiaggregants was significantly correlated with grade 2 or 3 LRT. According to Choe *et al.* (9), patients on anticoagulants were at substantial risk for acute or late

bleeding after EXRT for prostate cancer, and the authors suggested that surgery may be preferable to radiotherapy (RT) in these patients. They also suggest that lower RT doses or smaller target volumes should be considered for patients who are not surgical candidates. However, with a lower RT dose or smaller target volume, intermediate- or high-risk patients may not obtain a satisfactory outcome. Furthermore, in the study by Choe *et al.* (9), the patients and treatment appeared to be heterogeneous: one patient received a seed implant after 45 Gy, six were treated after radical prostatectomy; and the treatment field included the prostate and seminal vesicles for 30 patients and the whole pelvis for three patients. Although Vavassori *et al.* (10) have studied the correlation between acute GI toxicity and the use of anticoagulants/antiaggregants, HT and mean rectal radiation dose, they did not report late GI toxicity. In a study based on a questionnaire survey, Fiorino *et al.* (11) showed that the use of anticoagulants/antiaggregants had no significant relationship to grade 2 and 3 LRT. However, questionnaire-assessed toxicity may not correlate with RTOG/EORTC toxicity.

Preexisting vascular disease might have been the main cause of grade 2 or 3 LRT. Simizu *et al.* (15) reported late laryngeal radionecrosis in severe arteriosclerosis. They considered the general vascular condition of the patient to play a role in the rate and degree of development of radionecrosis. However, the use of anticoagulants/antiaggregants might have promoted LRT in addition to any preexisting general vascular condition. As a limit of the current study, it was difficult to clarify which vascular disease needed anticoagulants/antiaggregants or if the medication of anticoagulants/antiaggregants promoted grade 2 or 3 LRT. All we can conclude is that using anticoagulants/antiaggregants might be one cause of grade 2 or 3 LRT.

Further investigation is needed to confirm the relationship between the use of anticoagulants/antiaggregants and LRT. Nevertheless, watchful follow-up of patients treated with anticoagulants/antiaggregants after EXRT may be necessary.

Conclusion

General vascular disease treated with anticoagulants/antiaggregants appears to be correlated with grade 2 or 3 LRT after definitive EXRT for prostate cancer.

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Received December 26, 2008

Revised March 4, 2009

Accepted March 30, 2009