Clinical Predictors of Late Gastrointestinal Toxicity after Three-dimensional Conformal Radiotherapy for Localized Prostate Cancer

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Original Paper

Clinical Predictors of Late Gastrointestinal Toxicity after Three-dimensional Conformal Radiotherapy for Localized Prostate Cancer

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局所型前立腺癌に対する3次元原体照射後の晩期消化管障害に関連する臨床因子

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This study estimated the late gastrointestinal (GI) toxicity after three-dimensional conformal radiotherapy (3DCRT) with curative intent for localized prostate cancer (LPC) and assessed the correlated clinical factors. 88 LPC patients underwent 3DCRT between March 2004 and May 2007. The total dose was 74 Gy in 2-Gy daily fractions for each patient. The median patient age was 71 years (range 52-80). According to the National Comprehensive Cancer Network (NCCN) risk group classification, 6, 45, and 37 patients were low, intermediate, and high risk, respectively. There were 39, 34, and 15 patients at stages T1 to T3, respectively. Fifty six patients were given androgen deprivation therapy (ADT). There was coexisting hypertension (HT) in 17 patients, diabetes mellitus (DM) in 10, hemorrhoids in 9, and pre-existing gastrointestinal (GI) disease in 13. Four patients had undergone previous abdominal surgery. Twelve patients received anticoagulants/antiaggregants (A/A) for pre-existing vascular disease. The relationships between the following variables and late GI toxicity were accessed : NCCN risk, use of ADT, presence of HT, DM, hemorrhoid, pre-existing GI disease, A/A treatment, and history of abdominal surgery. Late GI toxicity of grade 2 and 3 occurred in one patient each. There was no grade 4 or higher late toxicity. Late GI toxicity of grade 2 or 3 at 3 years occurred in 3%. In univariate analysis, A/A treatment and pre-existing GI disease were significantly correlated with grade 2 or 3

late GI toxicity. A/A treatment and pre-existing GI disease appear to predict grade 2 or 3 late GI toxicity.

Introduction

Dose escalation of radiotherapy (RT) improves the treatment outcome of localized prostate cancer (LPC)[1-3]. However, late toxicity may limit the extent to which the dose may be escalated safely. The essential dose-limiting organs in external beam radiotherapy (EBRT) for LPC are the rectum and bladder.

Several publications have described the clinical factors related to late gastrointestinal (GI) toxicity[4-11]. However our previous report analyzed heterogeneous group including both intensity-modulated radiotherapy (IMRT) group and three-dimensional conformal radiotherapy (3DCRT) group[11].

In this study, we assessed clinical variables, including treatment with anticoagulants/antiaggregants, in relation to late GI toxicity grade 2 or worse in LPC patients who underwent curative 3DCRT.

Materials and Methods

Between June 2004 and May 2007, a total of 96 patients with clinically LPC were treated with 3DCRT. 8 of those patients were excluded from this analysis because of insufficient observation period. 88 patients were included in this study. Patient characteristics are shown in Table 1. Patients were classified into low-, intermediate-, and high-risk groups based on the National Comprehensive Cancer Network (NCCN) risk group classification. American Joint Committee on Cancer clinical T stage was used. Twelve patients (14%) had received anticoagulants/antiaggregants before, during, and after radiotherapy (RT) for cardiovascular or cerebrovascular disease. The Eastern Cooperative Oncology Group performance status (PS) during radiotherapy period was as follows. PS=0 in 82 patients, and PS=1 in 6. There was no PS=2 or higher patients in this series. Details of pre- or co-existing GI disease were as follows : colon polyps in 5 patients, gastric ulcer in 3, gastric cancer in 2, colon cancer in 1, enteritis in 1 and diverticulitis in 1. Presence of hemorrhoids was in 9. The consent of all patients was obtained before the study was carried out.

Radiotherapy : In planning 3DCRT, Eclipse (release 6.5 ; Varian Medical Systems, Palo Alto, CA) was used for dose calculations. The daily dose was 2.0 Gy per fraction, administered 5 days a week. The prescribed total dose for each patient was 74 Gy.

All patients treated with 3DCRT were immobi-

Table 1. Patient characteristics.

		n=88 (%)
Median age (range)(years)		71 (52-80)
NCCN risk group	Low	6 (7)
	Intermediate	45 (51)
	High	37 (42)
Clinical T stage	T1	39 (44)
	T2	34 (39)
	T3	15 (17)
Use of ADT	Yes	56 (64)
	No	32 (36)
Presence of hypertension	Yes	17 (19)
	No	71 (81)
Presence of diabetes mellitus	Yes	10 (11)
	No	78 (89)
Presence of GI disease	Yes	13 (15)
	No	75 (85)
Presence of hemorrhoid	Yes	9 (10)
	No	79 (90)
Prior abdominal surgery	Yes	4 (5)
	No	84 (95)
Use of A/A	Yes	12 (14)
	No	76 (86)

NCCN=national comprehensive cancer network ; ADT =androgen deprivation therapy ; GI=gastrointertinal ; A/A=anticoagulants/antiaggregants

lized 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 QXi). 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.

After the treatment planning, one pair of orthogonal (anteroposterior (AP) and right-lateral) digitally reconstructed radiograph (DRR) was constructed in which the position of bony anatomy could be located. This image set constituted the reference image pair. For the verification of treatment fields on each RT day, the therapist acquired one pair of orthogonal electronic portal images (EPI) using the AP and left-right (L-R) set-up fields ; these constituted the comparison image set. The portal images were taken using a Varian Oncology Systems an amorphous silicon flat-panel electronic portal imager (Varian Medical Systems, Palo Alto, CA) mounted on a dual energy Clinac 2100EX accelerator. The daily repositioning of the patients before each treatment fraction was accomplished through image matching of the EPI to the reference DRR based on bony anatomy.

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 5 to 47 months (median, 23).

Toxicity scoring : Late toxicity appeared more than or equal to 90 days after the initiation of EBRT and was scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) morbidity scores[16,17]. In brief as for GI toxicity, moderate diarrhea and colic, bowel movements of more than 5 times daily, 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 late GI toxicity. The complication rates were determined using Kaplan-Meier estimates. The time to grade 2 or worse late GI toxicity were fit to log-rank tests estimating the clinical variables including presence of hypertension, presence of diabetes mellitus, NCCN risk group classification, use of androgen deprivation therapy (ADT), presence of pre- or co-existing GI disease, presence of hemorrhoid, history of abdominal surgery, and treatment with anticoagulants/antiaggregants. Statistical analyses were performed using the Statistical Package for Social Sciences, version 11.0, for Windows. $AP<0.05$ significance level (2-sided) was considered for all statistical tests.

Results

Late GI toxicity of grades 2 and 3 occurred in one patient each. No patient developed grade 4 or higher late GI and GU toxicity. Late GI toxicity of grade 2 or 3 at 3 years occurred in 3%. The median time to developing grade 2 or 3 late GI toxicity was 12 months (range, 9-14). In univariate analysis, treatment with anticoagulants/antiaggregants correlated with grade 2 or 3 late GI toxicity, as pre- or co-existing GI disease did, whereas presence of hypertension, presence of diabetes mellitus, presence of hemorrhoid, NCCN risk group, prior abdominal surgery, and use of ADT were not (Table 2). Among those patients who used anticoagulants/antiaggregants, the 3-year incidence of late GI grade 2 or 3 was 19%, compared with 0% for those who did not receive anticoagulants/antiaggregants ($P=0.0006$).

Table 2. Univariate analysis results for Grade 2 or 3 late GI toxicities

Factors	*P* value
NCCN risk group	0.25
Use of ADT	0.76
Hypertension	0.49
Diabetes mellitus	0.068
Hemorrhoid	0.71
Pre- or co-existing GI disease	0.0005
Prior abdominal surgery	0.74
Anticoagulants/antiaggregants	0.0006

NCCN=national comprehensive cancer network ; ADT =androgen deprivation therapy ; GI=gastrointertinal

Discussion

In current study, treatment with anticoagulants/antiaggregants correlated significantly with grade 2 or 3 late GI toxicity after definitive 3DCRT for localized prostate cancer, as did pre- or co-existing GI disease, although the other clinical variables were not related statistically. However, it was difficult to ascertain whether the other co-existing morbidities did not have relationship to late GI toxicity or not, because our assessment was retrospective study.

Some studies have reported that several clinical factors are related to late GI toxicity. According to Liu et al.[6], coexisting GI disease increased the risk of late grade 2 or 3 GI toxicities as well as our report. Skwarchuk et al.[4] and Herold et al.[7] 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[4-6,8,9], and some have also described an association between use of hormonal therapy (HT) and late GI toxicity[5,6,10]. In contrast, like us, Zelefsky et al.[9] could not identify any relationship between HT and late GI toxicity.

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 late GI toxicity. According to Choe et al.[12], patients on anticoagulants were at substantial risk for acute or late bleeding after EBRT for prostate cancer, and the authors suggested that surgery might be preferable to 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.[12], 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. In their other publication[13], Choe et al. reported that patients taking anticoagulation therapy have a substantial risk of bleeding toxicity from EBRT. However, their patients also seemed to be heterogeneous in order to include 3DCRT patients group and IMRT patients group, as well as our previous study[11]. Although Vavassori et al.[14] have studied the correlation between acute GI toxicity and the use of anticoagulants/antiaggregants, HT, and mean rectal radiation dose, they have not reported late GI toxicity. In a study based on a questionnaire survey, Fiorino et al.[15] have shown that the use of anticoagulants/antiaggregants had no significant relationship to grade 2 and 3 late GI toxicities. However, questionnaire-assessed toxicity may not correlate with RTOG/EORTC toxicity.

Choe et al.[18] demonstrated that the use of anticoagulation therapy is associated with improved PSA control in patients with LPC who receive RT. The potential benefit may be pronounced in patients with high-risk disease but no overt evidence of metastasis. However, the use of anticoagulants is associated with an elevated risk of bleeding complications, which may be even more significant in patients with cancer. Therefore, according to them, the risk of

serious bleeding must be weighed against the potential benefit. Additional studies investigating new anticoagulants with lower bleeding risk will be necessary.

Preexisting vascular disease might have caused grade2 or 3 late GI toxicities as main reason. Simizu et al.[19] reported late laryngeal radionecrosis in severe arteriosclerosis. They considered general vascular condition of the patient to increase the rate and degree of development of radionecrosis. However, the use of anticoagulants/antiaggregants might have promoted late GI toxicity in addition to preexisting general vascular condition. As limit of the current study, it was difficult to clarify which vascular disease needed anticoagulants/antiaggregants or the medication of anticoagulants/antiaggregants promoted grade 2 or 3 late GI toxicities. In addition, the current number of patients was so small that it is difficult to show significant relationship between late GI toxicities and the use of anticoagulants/antiaggregants. Further investigation is needed to confirm the relations.

In conclusion, general vascular disease treated with anticoagulants/antiaggregants and presence of pre- or co-existing GI disease appear to be correlated with grade 2 or 3 late GI toxicities after 3DCRT for LPC. Watchful follow-up of patients treated with anticoagulants/antiaggregants after EBRT may be necessary.

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