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Rectal Toxicity After Extremely Hypofractionated Radiotherapy Using a Non-Isocentric Robotic Radiosurgery System for Early Stage Prostate Cancer

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Abstract

Background: The aim of the study was to evaluate toxicity after extremely hypofractionated radiotherapy (EHF-RT) using a non-isocentric robotic radiosurgery system for early stage prostate cancer.

Methods: Eligibility criteria of this feasibility study were 50 - 84 years old, and low-risk to intermediate-risk disease. The prescribed dose to the iso-dose line of 95% of planning target volume was 35 Gy in five fractions over 2 weeks. The primary endpoint was the incidence of ≥ grade 2 acute toxicity which indicated symptoms requiring medications.

Results: We enrolled 20 patients from December 2012 to August 2014, and the median follow-up time was 30 months (range: 18 - 36). Sixteen patients had a short overall treatment time (OTT) of EHF-RT (9 - 10 days), and four patients had a long OTT (11 - 12 days) because of national holidays and patient's preference. The incidences of ≥ grade 2 acute toxicity in all sites, that in the rectum, and that in the genitourinary system, were 30%, 20%, and 10%, respectively. No patient developed severe acute toxicity (≥ grade 3). Among 16 patients with a short OTT of EHF-RT, four patients developed grade 2 acute rectal toxicity. Rectum-$V_{28\ Gy}$ (rectal volume receiving ≥ 28 Gy) of 3.8 mL or higher had a tendency to increase grade 2 acute rectal toxicity (P = 0.058). One patient developed grade 3 late rectal toxicity and no patient developed severe late genitourinary toxicity.

Conclusion: The incidences of ≥ grade 2 acute toxicity in all sites and that in the rectum after EHF-RT of 35 Gy in five fractions were 30% and 20%, respectively. High rectum-$V_{28\ Gy}$ was associated with grade 2 acute rectal toxicity after EHF-RT for early prostate cancer.

Keywords: Hypofractionated radiotherapy; Prostate cancer; Rectal toxicity; Stereotactic body radiotherapy

Introduction

External beam radiotherapy is one of the standards of care for localized prostate cancer. The conventionally fractionated three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) using 2 Gy fraction size have been commonly applied in clinical practice. Several randomized clinical trials demonstrated that a high-dose conventionally fractionated radiotherapy increased progression-free survival compared to the low-dose radiotherapy of 66 - 70 Gy, albeit not overall survival [1, 2]. The recent advanced technology including IMRT and image-guided radiotherapy (IGRT) permits hypofractionated radiotherapy using a large fraction size of higher than 2 Gy [3]. Hypofractionated radiotherapy with a large fraction size has been presumed as a biologically effective approach for cancers with a low alpha-beta ratio compared to conventionally fractionated radiotherapy [3, 4]. Stereotactic body radiotherapy (SBRT) with an extremely large fraction size of 6 - 18 Gy has emerged, and SBRT for the prostate cancer with a low alpha-beta ratio has been investigated to increase the tumor control, as well as shorten treatment regimen [5-7]. The safety and efficacy of extremely hypofractionated radiotherapy (EHF-RT) using SBRT technique for prostate cancer have not been established [7, 8]. We conducted a feasibility study to evaluate the rectal and genitourinary toxicity after EHF-RT using a non-isocentric robotic radiosurgery system for early stage prostate cancer.

Materials and Methods

Eligibility criteria for enrollment in the prospective study

Eligibility criteria of this feasibility study were as follows: 1)

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Table 1. Dose Targets and Constraints for Treatment Planning

PTV	D (1 mL) < 42 Gy
	D (95%) ≥ 35 Gy
	D (98%) ≥ 33.25 Gy
Rectum	D (1 mL) ≤ 36.75 Gy
	D (3 mL) ≤ 33.25 Gy
	D (10%) ≤ 31.5 Gy
	D (20%) ≤ 28 Gy
	D (50%) ≤ 17.5 Gy
Colon	D_{max} ≤ 38 Gy
	D (20 mL) < 25 Gy
Bladder	D (1 mL) < 38 Gy
	D (10%) ≤ 31.5 Gy
	D (50%) ≤ 17.5 Gy
Urethra	D (1 mL) < 37.45 Gy
Penile bulb	D_{max} ≤ 35 Gy
	D (3 mL) < 20 Gy
Femoral head	D_{max} ≤ 30 Gy
	D (10 mL) < 20 Gy

PTV: planning target volume; D (x mL): radiation dose covered irradiated volume (x mL); D (x %): irradiated volume (x % of the risk organ or target volume) covered by high radiation dose; D_{max}: maximum point-dose which is allowed.

50 - 84 years old, 2) performance status 0 - 1, 3) adenocarcinoma, 4) low-risk disease (T1-T2a and initial prostate specific antigen (iPSA) < 10 ng/mL and Gleason score (GS) ≤ 6), or a part of intermediate-risk disease (T1-T2a and iPSA 10 - 20 ng/mL and GS ≤ 6, or T1-T2a and iPSA < 10 ng/mL and GS = 7), and 5) written informed consent [9]. Exclusion criteria were active second malignancy, uncontrolled infection, mental disorder, uncontrolled diabetes mellitus, interstitial pneumonitis, collagen vascular diseases, heart failure, and previous history of radiofrequency ablation therapy for prostate cancer. A short-course induction hormonal therapy (≤ 8 months) was allowed. The primary endpoint was the incidence of ≥ grade 2 acute toxicity within 90 days after the initiation of EHF-RT. The secondary endpoints were 2-year overall survival rate, 2-year clinical progression-free survival rate, biochemical failure, failure pattern, and late toxicity. This study was approved by the institutional review board (No. 12-147), and was initiated in November 2012 (Trial registration number: UMIN000009615).

Radiotherapy planning and treatment

Three fiducial gold markers were implanted into the prostate, enabling real-time tracking and automatic beam adjustment for inter- and intra-fractional prostate motion. Computed tomography (CT) for radiotherapy planning was performed 1 week later after fiducial implantation. All patients were placed in the supine position, and a customized vacuum-lock bag was usually used for patient's immobilization. CT scanning was mainly performed using a 2.5-mm slice thickness and 1.375-mm slice step. No respiratory control system was applied. An empty rectum and moderately full bladder were required. A urethra catheter was inserted for its identification on the planning CT images, but it was not inserted at each treatment.

The clinical target volume (CTV) for low-risk disease was defined as the prostate only, and that for intermediate-risk disease was defined as the prostate plus proximal seminal vesicles. The planning target volume (PTV) equaled the CTV expanded 3 mm posteriorly and 5 mm in all other dimensions. Treatment planning was performed using radiation planning system software Multiplan version 4.0.3 (Accuray Inc., Sunnyvale, CA). The Monte Carlo algorithm was used to evaluate correctly the heterogeneous tissue density. Non-isocentric robotic radiosurgery system (CyberKnife 2, Sunnyvale, CA) applied 6 MV X-rays. The prescription dose was 35 Gy in 5 fractions over 2 weeks, and the iso-dose line of 35 Gy covered at least 95% of PTV. The normal tissue dose constraints were shown in Table 1. Each treatment was mainly performed on every other day.

Patient follow-up and data analysis

Clinical evaluation and PSA measurements were performed at 3 and 6 months after the initiation of EHF-RT, and then every 6 months up to at least 2 years. Overall survival time was defined as the time from registration to death due to any causes. Clinical progression-free survival time was defined as the time from registration to the first event of either clinically detectable progressive disease at any sites or death due to any causes. The Kaplan-Meier method was applied to estimate survival rates. PSA nadir was defined as a lowest PSA value for the patients with at least 1-year PSA follow-up after the trial registration. PSA failure was defined according to the Phoenix definition (PSA > 2 ng/mL above the observed PSA nadir) [10]. PSA bounce was defined as an increment of PSA above the observed nadir higher than 2 ng/mL, with a subsequent decline in PSA without further treatment. Toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 4.0) [11]. Statistical difference between two categorical variables was analyzed using Chi-squared test. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using JMP software version 11 (SAS Institute, Cary, NC).

Results

Twenty patients (17 patients from Saitama Medical University, two patients from Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, and one patient from Yokohama Saiseikai Hospital) were enrolled from December 2012 to August 2014 (Table 2). The median age was 70 years old (range: 57 - 78). Twelve patients had low-risk diseases and eight had intermediate-risk diseases. Two patients received short-course induction hormonal therapy (2 and 8 months). All

Table 2. Patient's Characteristics

	Number of patients (%)	
Median age (range)		70 years (57 - 78)
Initial IPSS		
0 - 5	12 (60)	
6 - 10	4 (20)	
11 - 16	4 (20)	
Initial PSA (range)		6.92 ng/mL (3.3 - 14.32)
< 10 ng/mL	18 (90)	
> 10 ng/mL	2 (10)	
Gleason score		
3+3	14 (70)	
3+4	3 (15)	
4+3	3 (15)	
Clinical T stage		
T1c	16 (80)	
T2a	2 (10)	
T2b	1 (5)	
T2c	1 (5)	
Risk group		
Low-risk	12 (60)	
Intermediate-risk	8 (40)	
Hormonal therapy		
Yes	2 (10)	
No	18 (90)	
Median CTV volume (range)		23.75 mL (11.1 - 99.0)
Median PTV volume (range)		50.3 mL (27.6 - 155.7)

IPSS: international prostate symptom score; PSA: prostate specific antigen; CTV: clinical target volume; PTV: planning target volume.

patients received the planned EHF-RT of 35 Gy in 5 fractions. Sixteen patients had a short OTT of EHF-RT (9 - 10 days), and four patients had a long OTT (11 - 12 days) because of national holidays and patient's preference. The median follow-up time was 30 months (range: 18 - 36), and all 19 surviving patients were followed at least 2 years.

The incidences of grade 2 or worse acute toxicity in all sites, that in the rectum, and that in genitourinary system were 30%, 20%, and 10%, respectively. Grade 1 and 2 acute rectal toxicity occurred in seven patients (35%) and four patients (20%), respectively, and no patient developed grade 3 or worse acute toxicity. These four patients with grade 2 acute rectal toxicity developed a moderate to severe fecal frequency at 1 week later after EHF-RT completion. The proctitis disappeared within 1 week after usage of steroidal enema. Among 16 patients with a short OTT, four patients developed grade 2 acute rectal toxicity, and rectum-$V_{28\ Gy}$ (rectal volume receiving ≥ 28 Gy) of 3.8 mL or higher was associated with grade 2 acute rectal toxicity (36.3% vs. 0%, P = 0.058) (Table 3). Four patients with a long OTT did not develop grade 2 or worse acute rectal toxicity. Two patients developed transitional grade 2 acute genitourinary toxicity, but urinal frequency disappeared by conservative medications.

One patient with grade 2 acute proctitis developed grade 3 late rectal toxicity. He suffered from atrial fibrillation and took anti-platelet drug since long before EHF-RT. Rectal bleeding was found at 5 months after EHF-RT, and conservative therapies including laser therapy and hyperbaric oxygen therapy were performed for 6 months. However, these conservative therapies did not work, and he received permanent colostomy at 12 months after EHF-RT. Grade 1 late rectal toxicity including mild fecal frequency and defecation pain occurred in three patients (15%). No severe late genitourinary toxicity (≥ grade 2) occurred until the last follow-up time.

Two-year overall survival and 2-year clinical progression-free survival rates were 95% and 95%, respectively. One patient died due to a traffic accident without PSA failure and clinically progressive disease at 18 months after EHF-RT. No patient received adjuvant hormonal therapy after EHT-RT. No patient developed biochemical failure and clinical progression

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Table 3. Acute Rectal Toxicity and Dosimetric Parameters for 16 Patients Treated Extremely Hypofractionated Radiotherapy Within 10 Days

Dosimetric parameters	Number of patients	≥ grade 2 rectal toxicity (%)	P value
Maximum dose			
< 38 Gy	11	27.2	0.752
≥ 38 Gy	5	20.0	
Rectum-$V_{31.5\ Gy}$			
< 2 mL	6	16.6	0.542
≥ 2 mL	10	30.0	
Rectum-$V_{28\ Gy}$			
< 3.8 mL	5	0	0.058
≥ 3.8 mL	11	36.3	
Rectum-$V_{24\ Gy}$			
< 7 mL	8	12.5	0.239
≥ 7 mL	8	37.5	
Rectum-$V_{17.5\ Gy}$			
< 12 mL	7	14.2	0.372
≥ 12 mL	9	25.0	

Rectum-$V_{x\ Gy}$: % rectal volume receiving > x Gy.

until the last follow-up time. The median time to achievement of PSA nadir was 30 months (range: 18 - 36), and the median PSA nadir was 0.729 ng/mL (range: 0.027 - 1.681). Seven patients (35%) had a nadir < 0.40 ng/mL, five patients (25%) had a nadir 0.40 - 1.00 ng/mL, and eight patients (40%) had a PSA nadir > 1.00 ng/mL. PSA bounce was found in two patients.

Discussion

The incidence of severe rectal toxicity after conventional fractionated IMRT for localized prostate cancer has been relatively low [4]. Zelefsky and colleagues evaluated 772 patients treated with conventional fractionated IMRT of 81 - 86.4 Gy [12]. They reported that only 4% of the patients developed acute rectal toxicity which indicated symptoms requiring medications, and no patient experienced severe rectal toxicity for the median follow-up time of 24 months (range: 6 - 60). Kazt and colleagues reported that grade 2 acute rectal toxicity occurred in 3.5-4% of the 304 patients treated with EHF-RT of 35 - 36.5 Gy using a non-isocentric robotic radiosurgery system, and no patient developed grade 3 or worse rectal toxicity [7]. On the other hands, Kim and colleagues evaluated 91 patients treated with EHF-RT of 47.5 - 50 Gy, and reported that the incidence of grade 2 or worse acute rectal toxicity was about 25% [13, 14]. Six patients treated with 50 Gy developed severe rectal toxicity with the median time to onset of 9.5 month, and five patients of them required salvage colostomy. King and colleagues reported that EHF-RT of 36.5 Gy in 5 fractions delivered three times a week on alternating days showed less frequent rectal toxicity compared to consecutive daily treatment regimen [15]. In our study, four patients with a short OTT (≤ 10 days) developed grade 2 acute rectal toxicity. The treatment interval of 48 h does not seem to be enough for sub-lethal damage repair after large fraction size. Two times a week regimen should be evaluated to avoid severe rectal toxicity.

It has been supposed that severe rectal toxicity is observed when the dose exceeds a threshold of inactivation of stem cells in the rectal wall, and remaining stem cells within the rectal wall exposed to dose levels below this threshold would migrate toward the injured rectal mucosa. Kim and colleagues analyzed the relationship between dosimetric parameters and rectal toxicity after EHF-RT of 47.5 - 50 Gy in 5 fractions, and reported that acute rectal toxicity (≥ grade 2) was significantly correlated with irradiated area of > 50% circumference of rectal wall with 24 Gy [14]. They examined the previously reported preclinical models and their own clinical data, and reported that an irradiated rectal wall volume of 24 - 39 Gy in 5 fractions was associated with a risk of acute rectal toxicity [14, 16]. In our study, high rectum-$V_{28\ Gy}$ was associated with high incidence of grade 2 acute rectal toxicity. However, other dosimetric parameters were not associated with rectal toxicity because of small sample size and few adverse events.

HYpofractionated irradiation for PROstate cancer (HYPRO) trial was a randomized, non-inferiority, phase 3 trial which compared conventionally fractionated radiotherapy of 78 Gy in 39 fractions with hypofractionated radiotherapy of 64.6 Gy in 19 fractions [4]. Three-year cumulative incidence of grade 2 or worse late rectal toxicity was 17.7% in conventional fractionation group versus 21.9% for hypofractionation group, and cumulative incidence of grade 3 or worse late rectal toxicity was 2.6% in the conventional fractionation group and 3.3% in the hypofractionation group. Only one patient (5%) developed grade 2 or worse late rectal toxicity in our study. But we did not integrate the qualification of usage of antiplatelet agents into our exclusion criteria, and one patient who

took it developed grade 3 late rectal toxicity. Our inappropriate exclusion criteria and small sample size made it impossible to achieve a definitive conclusion about the relationship of dosimetric parameters and late rectal toxicity after EHF-RT.

There are two potential clinical benefits of EHF-RT for localized prostate cancer. The first potential benefit is a possibility of increment of biological control. Hypofractionated radiotherapy using a large fraction size has been presumed as biologically effective approach for cancers with a low alpha-beta ratio compared to conventionally fractionated radiotherapy [3, 4]. A lower PSA nadir has been thought as potential early surrogate marker for disease control [13, 17, 18]. Zietman and colleagues evaluated 314 consecutive patients with T1-2 disease treated by conventional fractionated radiotherapy, and reported that a PSA nadir of less than 0.5 ng/mL represented an early surrogate for subsequence freedom from biochemical failure [17]. Boike and colleagues reported that a PSA nadir was around 0.2 ng/mL in most patients who received EHF-RT of 45 - 50 Gy in 5 fractions [13]. King and colleagues reported that 78% of the patients who received EHF-RT of 36.5 Gy in 5 fractions achieved a PSA nadir < 0.4 ng/mL, and 35% of our patients achieved a PSA nadir < 0.4 ng/mL [19]. On the other hand, Pollack and colleague reported that a PSA nadir was not a surrogate maker for freedom from failure including biochemical failure and/or clinical failure after conventional fractionated dose-escalated radiotherapy [18]. The second potential benefit is to avoid prolongation of OTT of radiotherapy. Thames and colleagues conducted the retrospective study including 4,839 patients with localized prostate cancers who received conventional fractionated radiotherapy, and reported that among patients with the low-risk to intermediate-risk disease who received 70 Gy or higher, 1-week prolongation of OTT of radiotherapy led to 6% decline of biochemical control [20]. EHF-RT provides a short OTT regimen of only 2 weeks.

There are some limitations of our study because of small sample size and few adverse events. Further study is required to establish a confidential dose-constraint for acute and late rectal toxicity and adequate treatment schedule of EHF-RT for early stage prostate cancer.

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Conflicts of Interest

None.

Author Contributions

Conception and design: Naoto Shikama, Yu Kumazaki, Keiji Nihei, Nobuhiro Tsukamoto. Manuscript writing: all authors. Final approval of manuscript: all authors.

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