Acute Toxicity After CyberKnife-Delivered Hypofractionated Radiotherapy for Treatment of Prostate Cancer

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Objective: To evaluate acute toxicity outcomes of prostate cancer patients treated with CyberKnife-delivered hypofractionated radiotherapy.

Methods: This study was a retrospective chart review analysis of the first 50 patients treated with CyberKnife radiotherapy for prostate cancer. Most patients were affected with early to intermediate stage prostate cancer. Two patients had metastatic disease at presentation and were excluded. A total of 37 patients received irradiation at a dose of 35 to 37.5 Gy in 5 fractions of 7 to 7.5 Gy per fraction. Assuming an alpha/beta ratio of 1.5 Gy, this process delivered an equivalent dose of 85 to 96 Gy in 2 Gy fractions (EQD2). A subset of patients (n = 11) received standard linear accelerator-based pelvic radiation treatment either by intensity modulated radiation therapy or tomotherapy and received a boost via the CyberKnife at a dose of 17.6 to 25 Gy in 2 to 5 fractions (EQD2= 46.6–72 Gy). The acute toxicities were recorded using the Common Terminology Criteria for Adverse Events, version 3.0, throughout treatment and at patients' follow-up visits.

Results: The median patient age at presentation was 66 years (range, 46–80). The mean pretreatment prostate specific antigen and Gleason scores were 9.16 ng/mL and 7, respectively. Grade 2 acute genitourinary toxicity was reported by 10% of patients (n = 5). Only 3 patients reported grade 3 acute genitourinary toxicity. No gastrointestinal grade 2 or grade 3 toxicities were reported.

Conclusions: CyberKnife-delivered hypofractionated radiotherapy for the treatment of prostate cancer has an acceptable acute toxicity profile.

Key Words: prostate cancer, hypofractionation, stereotactic body radiation therapy, acute toxicity

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Prostate cancer is the most common noncutaneous cancer in men, with an estimated 186,000 cases diagnosed in 2008 according to the National Cancer Institute.[1] It is the second leading cause of cancer-related deaths (~30,000/y).[1] The absolute number of prostate cancer deaths has been steadily decreasing, which can be attributed to early detection because of the use of the prostate-specific antigen (PSA) screening test and the transrectal ultrasound-guided extended pattern biopsy.

Recent analysis of the radiobiological properties of the prostate tumors suggests that their alpha/beta ratio may be as low as 1.5 Gy,[2–4] indicating that they are more sensitive to higher doses of radiation per fraction. This low ratio is the rationale for hypofractionation of definitive therapy (fewer number of fractions), resulting in an attractive treatment option with respect to treatment duration and logistics. Retrospective evidence further supports the fact that prostate cancer treatment can be achieved via a hypofractionated regimen. Retrospective studies from the United Kingdom[5] show that men who were treated between the 1960s and the1980s with a hypofractionated regimen because of lack of machine availability achieved results comparable to those from other reported series.[6–10] A more contemporary report of the UK experience confirms that hypofractionation is feasible and results in low bladder and rectal toxicities.[11] Other prospective single-arm and randomized trials support the idea that a hypofractionated regimen for the treatment of prostate cancer is feasible.[12,13]

Radiation therapy for treatment of prostate cancer has evolved over the years, with the goal being to achieve high conformality to the prostate whereas avoiding surrounding sensitive tissues such as the bladder and rectum. High-dose rate (HDR) brachytherapy has gained popularity and has been used either as monotherapy in patients with low-risk prostate cancer or as a boost after intensity-modulated radiation therapy (IMRT) in patients with intermediate- to high-risk prostate cancer.[14,15] HDR brachytherapy is, however, an invasive procedure with the associated risks of infection, bleeding, and reactions to anesthesia. It has been shown that HDR dosimetry can be closely replicated in a minimally invasive manner with the use of stereotactic body radiation therapy (SBRT).[16] One platform that delivers SBRT is the CyberKnife System (Accuray, Inc, Sunnyvale, CA). It consists of a 6-MV linear accelerator mounted on a robotic arm capable of moving within 6 degrees of freedom (independent linear and rotational motion, in the direction of, and about each of the 3 three-dimensional axes, x, y, z). In contrast, most conventional linear accelerators have 3 degrees of freedom to account for patient or target motion (3 degrees of freedom—linear motion: in/out, up/down, and left/right). A unique feature of the CyberKnife is its ability to track the motion of the prostate in real time during radiation treatment by imaging the positions of 3 to 4 gold fiducial seeds placed in the prostate prior to treatment planning. Depending on the motion of the prostate, the machine automatically repositions the robotic arm-mounted linear accelerator in response to variations in target position and delivers 100 to 200 noncoplanar pencil beams to the prostate, limiting the dose to the surrounding tissues. The radiation treatment is delivered in a hypofractionated regimen: The total dose is low relative to the conventional dose, but the dose per fraction is increased so the biologic effect to the tumor may be greater. In this article, we assess the acute gastrointestinal (GI) and genitourinary (GU) toxicities in 48 men with prostate cancer treated with the CyberKnife.

MATERIALS AND METHODS

A retrospective chart review was performed for the first 50 patients treated with CyberKnife external beam radiation therapy between October 2006 and August 2008. Two of 50 patients had metastatic disease at presentation and were excluded from the study. The remaining patients had T1–T3 prostate cancer. The median age was 66 years, with a range of 46 to 80 years. All patients had a diagnosis of prostate adenocarcinoma, which was confirmed by biopsy. Their pretreatment PSA values ranged from 0.13 to 59.6 ng/mL (normal range, 0–4 ng/mL), with mean and median values of 9.34 and 6.05 ng/mL, respectively. The mean Gleason score was 7.

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Of the 48 patients, 16 did not have any reported comorbidities, and the remainder had a history of at least one other comorbidity including hypertension, coronary artery disease, obesity, and smoking. Twelve patients received hormone therapy. Patient and tumor characteristics are summarized in Table 1.

The initial patient consultation consisted of a detailed history, with special attention to baseline GI and GU symptoms (Table 2) and a physical examination. Patient preparation prior to treatment included placing fiducial markers into the prostate and creating a custom-fit body mold to minimize movement during treatment. All patients had thin-cut (1.5 mm) planning CT, and/or thin-cut (1.5 mm) planning MRI, to outline the clinical target volume (CTV) with margins to generate the planning target volume (PTV). The CTV included the prostate gland only, and the PTV consisted of CTV with a 5 mm margin in all directions except in the posterior of the gland, where a margin of 3 mm was used. In the majority of cases, the urethra was neither visualized nor contoured, and was included in the CTV. The seminal vesicles were not contoured, and were therefore not included in the PTV. The mean PTV was 83 cm^3 with a range of 21 to 243 cm^3.

Treatment planning was done by the inverse planning technique, with the goal to achieve high conformality with rapid dose fall-off away from the target. The dose was prescribed to the PTV with ≥97% coverage, and an isodose line of 85% with a maximum dose of 115%. The maximum rectal dose was limited to 1 cm^3 receiving <36 Gy and 50% of the volume receiving <50% of the prescribed dose. The bladder was limited to 10 cm^3 receiving <37 Gy.

A total of 37 patients were treated exclusively with the CyberKnife for 5 fractions of 7 to 7.5 Gy/fraction, to a total dose ranging from 35 to 37.5 Gy. Assuming an alpha/beta ratio of 1.5 Gy, this regimen delivered an equivalent dose of 85 to 96 Gy in 2 Gy fractions (EQD2). The remaining 11 patients received other forms of treatment (IMRT; Tomotherapy, TomoTherapy Inc, Madison, WI) and subsequently received a boost to the prostate via the CyberKnife. Of 11 patients 8 received a boost in 2 fractions, ranging from 8.8 to 10.5 Gy/fraction (EQD2 = 51.8–72 Gy, assuming alpha/beta 1.5 Gy). Two patients received a boost in 5 fractions of 5 Gy/fraction (EQD2 = 46.4 Gy), and 1 patient received a boost of 8 Gy/fraction in 3 fractions (EQD2 = 65 Gy). These variations were the result of the individual preferences of the attending radiation

TABLE 1. Patient and Tumor Characteristics

Characteristics	
Age (yr)	
Mean	67
Range	46–80
T stage, n (%)	
T1	33 (69)
T2	14 (29)
T3	1 (2)
Gleason score, n (%)	
2–6	25 (52)
7	14 (29)
8–10	9 (19)
Pretreatment PSA, n (%)	
PSA <10 mg/L	33 (69)
10 ≤ PSA ≤ 20 mg/L	10 (21)
PSA >20 mg/L	5 (10)
Comorbidities, n (%)	
None	16 (33)
≥1	32 (67)
Hormones, n (%)	
Yes	12 (25)
No	38 (75)

PSA indicates prostate specific antigen.

TABLE 2. Baseline and Post-treatment Morbidities

	No. Patients (%)			
Toxicity	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**
Baseline symptoms, all patients				
Genitourinary				
Frequency/nocturia	21 (44)	26 (54)	1 (2)	0 (0)
Retention/incomplete emptying	38 (79)	9 (19)	1 (2)	0 (0)
Incontinence	47 (98)	1 (2)	0 (0)	0 (0)
Dysuria	47 (98)	1 (2)	0 (0)	0 (0)
Overall		37 (77)	2 (4)	0 (0)
Gastrointestinal				
Diarrhea	45 (94)	3 (6)	0 (0)	0 (0)
Post-treatment symptoms*, all patients				
Genitourinary				
Frequency/nocturia	25 (52)	17 (35)	3 (6)	3 (6)
Retention/incomplete emptying	44 (92)	3 (6)	1 (2)	0 (0)
Incontinence	47 (98)	1 (2)	0 (0)	0 (0)
Dysuria	41 (86)	5 (10)	1 (2)	1 (2)
Overall		26 (54)	5 (10)	4 (8)
Gastrointestinal				
Diarrhea	43 (90)	5 (10)	0 (0)	0 (0)
Post-treatment symptoms*, separated by treatment group				
CyberKnife monotherapy group, n = 37				
Genitourinary				
Frequency/nocturia	21 (57)	13 (35.1)	1 (2.7)	2 (5.4)
Retention/incomplete emptying	34 (92)	3 (8.1)	0 (0)	0 (0)
Incontinence	36 (97)	1 (2.7)	0 (0)	0 (0)
Dysuria	31 (84)	4 (10.8)	1 (2.7)	1 (2.7)
Overall		21 (57)	2 (5)	3 (8)
Gastrointestinal				
Diarrhea	32 (86.5)	5 (13.5)	0 (0)	0 (0)
CyberKnife boost group, n = 11				
Genitourinary				
Frequency/nocturia	4 (36)	4 (36)	2 (18)	1 (9)
Retention/incomplete emptying	10 (91)	0 (0)	1 (9)	0 (0)
Incontinence	11 (100)	0 (0)	0 (0)	0 (0)
Dysuria	10 (91)	1 (9)	0 (0)	0 (0)
Overall		5 (45)	3 (27)	1 (9)
Gastrointestinal				
Diarrhea	11 (100)	0 (0)	0 (0)	0 (0)

*Post-treatment symptoms were highest scores obtained during any follow-up visit (mean and median times at follow-up are 12 and 11.5 wk, respectively, with a range of 4–24 wk).

TABLE 3. Fractionation Schedule and Total Doses Received

No. Patients, n	No. Fractions	Dose/Fraction (Gy)	Total Dose (Gy)	EQD2, $\alpha/\beta = 1.5$ Gy
CyberKnife monotherapy				
5	5	7.0	35.0	85.0
4	5	7.25	36.25	90.0
28	5	7.5	37.5	96.0
Boost to prostate				
1	2	8.8	17.6	51.8
2	2	9.5	19.0	59.7
5	2	10.5	21.0	72.0
1	3	8.0	24.0	65.0
2	5	5.0	25.0	46.4

Gy indicates Gray.

oncologists who favored lower doses per fraction for larger prostate volumes. Doses received are summarized in Table 3.

The acute toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0,[17] which were measured throughout treatment and up to 24 weeks postradiation. The follow-up visits were scheduled between 4 and 24 weeks after the end of treatment. The mean and median follow-up times were 12 and 11.5 weeks, respectively. The highest symptom score, which was obtained either during treatment or at follow-up visits, was used to record the acute toxicities. The mean post-treatment PSA value was 2.41 ng/mL at a mean follow-up time of 12 weeks. However, only 28 patients had PSA results for the follow-up visits.

RESULTS

All 48 patients completed the treatments. As mentioned previously, Table 2 summarizes the pretreatment symptoms and post-treatment acute GU and GI toxicities, according to the CTCAE scale. The highest toxicity score for each patient was used to calculate the CTCAE value. Nine patients were free of both pretreatment GU and GI symptoms, and most of the symptoms experienced by other patients before treatment were those of frequency, urgency, and nocturia. Three patients experienced pretreatment GU symptoms equivalent to CTCAE grade 2, one of which was attributed to the patient's long history of BPH and incontinence.

Eight patients either did not complain of any GU or GI symptoms post-treatment or complained of a mild increase in frequency/nocturia (but less than twice normal frequency). Acute grade 1 GU and GI toxicities were found in 54% and 10% of patients, respectively. Acute grade 2 GU toxicities were found in only 10% of patients and included symptoms of frequency/nocturia and dysuria because of epididymitis from fiducial placement. Acute grade 3 GU toxicities were reported by 8% of patients and included symptoms such as frequency, nocturia, and dysuria. No grade ≥2 GI toxicity was seen. Table 2 also separates the post-treatment symptoms by the patient treatment group (CyberKnife monotherapy vs. CyberKnife boost to prostate). It can be seen that about a third of patients in the boost group experienced grade ≥2 GU symptoms, and no one in the boost group experienced any GI symptoms. In general, the majority of side effects were in the form of GU toxicities for both treatment groups, and highest toxicity scores were recorded immediately after or within 1 month of treatment. However, most symptoms returned to baseline within a 3-month period.

In a hypofractionated regimen, however, the development of late toxicities may be increased. These patients will be included in a longer study to analyze the potential late toxicities and treatment efficacy.

DISCUSSION

Acute toxicities were compared with those resulting from 3-dimensional conformal radiation therapy (3D-CRT), IMRT, HDR brachytherapy, and SBRT. These results are summarized in Table 4. Caution should be used when comparing the data from different

TABLE 4. Acute Toxicities From Other Studies

Study	No. Patients	Toxicity Scale	Genitourinary Toxicity (%)				Gastrointestinal Toxicity (%)			
			G1	G2	G3	G4	G1	G2	G3	G4
3D-conformal RT										
Michalski et al[18]	225	RTOG	56*†	40*	3*	0*	*	*	*	*
Zietman et al[6]	393	RTOG	37	46	1	1	28	49	0.5	0
Peeters et al[7]	669	RTOG	46†	41	13	0	51#	44	5	0
IMRT										
Zelefsky et al[8]	772	RTOG	38	28	0		22	4	0	0
De Meerleer et al[9]	114	RTOG	47	36	7	0	44	29	0	0
Lim et al[10]	66	CTCAE, v3	95	36	8	0	39	6	0	0
HDR brachytherapy										
Yoshioka et al[19]	43	RTOG	37	23	0	2	7	5	0	0
Corner et al[20]	129	RTOG/CTC		Used IPSS score			40	10	0	0
SBRT										
Madsen et al[21]	40	RTOG	28	20.5	1	0	26	13	0	0
Current study	48	CTCAE, v3	54	10	8	0	10	0	0	0

*The values for both genitourinary and gastrointestinal toxicities were combined.

†The value includes patients with both grade 0 and 1 toxicities.

CTC indicates common toxicity criteria; CTCAE, Common Terminology Criteria for Adverse Events, version 3.0; HDR, high-dose rate; IMRT, intensity-modulated radiation therapy; IPSS, International Prostate Symptom Score; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy; 3D, three-dimensional.

facilities and investigators because the toxicity scales and the use of medications to treat the symptoms may vary. Additionally, toxicity recordings include a degree of subjectivity because the descriptions of toxicities are not precise.

Three-dimensional conformal therapy reports showed a higher overall rectal and grade ≥2 urinary morbidity. Michalski et al[18] reported acute toxicities for 219 patients. The patients were stratified into 2 categories on the basis of the risk of seminal vesicle invasion and were treated with 2 Gy fractions to a total of 78 Gy to the prostate only or 54 Gy to prostate + seminal vesicle and a boost to the prostate to 78 Gy. The authors reported overall GU and GI grade ≥2 toxicity in 40% and 47% of patients, respectively.

Zietman et al[6] randomized 393 patients to receive either a conventional dose of 70.2 Gy or an escalated dose of 79.2 Gy using a combination of conformal photon and proton beams. They used the Radiation Therapy Oncology Group (RTOG) toxicity criteria and reported 48% and 50% grade ≥2 GU and GI toxicities, respectively. Peeters et al[7] reported results from a multicenter randomized trial. A total of 669 patients were randomized to receive 68 or 78 Gy to either the prostate alone or the prostate + seminal vesicle and showed grade ≥2 being at least 47% for GU and at least 50% for GI morbidity.

The IMRT reports show reduced or comparable results for acute GU and GI toxicities. Zelefsky et al[8] reported acute toxicities in 772 patients with prostate cancer treated with high-dose IMRT (81–86.4 Gy) and found that the incidence of acute rectal toxicity was reduced compared with that observed with conventional 3D-CRT. The same report mentions that the incidence of acute urinary symptoms was not significantly different from those reported in previous studies.

De Meerleer et al[9] used the RTOG scale to record the acute toxicity after IMRT in 114 patients. They found grade 1 and grade 2 rectal toxicity to be 44% and 29%, respectively, leaving about 35% without rectal symptoms. They reported grade 1 and grade 2 GU toxicity to be at 47% and 36%, respectively.

Lim et al[10] conducted a prospective phase I study of 66 high-risk patients who had hypofractionated accelerated radiotherapy, with a concomitant IMRT boost and elective pelvic nodal radiation. They assessed acute toxicities according to the CTCAE, version 3.0 criteria; they found that only 5 patients reported grade 3 GU acute toxicity and no patients had grade 3 or greater GI acute toxicity.

In a retrospective study from Japan, Yoshioka et al[19] reported acute toxicities after HDR brachytherapy as monotherapy for 43 patients, mostly from intermediate to high-risk categories. They treated the patients in 8 or 9 fractions at 6 Gy/fraction and assessed toxicities using the RTOG criteria. Five percent of patients complained of grade ≥2 GI toxicity and 25% of patients reported grade ≥2 GU toxicity. However, only 55% of patients had no biochemical evidence of disease.

Corner et al[20] completed a phase II HDR brachytherapy as a monotherapy study in which they treated 110 patients in 3 or 4 fractions to a total of 31.5 to 36 Gy. Both GU and GI acute toxicities peaked about 2 weeks after treatment but started to decline and were almost back to baseline by 12 weeks after treatment.

Several SBRT exist that suggest a tolerable acute toxicity profile. Madsen et al[21] reported acute toxicities for 40 patients treated in 5 fractions to a total dose of 33.5 Gy. The acute toxicities were assessed through American Urological Association and common toxicity criteria. Twenty-one percent and 13% of patients reported grade ≥2 GU and GI toxicities, respectively.

King et al[22] reported preliminary results from a phase II clinical trial for 41 patients treated with the CyberKnife hypofractionated regimen in 5 fractions to a total dose of 36.25 Gy. They assessed toxicities using the International Prostate Symptom Score and RTOG criteria and reported a favorable acute toxicity profile.

In general, the acute toxicities established in our study were more frequent for GU than for GI symptoms, similar to what has been reported in the literature for IMRT.[8–10] Additionally, the results from our study show that most CTCAE grade ≥2 results for both GU and GI symptoms were comparable to or lower than those that have been reported for either IMRT or 3D-CRT and HDR brachytherapy.[6,7,18–20] Roughly about a third to a half of patients experienced grade ≥2 toxicity in both IMRT and 3D-CRT studies, whereas that percentage in our study is lower. However, the percentage of patients experiencing GU grade 1 toxicity in this study is comparable to those reported in the literature.[6–9,18–20]

Some of the limitations of this study are the retrospective nature of the project, the small number of patients, and the variations in dose and fractionation schedules (especially in the boost-to-prostate subset). The data gathered only support the acute toxicity data because of the short follow-up time. To date, with the median follow-up period of 12 weeks, the mean PSA value has decreased from 9.34 to 2.41 ng/mL; however, only 28 patients completed PSA testing post-treatment. With the hypofractionated regimen, one has to be careful about assessing the late toxicities; therefore, a longer follow-up period is needed to determine both the development of late toxicities and the treatment efficacy.

CONCLUSION

In general, patients who presented with symptoms before radiation treatment had a slight increase in the severity of their symptoms, and most of them returned to baseline within 6 to 8 weeks after treatment. The use of CyberKnife-delivered hypofractionated radiotherapy for treatment of prostate cancer shows promising results in terms of acute toxicity profiles. However, larger, prospective randomized studies with a longer follow up are desirable to confirm this result.

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