Treatment Outcomes of CT-guided High-dose 3-dimensional Conformal Radiotherapy for Localized Prostate Cancer

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Abstract

Purpose: We studied the treatment outcomes of CT-guided 3-dimensional conformal radiotherapy (3DCRT) for localized prostate cancer using doses of 74–76 Gy.

Materials and Methods: In total, 139 patients with T1c to T3bN0M0 prostate cancer were enrolled between October 2007 and May 2014 in this retrospective study. The median patient age was 74 years (range, 56–81 years). There were 13 low-risk, 30 intermediate-risk, and 96 high-risk patients according to National Comprehensive Cancer Network definitions. Androgen deprivation therapy (ADT) was used in 123 patients (88%), with a median treatment period of 25 months (range, 1–128 months). Biochemical relapse was evaluated according to the Phoenix definition, while adverse events were evaluated according to Common Terminology Criteria for Adverse Events (version 4.0). Median follow-up was 42 months (range, 13–94 months).

Results: Three-year biochemical relapse-free survival (bRFS) rates were 100%, 100%, and 92%, respectively, for low-risk, intermediate-risk, and high-risk groups, while 3-year overall survival was 100%, 96%, and 95%, respectively. Meanwhile, 3-year distant metastasis-free survival was 100%, 100%, and 96%, and 3-year cause-specific survival was 100%, 100%, and 98%. Multivariate analysis showed that long-term ADT (24 months or longer) was a factor influencing bRFS in the high-risk group (hazard ratio 0.23, $p = 0.044$). Rates of grade 2 late rectal and urinary toxicities were 3.6% and 0.7% respectively, while no grade 3 or higher toxicities were observed.

Conclusion: These results demonstrate the safety of high-dose CT-guided 3DCRT performed at our hospital.

Key words

prostate cancer, image-guided radiotherapy, 3-dimensional conformal radiotherapy,
androgen deprivation therapy, biochemical relapse-free survival

Introduction

The rate of detection of localized prostate cancer has increased due to the prevalence of prostate-specific antigen (PSA) testing. While external irradiation is standard radical therapy for localized prostate cancer, 72 Gy or higher doses of irradiation is required to achieve local control comparable to radical prostatectomy¹⁾. Conventional external irradiation, which requires a sufficient margin from the target in consider-

ation of physiological movement of prostate position, cannot be administered at doses higher than 70 Gy to avoid late injury. In recent years, image-guided radiotherapy (IGRT), which involves CT-based targeting and positional correction before irradiation to enhance accuracy, has been increasingly used, allowing dose escalation to 70 Gy or higher. Randomized studies have shown that high-dose external irradiation of 78 Gy or higher improves rates of biochemical control for prostate cancer^{2–7)}. Two image-guided high-

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precision methods introduced to mitigate risks of late injury associated with higher doses have been reported to be effective: 3-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT)^{8,9)}. St. Marianna University School of Medicine Hospital began treating prostate cancer with CT-guided 3DCRT in October 2007. The purpose of this study is to evaluate treatment outcomes of CT-guided 3DCRT for localized prostate cancer.

Materials and Methods

The subjects in the current study are 139 prostate cancer patients (stage T1c to T3b N0M0) who received CT-guided 3DCRT at our hospital between October 2007 and May 2014 (**Table 1**). Adenocarcinoma was confirmed for all subjects through histological diagnosis following biopsy. Risk classifications used definitions from the National Comprehensive Cancer Network: low-risk is T1–T2a with PSA of < 10 ng/mL and Gleason score (GS) of ≤ 6; intermediate-risk is T2b–T2c with PSA of 10–20 ng/mL and GS of 7; and high-risk is T3 or PSA of > 20 ng/mL or GS of 8–10. Patients with T4 cancer or a history of pelvic surgery were excluded. Abdominal CT and bone scans were used for pre-treatment evaluation. Written informed consent was obtained from all patients prior to treatment, and this study was approved by St. Marianna University School of Medicine Hospital's Institutional Review Board (#2972).

Radiotherapy

Treatment planning

Treatment-planning CT scans were performed at 3 mm slice thickness with the patients in a supine position and their legs immobilized with heel supports (Engineering System Co., Ltd., Japan). Patients refrained from urinating in the 30 minutes prior to the planning CT examination or radiotherapy. The treatment planning system used was Xio (Computerized Medical Systems, St Louis, MO), while the superposition algorithm was used for calculations. Clinical target volume (CTV) included prostate only for low-risk patients, and both prostate and proximal seminal vesicles for intermediate-risk and high-risk patients. For T3b patients, the entire seminal vesicle was included. Rectal volume was defined as 2 cm extending beyond the CTV cranially and caudally. Planning target volume (PTV) was considered equal to CTV. A rectangular rotational beam combined with five fixed beams were used for the 3DCRT¹⁰⁾. The rotational beam center and isocenter of fixed beams were the

Table 1. Patient Baseline Clinical and Treatment Characteristics

Age (years)	median 74 (range, 56-81)	
	n	%
T stage		
T1c	77	55
T2	46	33
2a	10	
2b	9	
2c	27	
T3	16	12
3a	11	
3b	5	
PSA (ng/mL)		
<10	40	29
10-20	36	26
>20	63	45
Gleason Score		
≤6	21	15
7	49	35
8-10	69	50
Risk groups		
Low	13	9
Intermediate	30	22
High	96	69
ADT		
Yes	123	88
No	16	12
ADT rate		
Low	7/13	54
Intermediate	21/30	70
High	95/96	99
ADT duration in high-risk group		
short-term (<24 m)	34	36
long-term (≥24 m)	61	64
Riotherapy dose (Gy)		
74	45	32
76	94	68

PSA: Prostate-specific antigen, ADT: Androgen deprivation therapy, m: Month

center of the PTV. Using a beam's-eye view, 1 cm margins were set to ensure full coverage of the PTV. A multi-leaf collimator was used to help ensure that rectal V70 (percentage of rectal volume receiving 70 Gy or more radiation) was 10% or lower by adjusting rectal-side margins. Finally, fixed-beam gantry angles and dose weight from each beam were adjusted for homogenous dose distribution over the PTV.

Image-guided radiotherapy (IGRT)

The linear accelerators used were the Fusion of CT and Linac (FOCAL) unit (Toshiba Medical Systems, Tochigi, Japan) and Elekta Synergy (Elekta, AB, Stockholm, Sweden). For every treatment fraction, the patients were initially prepared using laser marks on their skin, and then repositioned using in-room CT. The FOCAL unit (purchased 2007) used 10 MV x-rays for radiotherapy, while the Elekta Synergy unit (purchased 2013) used 6 MV x-rays follow-

ing position correction with cone-beam CT and HexaPOD evo.

All patients were treated to their prescribed dose in daily 2 Gy fractions. Total dose was 74 Gy for the low-risk group and 74 Gy to 76 Gy for the intermediate- and high-risk groups (74 Gy in 32 patients and 76 Gy in 94 patients). Median dose irradiated to 95% of PTV (PTV D95) was 74.3 Gy (range, 57.8–76.2 Gy), while median rectal V70 was 4.3% (range, 0–13.7%).

Hormone therapy

Androgen deprivation therapy (ADT) was used at the discretion of the treating physician. Specifically, two patients received bilateral orchiectomy, two patients received oral anti-androgen, and 119 patients received oral anti-androgen and luteinizing hormone-releasing hormone (LH-RH) agonist therapy. One hundred and twenty-three (88%) out of 139 patients received ADT, and the median duration was 25 months (range, 1–128 months). Among these patients, 23 patients (19%) received only neoadjuvant ADT, and the other 100 patients (81%) were treated with neoadjuvant ADT, concurrent and adjuvant ADT. ADT treatment rates by risk group were 7/13 low-risk patients (54%), 21/30 intermediate-risk patients (70%), and 95/96 high-risk patients (99%). Median duration between initiation of ADT and start of 3DCRT was 9 months (range, 0–91 months). Long-term ADT (24 months or longer) was administered to low- (n=3), intermediate- (n=4), and high-risk patients (n=61).

Follow-up

Patients were examined and PSA measured every 3 to 6 months following radiotherapy completion, with diagnostic imaging performed in patients with suspected biochemical or clinical relapse. Adverse

events were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (Ver. 4.0) (Table 2).

Outcomes

The primary endpoint used in the study was biological relapse-free survival (bRFS). Biochemical relapse was defined according to the RTOG/ASTRO Phoenix Consensus Conference definition (an increase in the PSA concentration of ≥ 2 ng/mL above the nadir)¹¹. Secondary endpoints were overall survival (OS), distant metastasis-free survival (DMFS), and cause-specific survival (CSS), with metastasis determined through imaging.

Statistical analysis

Survival was calculated according to the Kaplan-Meier method, with day 1 as the day of initiation of radiotherapy. Survival rates among groups were compared with the log-rank test. The Cox proportional hazard model was used to assess factors affecting bRFS of high-risk patients; factors were pre-treatment PSA (≤ 20 ng/mL vs. > 20 ng/mL), GS (< 8 vs. 8–10), T stage (1–2 vs. 3), ADT duration (< 24 months vs. ≥ 24 months), and total dose (74 Gy vs. 76 Gy). Factors with $p < 0.5$ under univariate analysis were used for multivariate analysis. Intergroup rectal V70 comparisons used the t-test. Statistical significance level was set at $p < 0.05$. Software used for statistical analysis was R version 3.2.1.

Results

Median follow-up period was 42 months (range, 13–94 months) for surviving patients. PSA relapse was observed in nine patients, all of whom were high-risk and three of whom had distant metastases. Three-year bRFS rates in low-, intermediate-, and high-risk groups were 100%, 100%, and 92%, re-

Table 2. National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.0)

Adverse Event	Grade				
	1	2	3	4	5
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

spectively (**Fig. 1**), demonstrating significantly worse results for the high-risk group ($p = 0.03$). **Table 3** shows the result of analysis of factors affecting bRFS in high-risk patients. Univariate analysis revealed no significant factors, but in multivariate analysis, ADT of 24 months or longer was an independent prognostic factor (HR 0.23, 95% CI 0.05–0.96, $p = 0.044$).

At the time of the analysis, 10 out of 139 patients had died. Of these, two died of prostate cancer, five of other malignant tumors (one each of gastric lymphoma and lung, gastric, pancreas, and bladder cancers), and one each from chronic obstructive pulmonary disease (COPD), renal failure, and pneumonia.

Three-year OS rates in low-, intermediate-, and high-risk groups were 100%, 96%, and 95%, respectively ($p = 0.66$) (**Fig 2**), while 3-year DMFS rates were 100%, 100%, and 96%, respectively ($p = 0.23$) (**Fig. 3**). Finally, 3-year CSS rates were 100%, 100%, and 98%, respectively ($p = 0.31$) (**Fig. 4**) in low-, intermediate-, and high-risk groups.

Acute toxicity was observed in one patient with grade 2 urethral stenosis, who completed treatment with 74 Gy. All other patients completed planned radiotherapy. Grade 2 late rectal toxicity was observed in five patients (3.6%), with a mean time to rectal bleeding of 8.8 months (range, 7–12 months) following completion of radiotherapy. Mean rectal V70 was 6.2% (range, 4.2–8.6%) for the five patients with rectal toxicity, and 4.6% (range, 0–13.7%) for the 134 patients with no rectal toxicity ($p = 0.16$). The only instance of late urinary toxicity observed was in one patient (0.7%) with grade 2 urethral stenosis. No grade 3 or higher acute or late toxicities were observed.

Discussion

We studied treatment outcomes from CT-guided high-dose 3DCRT performed at our hospital. Toxicity was within the tolerable range, and results demonstrated safety. Low- and intermediate-risk groups demonstrated 100% 3-year bRFS; the rate for the

Fig. 1. Biochemical relapse-free survival by risk stratification for 139 men treated for localized prostate cancer with CT-guided 3DCRT.

Table 3. Statistical Analysis of Predictors for the Biochemical Relapse-free Survival of High-risk Patients

Variable	Univariate		Multivariate	
	p value	HR(95% CI)	p value	HR(95% CI)
PSA (≤ 20 ng/mL vs. >20 ng/mL)	0.15	4.45 (0.55- 35.62)	0.16	4.57 (0.52- 39.83)
Gleason Score (<8 vs. 8-10)	0.14	0.37 (0.09- 1.41)	0.46	0.60 (0.15- 2.36)
T stage (1-2 vs. 3)	0.99	1.00 (0.20- 4.99)		
ADT duration (<24 m vs. ≥ 24 m)	0.06	0.27 (0.06- 1.09)	0.044	0.23 (0.05- 0.96)
Radiation dose (74Gy vs. 76Gy)	0.65	1.46 (0.27- 7.81)		

PSA: Prostate-specific antigen, ADT: Androgen deprivation therapy, m: Month, HR: Hazard ratio, CI: Confidence interval

Fig. 2. Overall survival by risk stratification for 139 men treated for localized prostate cancer with CT-guided 3DCRT.

Fig. 3. Distant metastasis-free survival by risk stratification for 139 men treated for localized prostate cancer with CT-guided 3DCRT.

high-risk group was significantly worse at 92%. At other facilities, 3-year bRFS was reported to be 97–100%, 95–100%, and 90–92% in low-, intermediate-, and high-risk patients, respectively. The results from the present study were similar to those reported at other facilities, although the duration of follow-up was shorter (Table 4); possible reasons are shortness of the follow-up period, efficacy of CT-guided high-dose 3DCRT, and high rates of ADT with longer treatment periods for high-risk patients. However, drawing concrete conclusions is difficult.

Randomized studies to date have shown the necessity for long-term (24 -months) adjuvant ADT with external irradiation for high-risk patients. In contrast, shorter periods of ADT (6 months) are con-

sidered effective for intermediate-risk patients, and ADT is considered unnecessary for low-risk patients^{12–14}). However, this data is for doses of 70 Gy or lower, and the efficacy of adjuvant ADT and optimal treatment periods for intermediate- and high-risk patients receiving 74–80 Gy, which is currently becoming the standard dose, remains unknown. Zapatero et al.¹⁵) compared short- (4 -months) and long-term (24 -months) ADT combined with 76–82 Gy 3DCRT in intermediate- and high-risk patients in a randomized study; results showed that long-term ADT improved biochemical disease-free survival, metastasis-free survival, and OS. Long-term ADT was particularly effective in high-risk patients. We only studied prognostic factors for high-risk patients, as no low- or in-

Fig. 4. Cause-specific survival by risk stratification for 139 men treated for localized prostate cancer with CT-guided 3DCRT.

Table 4. Literature Review

Author	RT dose (Gy)	Method	Risk group	ADT rate (%)	ADT duration (m)	bRFS (%)	DMFS (%)	CSS (%)	OS (%)
Martin JM (8)	79.8	IG-3DCRT or IG-IMRT	low	13.6	<6	5-year 88.4	-	-	-
			intermediate	11	<6	76.5	-	-	-
			high	45.9	24-36	77.9	-	-	-
Spratt DE (18)	86.4	IMRT	low	27.5	6	7-year 98.8	99.4	100	-
			intermediate	47.8	6	85.6	94.1	96.7	-
			high	91.3	6-24	67.9	82	91.9	-
Takeda k (17)	76 or 80	IG-IMRT	intermediate	67	med 5 (4-32)	5-year 100	100	100	100
			high	95	med 12 (2-88)	82.2	95	100	91.7
Zapatero A (15)	76-82	3DCRT	intermediate	100	short-term (4)	5-year 88	89	-	91
					long-term (24)	92	94	-	94
			high	100	short-term (4)	76	79	-	82
					long-term (24)	88	94	-	96
Our study	74 or 76	IG-3DCRT	low	54	med 21 (8-45)	3-year 100	100	100	100
			intermediate	70	med 10 (1-48)	100	100	100	96
			high	99	med 29 (2-128)	92	96	98	95

IG: Image-guided, 3DCRT: 3-dimensional conformal radiotherapy, IMRT: intensity-modulated radiotherapy, ADT: Androgen deprivation therapy, bRFS: biochemical relapse-free survival, DMFS: Distant metastasis-free survival, CSS: Cause-specific survival, OS: Overall survival, med: Median

intermediate-risk patients exhibited biochemical relapses. Multivariate analysis showed that only ADT of 24 months or longer was an independent factor for improving bRFS. Although this study is limited by the small number of patients analyzed and the nature of retrospective studies, results suggest that long-term ADT improves bRFS in the dosage range of 74–76 Gy, as well as in lower doses.

No low- or intermediate-risk patients exhibited distant metastases or died of prostate cancer. Three-year DMFS and 3-year CSS rates for high-risk patients were 96% and 98%, respectively. At other facilities, 3-year DMFS was reported to be 100%, 98–100%, and 95–97% in low-, intermediate-, and high-

risk patients, respectively, and 3-year CSS was reported to be 100%, 99–100%, and 98–100%, respectively. The results from the present study were similar to those reported at other facilities, although the duration of follow-up was shorter (**Table 4**). Despite confounding factors, such as the shortness of follow-up period and effects from ADT, this study showed low rates of distant metastases and death from prostate cancer even in high-risk patients with localized prostate cancer following treatment with CT-guided high-dose 3DCRT. The key to improving OS is discovering malignant tumors other than prostate cancer early and controlling chronic diseases.

The only acute toxicity observed was in one pa-

tient with a grade 2 event, which was within permissible levels. The reported incidence of grade 2 or higher late rectal and urinary toxicities due to 66–86.4 Gy external irradiation is 1–9% and 6.3–21.1%, respectively^{16–19}). In our study, the rates of grade 2 late rectal and urinary toxicities were 3.6% and 0.7%, respectively, while no grade 3 or higher toxicities were observed. Rectal volume exposed to high-dose radiation is a key risk factor for late rectal toxicity, which has been shown to increase significantly at rectal V70 of > 15%¹⁹). Risk factors reported for late urinary toxicity include urinary toxicity during the radiotherapy treatment period, high-dose radiation, and treatment with non-IGRT⁹⁾¹⁶⁾. Possible reasons for low incidence of grade 2 or higher late rectal and urinary toxicities in the current study include accurate IGRT, and the relatively low volume of the rectum subject to high-dose radiation (rectal V70 = median 4.3%). Currently our hospital is in the process of transitioning from CT-guided 3DCRT for prostate cancer to CT-guided IMRT. Total dose will remain at 76 Gy based on treatment experience to date, but IMRT offers better spatial dose distribution than 3DCRT, so treatment outcomes may improve.

In conclusion, this study examined treatment outcomes of CT-guided high-dose 3DCRT for localized prostate cancer. Adverse events were within permissible levels, indicating the safety of the treatment. Three-year bRFS rates were good, but significantly worse in the high-risk group compared to low-risk and intermediate-risk groups. Long-term ADT (24 -months or longer) influenced bRFS in the high-risk group. Distant metastases and death from prostate cancer were observed in several patients in the high-risk group. Going forward, further follow-up and observation are warranted in order to better evaluate long-term outcomes.

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