Medical Dosimetry ▮ (2016) ▮▮▮–▮▮▮

Medical Dosimetry

journal homepage: www.meddos.org

Acute toxicity and its dosimetric correlates for high-risk prostate cancer treated with moderately hypofractionated radiotherapy

Moses Arunsingh, M.D., Indranil Mallick, M.D., D.N.B., Sriram Prasath, M.Sc, B. Arun, M.Sc, Sandip Sarkar, M.D., Raj Kumar Shrimali, F.R.C.R., Sanjoy Chatterjee, F.R.C.R., and Rimpa Achari, M.D.

Department of Radiation Oncology, Tata Medical Center, Kolkata, India

ARTICLE INFO

Keywords:
Hypofractionated radiation therapy
Acute toxicity

ABSTRACT

Aims: To report the acute toxicity and the dosimetric correlates after moderately hypofractionated radiotherapy for localized prostate cancer.

Methods: A total of 101 patients with localized prostate cancer were treated with image-guided intensity-modulated radiation therapy. Patients were treated to 65 Gy/25 Fr/5 weeks ($n = 18$), or 60 Gy/20 Fr/4 weeks ($n = 83$). Most (82.2%) had high-risk or pelvic node-positive disease. Acute toxicity was assessed using Radiation Therapy Oncology Group (RTOG) acute morbidity scoring criteria. Dose thresholds for acute rectal and bladder toxicity were identified.

Results: The incidence of acute grade 2 GI toxicity was 20.8%, and grade 2 genitourinary (GU) toxicity was 6.9%. No Grade 3 to 4 toxicity occurred. Small bowel toxicity was uncommon (Gr 2 = 4%). The 2 Gy equivalent doses (EQD2) to the rectum and bladder ($\alpha/\beta = 3$) calculated showed that the absolute doses were more consistent predictors of acute toxicities than the relative volumes. Those with grade 2 or more GI symptoms had significantly higher $V_{EQD2\text{-}60\ Gy}$ (13.2 *vs* 9.9 cc, $p = 0.007$) and $V_{EQD2\text{-}50\ Gy}$ (20.6 *vs* 15.4 cc, $p = 0.005$). Those with grade 2 or more GU symptoms had significantly higher $V_{EQD2\text{-}70\ Gy}$ (30.4 *vs* 18.4 cc, $p = 0.001$) and $V_{EQD2\text{-}65\ Gy}$ (44.0 *vs* 28.8 cc, $p = 0.001$). The optimal cutoff value for predicting grade 2 acute proctitis, for $V_{EQD2\text{-}60\ Gy}$ was 9.7 cc and for $V_{EQD2\text{-}50\ Gy}$ was 15.9 cc. For grade 2 GU symptoms, the threshold values were 23.6 cc for $V_{EQD2\text{-}70\ Gy}$ and 38.1 cc for $V_{EQD2\text{-}65\ Gy}$.

Conclusions: Hypofractionated radiotherapy for prostate cancer is well tolerated and associated with manageable acute side effects. The absolute dose-volume parameters of rectum and bladder predict for acute toxicities.

Introduction

The α/β ratio of any cell is a mathematical representation of the inherent radiation sensitivity of the cell. The α/β ratio of prostate has been estimated to be 1.5 Gy,[1] based on data from both brachytherapy and external beam treated patients. Multiple studies have been published exploring hypofractionated radiotherapy in prostate cancer. The results from large institutional series and several recently published randomized controlled trials have been encouraging with excellent biochemical control, supporting the initial prediction of low α/β ratio and, hence, more sensitivity to changes in the fractionation similar to that of late reacting tissues.[2-6]

The α/β ratio of the prostate is relatively much lower than the surrounding normal tissues allowing, in theory, for hypofractionation to be a safe approach. However, clinical evidence of safety for hypofractionated radiotherapy must be verified in different risk groups, treatment volumes and modalities. The dosimetric constraints for late toxicity of the rectum and bladder have been defined for treatment with standard fractionation.[7,8] Constraints have to be defined in the setting of higher doses per fraction. It is well recognized that acute rectal and urinary toxicity are among the strongest predictors for late toxicity.[9,10] Therefore, analyzing the incidence of acute toxicity following hypofractionated radiotherapy could provide an early insight into its safety and dosimetric correlates.

We are presenting our initial experience in treating patients with predominantly high-risk prostate cancer with a hypofractionated regimen from a cancer referral and treatment center in India. Furthermore, we have tried to evaluate the feasibility and

Reprint requests to: Indranil Mallick, Department of Radiation Oncology, Tata Medical Center, 14 MAR (EW) Newtown, Kolkata 700156, India.
E-mails: imallick@gmail.com; Indranil.mallick@tmckolkata.com

http://dx.doi.org/10.1016/j.meddos.2016.10.002

treatment tolerance for this regimen in our population. We also attempt to identify dosimetric correlates for predicting acute toxicities.

Methods and Materials

A total of 101 patients with localized prostate cancer were identified from our treatment records. These patients were treated with intensity-modulated radiation therapy (IMRT) using helical tomotherapy (HT) (Accuray Inc.) or static field/volumetric arc–based treatment on a Novalis Tx (Varian Medical Systems, Inc., and BrainLAB AG) system between July 2011 and January 2014.

All of these patients were staged and classified into National Comprehensive Cancer Network (NCCN) risk groups based on TNM stage, prostate-specific antigen (PSA), and Gleason score.[11] The low-risk group (T1 to T2b, Gleason score $\leq$ 6, PSA $\leq$ 10) patients, $n = 3$, received radiotherapy only to the prostate and no hormonal therapy. The intermediate-risk group (T2c, Gleason score 7, PSA $>$ 10 but $\leq$ 20) patients, $n = 15$, received radiotherapy to the prostate and the seminal vesicles (SV) and 6 months of androgen deprivation therapy. The high-risk and very high-risk group (T3 to 4, Gleason $\geq$ 8, PSA $>$ 20) patients, $n = 63$, received elective radiotherapy to the pelvic nodes in addition to the prostate and SV and 3 years of androgen deprivation therapy. The androgen deprivation was delivered either using surgical orchidectomy or using gonadotropin-releasing hormone analogs. The choice of orchidectomy for high-risk or node-positive patients was based mainly on patient preference and the relative low cost of this treatment.

Two different fractionation schedules were used, with 65 Gy/25 Fr/5 weeks being used in the first 18 patients (EQD2 76 Gy, assuming $\alpha/\beta = 1.5$) and the subsequent 83 being treated with 60 Gy/20 Fr/4 weeks schedule (EQD2 77.2 Gy, assuming $\alpha/\beta = 1.5$). Patients with high-risk or pelvic node-positive disease received elective pelvic nodal irradiation (45 Gy/25 Fr or 44 Gy/20 Fr) using a single-phase plan with simultaneous integrated boost to the prostate and SV and enlarged nodes.

All patients underwent a planning computed tomography (CT), with intravenous contrast, obtained on a GE Lightspeed 16 slice unit with a standard bladder filling protocol of 500 mL of water and a half-an-hour waiting period. No immobilization devices were used. All patients were scanned in the supine position using a knee rest from the Orfit AIO system.

The clinical target volume (CTV), planning target volume (PTV), intestinal cavity, rectum, bladder, femoral heads, and the penile bulb were delineated on the planning CT dataset. The prostate and seminal vesicle CTVs did not include an expansion over the anatomical structures. The diagnostic MRI was used for assessment of extracapsular extension, and the region of extension was incorporated into the CTV. This CTV was grown symmetrically by 7 mm for the high-dose PTV. The elective pelvic nodal CTV was delineated according to the Radiation Therapy Oncology Group (RTOG) guidelines.[12] The elective nodal CTV was grown by 5 mm for the elective dose PTV. The rectum was delineated according to the traditional definition as a whole organ from the anal verge to the rectosigmoid junction (where the rectum moves forward). The bladder was also outlined in its entirety.

A planning requirement of achieving 99% dose to the 95% of the PTV was aimed for. Planning constraints used were derived from Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) guidelines,[7,8,13,14] but modified to be tighter for the rectum ($V_{59\ Gy} < 7\%$, $V_{56\ Gy} < 15\%$, $V_{53\ Gy} < 20\%$, and $V_{47\ Gy} < 35\%$), bladder ($V_{59\ Gy} < 10\%$, $V_{56\ Gy} < 20\%$, $V_{53\ Gy} < 25\%$, and $V_{47\ Gy} < 35\%$), bowel ($V_{45\ Gy} <$ 90 cc), femoral head ($V_{15\ Gy} \leq 5\%$) and penile bulb ($V_{47\ Gy} \leq 50\%$).

Daily volumetric image guidance was used for all patients with either megavoltage CT or kilovoltage cone beam CT based on our own assessment of uncertainties.[15]

All of these patients were clinically assessed weekly during the delivery of radiation therapy and their acute toxicities were recorded according to the RTOG/EORTC acute radiation morbidity scoring criteria.[16] Following treatment, patients were followed up at 3 month intervals for the first 2 years and then at 6-month intervals subsequently. Late toxicities were monitored at these follow-up visits. All toxicities occurring after 90 days from the completion of radiotherapy were considered to be late toxicities.

In this study we attempted at identifying dosimetric correlates which predict acute toxicities for those undergoing hypofractionated radiotherapy. Receiver operating characteristic (ROC) curves were plotted for rectal and bladder dose-volume parameters to find out the parameters with the best area under curve (AUC) and optimal cutoff values in each parameter to predict the acute toxicities. We have also assessed the late toxicities of these patients and analyzed whether the incidence of acute toxicities is predictive of the incidence of late toxicities.

Results

Charts and dosimetric data of the first 101 consecutive patients treated with hypofractionated radiotherapy were retrospectively reviewed. Patient characteristics are detailed in Table 1.

Table 1
Patient characteristics

Character	Subgroups	*n*
Dose	65 Gy in 25	18
	60 Gy in 20	83
Risk group	Low	3
	Mid	15
	High and very high	62
	Node positive	21
T	T1	0
	T2	37
	T3a	50
	T3b	11
	T4	3
N	N0	80
	N1	21
Gleason	< 7	22
	$= 7$	47
	> 7	32
PSA	$<$ 10 ng/mL	22
	10 to 20 ng/mL	26
	$>$ 20 ng/mL	53
Hormonal therapy	No	3
	Orchidectomy	53
	GnRH analogs	45

GnRH = gonadotropin-releasing hormone.

Dosimetry

All patients received IMRT with the dosimetric criteria described in Methods and Materials section. The bladder and rectal dosimetry is listed in Table 2 where the doses from the 2 fractionation schedules have been converted to the equivalent doses at 2 Gy per fraction (EQD2). Doses achieved with IMRT were well within the currently recommended dose constraints.[7,8]

Acute toxicity

There was no grade 3 or grade 4 genitourinary (GU) or gastrointestinal (GI) toxicity reported in our patients. Grade 0, 1, and 2 GI toxicities were reported in 28.7%, 50.5%, and 20.8% of patients, respectively. Grade 0, 1, and grade 2 GU toxicities were reported in 43.6%, 49.5%, and 6.9% of patients respectively. Small bowel toxicity was negligible (grade 1 = 12.9% and grade 2 = 4%). There

Table 2
Rectal and bladder dosimetry

Structure	Dosimetric criteria	Value
Rectum	Volume (median)	53 cc
	Mean dose	41.06 Gy
	Mean EQD2 V_{70} (relative/absolute)	8% /4.39 cc
	Mean EQD2 V_{65} (relative/absolute)	14.68%/8.26 cc
	Mean EQD2 V_{60} (relative/absolute)	18.72%/10.61 cc
	Mean EQD2 V_{50} (relative/absolute)	29.04%/16.47 cc
Bladder	Volume (median)	312 cc
	Mean dose	37.32 Gy
	Mean EQD2 V_{70} (relative/absolute)	6.8%/19.2 cc
	Mean EQD2 V_{65} (relative/absolute)	10.38%/29.84 cc

An assumption has been made of an α/β of 3 Gy for both rectum and bladder for calculation of equivalent doses at 2 Gy per fraction (EQD2). For the dose fractionation schedule of 60 Gy/20 Fr/4 weeks, EQD2 70 Gy = $V_{59\ Gy}$; 65 Gy = $V_{59\ Gy}$; 60 Gy = $V_{53\ Gy}$; 50 Gy = $V_{47\ Gy}$; for the dose fractionation schedule of 65 Gy/25 Fr/5 weeks, EQD2 70 Gy = $V_{63\ Gy}$; 65 Gy = $V_{60\ Gy}$; 60 Gy = $V_{57\ Gy}$; 50 Gy = $V_{50\ Gy}$.