An investigation of dosimetric correlates of acute toxicity in prostate SBRT: dose to urinary trigone is associated with acute urinary toxicity.

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Abstract:

Aims

There are limited data on dosimetric correlates of toxicity in stereotactic radiotherapy (SBRT) for prostate cancer. We aimed to identify potential relationships between dose and toxicity using conventional dose-volume histograms (DVHs) and dose-surface maps (DSMs).

Methods

Urinary bladder trigone and rectum DSMs were produced for a single-institution service evaluation cohort of 50 patients receiving SBRT for localised prostate cancer, along with conventional DVHs for bladder and rectum. Patients had been prospectively recruited to this cohort and treated according to a pre-defined protocol to a dose of 36.25 Gy in 5 fractions. RTOG and IPSS (International Prostate Symptom Score) toxicity data were recorded prospectively. Logistic regression was used to identify dosimetric predictors of acute IPSS+10 (rise of 10 points or more above baseline) and G2+ RTOG toxicity.

Results

On univariate analysis, trigone area receiving 40 Gy and trigone Dmax were associated with IPSS+10 (OR 1.06 (1.02-1.11), p = 0.007 and OR 1.54 (1.06-2.25), p = 0.024, respectively). These two variables were highly correlated. In a multivariate model, including all baseline variables, trigone Dmax remained associated with IPSS+10 (OR 1.91 (1.13-3.22), p = 0.016). These findings were not significant with Holm-Bonferroni correction for multiple testing (corrected p value threshold 0.006). No associations were seen between rectal toxicity and DVH or DSM parameters.

Conclusions

Our study suggests a potential relationship between high doses to the urinary bladder trigone and patient-reported urinary toxicity in prostate SBRT, and is consistent with previous studies in conventionally fractionated radiotherapy, justifying further evaluation in larger cohorts.

Keywords: radiotherapy, stereotactic, prostate, toxicity, trigone, rectum

Introduction:

Stereotactic body radiotherapy (SBRT) is an established treatment for localised prostate cancer, where short fractionation schedules are appealing from a patient and institutional perspective[1](#_ENREF_1). Long-term follow-up and phase III trial data are awaited[2](#_ENREF_2). However, in contrast to conventionally fractionated radiotherapy (CFRT)[3](#_ENREF_3), [4](#_ENREF_4), there are relatively few data on how dose distributions to organs-at-risk (OAR) are related to toxicity to guide radiotherapy plan optimisation. Furthermore, these data have been based on information from dose-volume histograms (DVH) which do not provide spatial information about dose distribution.

Two relatively recent developments may help in the identification of dosimetric correlates of toxicity. First, the development of dose-surface map (DSM) techniques has provided a method to calculate the dose across the surface of a given hollow organ[5](#_ENREF_5). This allows the examination of how dose is distributed across the organ surface, and within specific subregions. Second, there are increasing data that dose distribution, and dose to specific subregions, within a given OAR may contribute to the development of toxicity. For example, in the urinary bladder, Ghadjar et al. have demonstrated a relationship between dose to the bladder trigone and urinary toxicity in CFRT using DVHs[6](#_ENREF_6). This stands in contrast to the typical method of contouring the entire bladder, which is greatly affected by filling status, and has yielded little useful data[4](#_ENREF_4). Furthermore, in the rectum, Kim et al. have identified a relationship between the lateral extent of a given rectal dose (measured on a single mid-prostate axial CT slice, i.e. not with a DSM technique) and rectal toxicity in SBRT[7](#_ENREF_7).

In this study, we extracted DSM data for bladder trigone and rectum from SBRT plans in our prospective cohort[8](#_ENREF_8), along with DVH data for bladder and rectum. The relationship between dose metrics and physician- and patient-reported acute toxicities was explored to identify potential dosimetric predictors for further investigation. A number of studies have demonstrated a significant association between acute and late toxicity, suggesting consequential late damage[9-12](#_ENREF_9). Therefore, the ultimate purpose of identifying such predictors would be to improve plan optimisation, with a view to maximising the efficacy-toxicity ratio for patients.

Methods and materials:

*Patients and follow-up:*

At the time of analysis, 50 patients had been recruited to our single-institution prospective service evaluation of SBRT for localised prostate cancer. This service evaluation was approved by our institutional Service Evaluation Committee. Patients gave written consent at the time of the clinical decision to proceed with SBRT. Inclusion criteria were: PSA ≤20, Gleason score 3+3 or 3+4, stage T2bN0 or lower, and no plan for treatment with androgen deprivation therapy (ADT). RTOG (Radiation Therapy Oncology Group) and IPSS (International Prostate Symptoms Score) toxicity was measured at the end of treatment, and every two weeks up to 12 weeks from starting treatment (this constituted the acute toxicity period). IPSS was also measured at baseline. Late toxicity was measured every 3 months in the first year and 6-monthly thereafter.

*Radiotherapy treatment:*

Patients were planned and treated according to a pre-defined protocol using the Cyberknife (Accuray, CA, USA) robotic radiosurgery system with intra-fraction motion correction. The planning process and dose constraints have been described previously[8](#_ENREF_8) and are identical to those used for the PACE (Prostate Advances in Comparative Evidence) trial (NCT01584258)[2](#_ENREF_2). Briefly, patients had fiducial marker insertion 7 days prior to planning CT and MRI. Imaging was done with a comfortably full bladder and following enemas given daily for 3 days. The clinical target volume (CTV) for patients with NCCN (National Comprehensive Cancer Network, USA) low-risk disease was the prostate only. For those with intermediate-risk disease, the CTV was the prostate plus proximal 1 cm of seminal vesicles (SV). Planning target volume (PTV) margins beyond CTV were 3 mm posteriorly and 5 mm in all other directions. The bladder and rectum was separately contoured as the entire organ, including contents. The rectum was contoured from anal verge to recto-sigmoid flexure. The dose prescribed to the 80% isodose was 36.25 Gy in 5 fractions given daily or alternate daily.

*Study data:*

Baseline clinical data known to be associated with significant urinary toxicity were collected, including age, presence of diabetes mellitus (DM), and pre-treatment α-blocker use. NCCN risk group (a surrogate for SV inclusion in CTV), CTV, rectum, and bladder volumes, and daily (treatment complete in ≤ 7 days) vs. alternate daily treatment were also recorded. DVH were calculated from Multiplan (version 5.1.2, Accuray, CA, USA), the Cyberknife planning system.

The general methodology to produce DSMs was as follows: both dose cube data and structure sets were exported from Multiplan in DICOM (Digital Imaging and Communications in Medicine) format. These were imported onto a dedicated analysis software, VODCA (Visualisation and Organisation of Data for Cancer Analysis, version 5.4b, Medical Software Solutions, GmbH), which allowed the extraction of DSMs for each patient. The algorithm used calculates the dose over the entire surface of a given organ. The organ is then “virtually unfolded” contour by contour, to produce a flat DSM (Figure 1). The algorithm cuts the contour in the vertical plane, either posteriorly or anteriorly, as required. Vertical resolution of the DSM was determined by CT scan slice thickness and was, therefore, 1 mm. Horizontal resolution was 1.3 mm, as defined by the VODCA software. The DSMs produced by VODCA were then converted to comma separated variable (CSV) files using an in-house script for the “R” computer program (The R Foundation for Statistical Computing; version 3.2.0)[5](#_ENREF_5). The resultant CSV file contains a two-dimensional grid with each cell containing the absolute dose at that point.

A methodology to produce a urinary bladder trigone DSM has been developed at our institution[13](#_ENREF_13). The bladder trigone was contoured retrospectively on all service evaluation patients. The contour was commenced at the level of the insertion of the ureters and completed at the urethral orifice, to form a triangular structure. The contour was “looped” forward into the bladder (the red contour in Figure 2). A subtraction method based on the study by Murray et al was used to isolate the trigone surface itself, to produce the trigone DSM (the dashed line in Figure 2)[13](#_ENREF_13).

Due to the paucity of data relating dosimetry to toxicity outcomes in SBRT, current dose constraints are based on consensus opinion[14-16](#_ENREF_14). Therefore, a systematic approach was used to explore dose-toxicity relationships. Dose distributions were quantified with 5 Gy increments from a minimum of 10 Gy. In addition, maximum doses were also recorded (as the highest point-dose in the DSM). From the bladder and rectum DVHs, the percentage volume of the organ receiving each dose level or above was recorded. From the trigone DSM, the percentage area receiving each dose level or above was recorded. Finally, for the rectal DSMs, the maximum lateral (left-right) and longitudinal (superior-inferior) extent of each dose level was recorded.

Toxicity outcomes of interest were RTOG grade 2 and above (G2+) urinary and bowel toxicity, along with a rise in IPSS score of 10 points or more from baseline (IPSS+10). IPSS+10 is reported by patients to represent a significant change[17](#_ENREF_17), and was previously used by Ghadjar et al. in their study correlating patient-reported urinary toxicity with trigone dose in CFRT[6](#_ENREF_6).

*Statistics:*

Baseline variables and number of patients experiencing a given toxicity outcome were reported with descriptive statistics. Spearman’s rank correlation coefficient was used to explore the correlation between G2+ RTOG toxicity and IPSS+10. The relationship between toxicity outcomes and baseline clinical and dosimetric variables was explored using univariate logistic regression, and reported using odds ratios with p-value and 95% confidence intervals. In view of the systematic analysis method used, a Holm-Bonferroni correction was used to explore the effect of multiple testing on the significance of the results. Before carrying out regression analysis, a correlation matrix was produced to check for high correlations between dosimetric variables, as these typically correlate strongly and may confound multivariate analysis. Multivariate logistic regression analysis was performed for significant dosimetric variables, informed by correlation plots, by combining dosimetric variables with all baseline clinical variables. Statistics were produced using SPSS (version 20; IBM, USA).

Results:

Fifty patients were included in the study and their demographics and baseline characteristics are shown in Table 1. The number of patients experiencing RTOG grade 2 or higher acute urinary and rectal toxicity, along with those experiencing IPSS+10, are recorded in table 2. A moderate correlation was found between RTOG G2+ urinary toxicity and IPSS+10 (r=0.62, p < 0.0005). Of patients experiencing G2+ toxicity, two had grade 3 urinary toxicities, one due to frequency, the other due to transient haematuria. There was no grade 4 or higher toxicity seen. By the end of the acute period, all toxicity had resolved to grade 1 or lower. The acute IPSS rise also returned to baseline (Figure 3). Correlation matrices for the dosimetric variables can be found in the Supplementary Materials (Supplementary Figures 4 and 5).

The logistic regression analysis of baseline and DVH bladder and DSM trigone dosimetric variables against IPSS+10 are shown in Table 3. Both the percentage area of trigone receiving 40 Gy or above and the maximum dose to this structure were strongly associated with IPSS + 10 (OR 1.06 (1.02-1.11), p = 0.007 and OR 1.54 (1.06-2.25), p = 0.024, respectively). However, Holm-Bonferroni correction gave an adjusted p value threshold for significance of 0.006, meaning these variables would not be considered significant when taking multiple testing into account. Trigone A40 and maximum dose were strongly correlated (r = 0.79; p < 0.0005) and therefore would confound a multivariate analysis if both were included. In view of this, multivariate analysis was performed by creating a multivariate model containing all baseline variables along with trigone Dmax only (the variable with the higher OR). This showed that trigone Dmax remained strongly associated with IPSS+10 (OR 1.91 (1.13-3.22), p = 0.016).

The results from the univariate logistic regression analysis for G2+ urinary toxicity are shown in Table 4, where only baseline IPSS was significantly associated with G2+ urinary toxicity (OR 4.19 (1.25-14.09), p = 0.021). However, in a multivariate model with all the other baseline variables, this was not significant. No dosimetric variables were significant.

No significant association was found between G2+ rectal toxicity and baseline or dosimetric variables (Table 5). The correlation plot for rectal dosimetric variables are shown in the Supplementary Materials.

Discussion:

Using a systematic approach to dosimetric analysis, our study has suggested a relationship between higher doses to the urinary bladder trigone and patient-reported acute urinary toxicity (IPSS+10) in prostate SBRT. This relationship persisted in multivariable analysis, and is consistent with previous studies in CFRT, notwithstanding the fact that correction for multiple testing (Holm-Bonferroni) showed that this association was just above the threshold for significance (p = 0.007 for trigone A40 vs. p = 0.006 for significance). This is the first study to suggest such a relationship in prostate SBRT. Furthermore, IPSS is a patient-reported outcome and, therefore, more likely to be meaningful with respect to patient quality of life than physician-reported scores. Acute urinary toxicity in our cohort was in keeping with previous SBRT studies[1](#_ENREF_1), and settled rapidly to baseline.

Our findings are supported by a number of studies in conventionally fractionated prostate treatments. Ghadjar et al. found that hotspots (>90.9 Gy in 48 fractions) in the bladder trigone were associated with late urinary toxicity in the form of IPSS+10[6](#_ENREF_6). This was in a cohort of 268 patients receiving IMRT. Using dose difference maps of the bladder, Heemsbergen et al. showed that doses ≥ 80 Gy in the trigonal region were associated with late urinary obstruction[18](#_ENREF_18). More recently, Murray et al. have demonstrated a correlation between trigone dose and acute urinary toxicity in patients treated in the DELINEATE study (ISRCTN04483921)[13](#_ENREF_13). Finally, in a study of patients having low dose-rate brachytherapy, Hathout et al. found that higher doses to the bladder neck (a structure incorporating the most inferior portion of the trigone) were significantly associated with acute and late urinary toxicity[19](#_ENREF_19). In addition, our findings are consistent with the low predictive power of whole bladder DVH parameters for urinary toxicity[4](#_ENREF_4).

The function of the urinary bladder trigone is not well understood, but it has potential roles in control of micturition, particularly initiation[20](#_ENREF_20). This is consistent with our findings, as the typical manifestations of radiotherapy-related urinary toxicity are frequency, urgency, and obstructive symptoms.

A drawback to this study is that we have only evaluated the relationship with acute toxicity (as there is insufficient follow-up to examine late toxicity at present). However, acute toxicity is important for two reasons. First, acute toxicity determines the tolerability of a treatment. This is an important consideration for patients when deciding on their treatment for prostate cancer, particularly as they are faced with a broad range of effective options (including surgery and brachytherapy). Secondly, a number of studies have demonstrated strong correlations between acute and late urinary[10](#_ENREF_10), [12](#_ENREF_12) and bowel[9](#_ENREF_9), [11](#_ENREF_11) toxicity, suggesting consequential late damage. However, it has been suggested that the correlation between baseline toxicity and late toxicity seen in some studies may confound this relationship. In our study, baseline IPSS was not associated with IPSS+10 (Table 3). However, it was associated with G2+ RTOG toxicity, demonstrating a potential interaction between baseline and acute symptoms. In addition, there was only a moderate correlation between IPSS+10 and G2+ RTOG toxicity, suggesting that physician-reported toxicity may not fully represent toxicity as experienced by patients.

This method does add significant time to the standard SBRT work flow. However, DSM evaluation tools could potentially be implemented within existing planning software, or, alternatively, a simple 3D volume structure as used by Ghadjar et al. may suffice for evaluating trigone maximum dose[6](#_ENREF_6). As SBRT prostate planning typically involves “pushing” dose away from the rectum, it may be that a significant portion of high dose is pushed toward the trigone just above the prostate. Developing appropriate trigone constraints, as suggested in this study, may help to avoid this and resultant toxicity. Interestingly, unlike an earlier study by King et al.[21](#_ENREF_21), we found no association between toxicity and whether treatment was given daily or alternate daily (Tables 3 and 4).

With respect to the rectal analysis, no correlation was found between G2+ toxicity and any baseline, DVH, or DSM measurement. Therefore, the results seen in the study by Kim et al. were not replicated[7](#_ENREF_7). In a dose-escalation study of 91 patients, this group found an association between the circumference of rectal wall receiving 24 Gy in 5 fractions and acute toxicity (this was measured on a single CT slice at the level of mid-prostate, rather than using a DSM). This lack of correlation seen within our data may be because the study was underpowered to detect this. Furthermore, there is significant inter- and intra-fraction variation in rectal volume, leading to differences in calculated and delivered dose[22](#_ENREF_22). Final, Wortel et al. have demonstrated (using subtraction DSMs) that high doses to specific areas of the rectal surface are associated with specific patient-reported toxicities[23](#_ENREF_23). However, as our dataset was relatively small with low heterogeneity, it would have been difficult for us to detect significant differences with this technique.

Conclusion:

We found that higher doses to the urinary bladder trigone DSM were associated with clinically significant rises in IPSS score during the acute toxicity period. Conventional DVHs for urinary bladder did not yield any significant associations. Furthermore, no significant correlations were found between rectal toxicities and rectal DVH or DSM measurements. Although not significant with Holm-Bonferroni correction for multiple testing, the relationship persisted in multivariate analysis, and is consistent with previous studies in CFRT, justifying further evaluation in larger cohorts, with the ultimate aim of reducing toxicity by appropriately optimising dose distributions.

Conflicts of interest:

N.J. van As is the chief investigator and Dr A.C. Tree is a co-investigator in the PACE trial, which is financially supported by Accuray Inc. A.C. Tree, N.J. van As, and D.R. Henderson have received educational grants from Accuray to facilitate attendance at international conferences. A.C. Tree has received honoraria for speaking, funding for a research fellow and travel expenses for educational meetings from Elekta. The Royal Marsden NHS Foundation Trust is in receipt of an unrestricted educational grant from Accuray to support a research fellow.

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