Association of bladder dose with late urinary side effects in cervical cancer high-dose-rate brachytherapy

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ABSTRACT

PURPOSE: The purpose of this work was to study the association between specific urinary sequelae and locally accumulated dose to the bladder wall and bladder neck in the treatment of cervical cancer with multifraction high-dose-rate (HDR) brachytherapy.

METHODS AND MATERIALS: A cohort of 60 cervical cancer patients, treated with both external beam and five HDR brachytherapy insertions between 2008 and 2014 at the BC Cancer Agency, was identified. The accumulated dose received over five brachytherapy sessions was evaluated for the bladder wall and bladder neck of each patient using dosimetric parameters calculated from deformably registered image data sets. These parameters were examined as potential predictors of urinary sequelae including hematuria, frequency, urgency, incontinence, stream, nocturia, and dysuria. Two different dichotomization schemes were evaluated for grouping patients into Case and Control groups. The two-sample Student’s t test was used for normally distributed samples and the Mann–Whitney nonparametric U test for non-normal distributions.

RESULTS: A strong association between dose to the bladder neck and incontinence was found (\( p = 0.001 \)). A statistically significant association (\( p < 0.05 \)) was also observed between urgency and certain bladder-wall parameters.

CONCLUSIONS: Localized dose to the bladder neck is a potential predictor of urinary incontinence, whereas weaker associations were observed between urgency and some bladder-wall parameters.

Keywords: High-dose-rate brachytherapy; Cervical cancer; Urinary late effects; Bladder neck; Bladder wall

Introduction

Although urinary dysfunction has long been recognized as one of the side effects following pelvic radiotherapy, the pathophysiology of radiation-induced damage to the bladder and the rest of the lower urinary tract has still not been fully understood (1). However, based on several animal studies using rat and mouse bladder, it has been established that the cell renewal rate in bladder transitional epithelium (a.k.a. urothelium) is low; therefore, stimulated proliferation does not start until months after irradiation (2–4). As a result, late radiation effects can be commonly observed in the bladder and urethra.

Radiation damage may affect the urine resistant membrane that lines the bladder, causing irritation and damage to the underlying tissue layers, which may result in urinary sequelae such as infection, pain, and hematuria (frequently having blood in the urine with the presence of clots). The smooth muscle fibers are also prone to radiation damage, causing edema and cellular destruction. This may change the bladder’s capacity, creating symptoms such as urinary frequency (need to void every 1–2 hour) and nocturia (frequent need to void during sleep).

Radiation damage to specific structures such as the urethra and bladder neck may be responsible for certain late urinary effects (1–7). Damage to the bladder vasculature may cause vascular occlusion and ischemia, which can lead to late bladder fibrosis and reduction of bladder capacity.
Hematuria can be speculated to correlate with high dose to small volumes of the bladder wall. However, there has not been enough investigation to strongly support this theory. Dose to the bladder neck may be predictive of incontinence, whereas other end points, such as frequency, urgency, and hematuria, are more likely associated with radiation-induced cystitis (1, 7).

When recording the urinary sequelae in practice, based on the LENT-SOMA system, the toxicity is summarized in one grade, which might be the average or maximum of individual symptom scores (8–10). However, considering that different forms of urinary dysfunction might have different underlying causes and mechanisms, combining individual toxicity scores might inhibit our understanding of the radiation dose effects in urinary morbidity. In fact, the focal and global injuries in bladder are believed to have different dose-volume relationships (1). Moreover, symptoms that are grouped together as one toxicity grade have different relative importance and effect on the quality of life of the patient, regardless of the assigned toxicity grade.

The drawback of “aggregating” large volumes of morbidity information into a single “statistic” has also been described by Rosewall et al. (11) both as “an imprecise method of describing the actual type of dysfunction experienced by a patient” and “detrimental when attempting to find a link between dysfunction and radiotherapy dose”. The same argument has also been promoted by Bentzen et al. (12), where the idea of averaging the individual LENT-SOMA organ scores is strongly rejected. Furthermore, it has been shown that different urinary symptoms have different temporal variations (13–15), which would affect the consistency of aggregated grades with different followup intervals.

It is therefore worthwhile to study each symptom individually in relation to radiation dose. Although there have been a few studies exploring the dose relationship for individual urinary symptoms, such as frequency and nocturia following prostate radiotherapy (13, 14), to the best of our knowledge, there have not been any studies investigating individual urinary symptoms in association with high-dose-rate intracavitary brachytherapy (HDR ICBT) dose for cervical cancer.

The normal tissue complication grades can be dichotomized at a certain cutoff point to separate the low- and high-toxicity (i.e., case and control) patient groups. There have been controversies and different approaches toward dichotomizing aggregated urinary toxicity grades using a cutoff point (11). Although most studies use Grade (G) 2 + urinary toxicity as a cutoff according to the Radiation Therapy Oncology Group system (16), some use both G2+ and G1+ (9) and some either G3+ (17) or G1+ (18). When the toxicity grades for different symptoms are averaged to get an overall toxicity grade, the ratio of subjects with Grade 3+ and even 2+ is usually very low compared to the control group. However, the distribution for each symptom varies, with some symptoms such as frequency showing many Grade 3+ subjects while hematuria shows very few. As previously discussed, the relative importance of these symptoms is also quite different, which must be taken into consideration when performing a dichotomized toxicity grade study.

This study aimed to look at the toxicity scores of each urinary symptom in relation to locally accumulated dosimetric and volumetric parameters for the bladder wall and bladder neck, in multifraction HDR brachytherapy for cervical cancer. For all the symptoms, except hematuria, two dichotomization regimens were used, one with G2+ and the other with G3+ cutoff. For hematuria only, G1+ and G2+ cutoffs were used, due to the nature of the complication and the observed distribution of toxicity grades.

Methods and Materials

The prospectively collected LENT-SOMA subjective urinary toxicity data for a cohort of 60 cervical cancer patients treated at the BC Cancer Agency (BCCA) during the period 2008–2014 were used. The characteristics of the patient cohort have been described in detail previously (19). Patient selection was based on the average toxicity grades where all subjects with aggregated toxicity Grade 2 and higher (total of 17) were included in the cohort, and the rest of the subjects (average Grade 0–1) were selected from the BCCA clinical cases treated with HDR ICBT to make a sample size of 60.

All patients were treated with concomitant chemoradiotherapy. The radiotherapy component consisted of 25 external beam radiotherapy (EBRT) fractions of 1.8 Gy and five HDR ICBT with nominal 6 Gy per fraction to the high-risk clinical target volume. The exact HDR fraction doses varied between 3 and 6 Gy due to factors such as disease extent and location of high-risk clinical target volume and organs at risk. Due to the small variation observed in the bladder EBRT dose across the cohort (mean bladder dose = 43.6 Gy ± 5%), the EBRT component was not included in the dosimetric analysis in this study. Moreover, the EBRT per-fraction dose distribution in the bladder wall was not available, as only a single image set (the planning CT) was available. This would potentially reduce the accuracy of EBRT + ICBT dose registration and was therefore avoided in this study.

The toxicity grades in each LENT-SOMA questionnaire were assessed on a 0–4 discrete scale for seven urinary sequelae through the relevant measure for each symptom, including dysuria (severity), urgency (prevalence), hematuria (prevalence), frequency (time separation), nocturia (number of times), incontinence (prevalence), and reduced urine stream (prevalence). For the majority of the patients, there was more than one questionnaire collected over the course of treatment followup. The toxicity grade assigned for the purpose of analyzing each of the seven urinary dysfunction symptoms was the “maximum” reported grade across all collected questionnaires. The distribution of the toxicity grades for every symptom across all subjects was studied.
For all the symptoms, the patients were dichotomized at two different cutoff points based on the toxicity grade level. The cutoff points were selected differently for hematuria due to the nature and scarcity of the complication. For all symptoms, a traditional G2 cutoff with Case = Grade 2 + and Control = Grade 0–1 groups was used. An additional, alternative grouping was also applied for each symptom, but the cutoffs for these varied based on the symptom, as follows: for hematuria, a G1-cutoff grouping was used, that is, Case = Grade 1+ and Control = Grade 0, and for all other symptoms, a G3-cutoff grouping, that is Case = Grade 3 + and Control = Grade 0–2 was used.

Each HDR ICBT fraction planning CT was retrospectively evaluated. The bladder neck location was identified in the planning CT based on the position of the Foley balloon and urethral catheter (Fig. 1). This was performed by first locating the Foley balloon and the urethral catheter, which is clearly visible inside the bladder when it is filled with contrast material. Since the Foley balloon is positioned in the bladder so that it sits at the bladder neck, the axial planes were scrolled through to find the slice at the bottom of the Foley balloon. Then, the sagittal and coronal orthogonal planes were rotated so that the urethral catheter was cut perpendicularly. The cursor was then positioned at the middle of the catheter when all three views were centered on the edge of the bladder outer contour. This position was recorded as the bladder-neck point, as shown in Fig. 1. During this process, the bladder wall contour was used as a guide so that the bladder neck position stays inside the bladder wall.

Quality assurance of the correct location of the bladder neck point was via an audit of 10% of the cases by a Radiologist at BCCA, who approved the bladder neck point localization in all the audited cases. Once located, the bladder neck point was used as the “seed” point for identification of a contiguous high dose volume in its vicinity (see in the following). In other words, a bladder neck volume structure was not explicitly identified.

To localize and accurately accumulate dose to the bladder over different HDR ICBT treatment fractions, a deformable registration method called coherent point drift (CPD) (20) was used. CPD is a (contour) point-based, rather than image-based, deformable registration method that was previously validated for deformable registration of bladder wall, as described and discussed in the study by Zakariaee et al. (19, 20). Briefly, the bladder wall doses over all BT fractions were accumulated by deforming the bladder contours from the treatment plan for each fraction onto a single reference bladder contour, using CPD. The resulting contour point deformation matrices were then used to map the doses from each fraction onto the reference bladder point set. Registered volumetric and dosimetric parameters for different absolute volumes and dose thresholds were calculated from the registered dose data for the bladder wall. Voxel-based registered EQD2 dose was determined using equations (3-4) in the study by Zakariaee et al. (19) and an \( \alpha/\beta \) of 3 Gy.

Fig. 1. Bladder neck location (blue cross) shown in three (noncardinal) orthogonal views. The location of the bladder neck is determined using the Foley balloon and catheter and the bladder wall contour. Note that since the orthogonal views are rotated from the original cardinal (sagittal, coronal, and axial) planes, the bladder wall contour looks slightly jagged. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
Because accumulation of dose over multiple brachytherapy fractions often results in two or more physically separated “hot spot” regions, particular emphasis was placed on the calculation of contiguous high dose volumes, as described in the study by Zakariaee et al. (19). In addition to bladder-wall parameters, three different contiguous dose-volume parameters ($BND_{0.1cm^3}$, $BND_{0.5cm^3}$, and $BND_{2cm^3}$) were evaluated in the bladder neck by using the location of the bladder neck point as the starting point of a contiguous volume search. Table 1 lists and defines all the parameters included in this study.

An analysis was performed to determine whether any of the bladder-wall and bladder-neck dose parameters were predictive of individual urinary sequelae. Age was also studied as a potential comorbidity parameter for urinary symptoms. In this analysis, the normality of the Case and Control groups’ distributions was tested for both groupings and all parameters, using the Shapiro–Wilk normality test, which was performed using SPSS Statistics software (IBM Corp, Armonk, NY; version 23). For the parameters/symptoms that passed the normality test, the parametric Student’s $t$-test was applied, with the null hypothesis that the means of Case and Control groups are equal. For those that did not pass the normality test, a nonparametric Mann–Whitney $U$ test was performed. The $p$-values calculated by these methods were used as a measure of the significance in the difference between Case and Control means. The statistical power (1-$\beta$) was measured using open source G*Power software (21), (Version 3.0.10), with the corresponding sample sizes,
means, and standard deviations in the Case and Control groups applied for each end point and each parameter.

Results

The toxicity grade distribution for all seven urinary symptoms across the cohort is shown in Fig. 2. Urgency and stream showed the most Grade 4 and Grade 3 complication levels, respectively. Hematuria showed the minimum number of Grade 4 and Grade 3 and also the maximum number of Grade 0 toxicity levels. Only 5% of the subjects had Grade 0 frequency, whereas >50% reported no signs of incontinence, dysuria, hematuria, and stream complications.

The bladder neck was not identifiable in one of the subjects; therefore, the total number of subjects included in the bladder neck dose analysis was 59 rather than 60. Figures 3–5 show box plots of the descriptive statistics for the registered dosimetric, volumetric, and bladder-neck dose parameters for Case and Control in the G2 cutoff compared to G1 and G3 compared to G1 groupings of incontinence, urgency, and hematuria symptoms. Theresults for the rest of the symptoms, which had nonsignificant outcomes, are included in the Supplementary material.

Table 2 lists the p-value and statistical power (1-β) results for the difference in the means of the Case and Control groups, based on the G2- and G3/G1-cutoff groupings of incontinence, urgency, and hematuria end points,
which showed the most significant results, with some of the parameters in each grouping. Among all the urinary end points, incontinence showed the lowest p-values for the parameters tested. The significant findings ($p < 0.05$) for incontinence were observed for all the bladder-neck dose parameters in both groupings. The smallest p-values and highest statistical powers among all the parameters, symptoms, and groupings tested were achieved for $BND_{0.1cm^3}$ and $BND_{0.5cm^3}$ in the G3-cutoff grouping ($p < 0.01$). The G2 grouping for incontinence showed $p < 0.1$ for three of the bladder-wall dosimetric parameters and $p < 0.05$ for $V_{3Gy}$. The G3 grouping resulted in $p < 0.1$ for two other wall parameters.

For urgency, the G2 grouping yielded $p < 0.05$ for $V_{3Gy}$, $EQD_{2cm^3}$, and $Idose$. However, the statistical power achieved for these parameters was smaller than the established threshold of 0.8 for avoiding type II error (i.e., false negative) in rejecting a null hypothesis (22). The G1 grouping for hematuria did not yield any significant findings; however, the G2 grouping for this end point showed $p < 0.1$ for four of the bladder-wall parameters. Age was also studied as a potential comorbidity factor for urinary complications and was not found a significant factor.

**Discussion**

All patients treated for cervical cancer treated with both external beam and HDR brachytherapy were prospectively evaluated using the LENT-SOMA system. Seven urinary symptoms were defined in the LENT-SOMA system. The toxicity grade distributions varied significantly among different urinary symptoms. Urgency and stream showed the highest Grade 4 and Grade 3 scores, respectively. Incontinence, dysuria, hematuria, and stream had more Grade
0 cases compared to urgency, frequency, and nocturia. These observations suggest that some symptoms, particularly frequency, urgency, and nocturia, might be due, at least in part, to other factors such as age, pelvic floor health, or a high level of liquid consumption. Therefore, it would have been helpful to have access to baseline (i.e., pretreatment) data, which was lacking in this study, to account for the pretreatment urinary function in the analysis.

Urgency and incontinence were the only symptoms that appeared to be associated \( (p < 0.05) \) with certain registered dose parameters. Hematuria showed some association based on \( p < 0.1 \) significance level. No sign of association was observed for frequency, nocturia, dysuria, and stream. This observation might be explained, for frequency and nocturia, by limited followup data, lack of baseline data, and the likelihood that the baseline values for these complications might be more variable than they are for the other parameters. On the other hand, the lack of significant results for dysuria and stream might simply be due to lack of a significant dose effect at the levels to which this patient group was exposed. Larger sample sizes and baseline information would be helpful in further investigation of these theories.

Overall, the G2 cutoff demonstrated the most significant results (18 and 6, respectively) compared to G3 cutoff (5 and 2, respectively). However, the most significant results of all \( (p < 0.01 \) and \( 1 - \beta > 0.9 \) were observed in the G3 grouping for bladder neck dose parameters as a predictor of incontinence.

The only bladder-wall parameters showing significant association with a urinary symptom were \( V_{3Gy} \), \( EQD_{2cm^3} \), and \( I_{dose} \), in the G2 grouping. The most significant results across all parameters were observed for incontinence using the G3 cutoff with both \( BND_{0.1cm^3} \), and \( BND_{0.5cm^3} \) \( (p = 0.001 \) and 0.003, respectively, with
the statistical power of 0.98 and 0.94). Significant results ($p < 0.05$) for incontinence were also obtained for all the bladder neck dose parameters in the G2 grouping. These findings suggest that dose to small volumes ($\sim 0.5$ cc) in the region of the bladder neck may best predict for incontinence, which supports our initial hypothesis. The fact that dose to a slightly larger volume of 2 cc around bladder neck was also a predictor for incontinence supports our initial hypothesis that aggregating different symptoms into a single score is not the most useful method for understanding the dose effect of urinary complications.

However, some of the parameters are highly correlated and therefore cannot be considered completely independent, for example, 0.92 for $D_{2,cm^3}$ vs. $D_{1,cm^3}$ and 0.95 for $EQD_{2,cm^3}$ vs. $EQD_{1,cm^3}$, where $R$ is the correlation coefficient. If considered independent, application of the Holm’s step-down approach (24) for controlling the familywise error rate (25) determined that true rejection of null hypothesis for bladder neck parameters and incontinence was established based on the G3 grouping.

### Conclusion

This study investigated the association between locally accumulated dose parameters and specific urinary symptoms. Within the limitations of this study, it was found that dose to small volumes of 0.5 and 2 cc around the bladder neck significantly predict for urinary incontinence. Urgency was associated with some bladder-wall parameters, most significantly with integral dose, and hematuria showed association with doses to small bladder-wall volumes. However, the statistical power for these results was smaller than the accepted threshold of 0.8. Therefore, although these findings for urgency and hematuria are of interest and promising, more investigation and larger sample sizes are required before drawing conclusions.
Lack of baseline data and insufficient followup for a few subjects in this study may have prevented detection of a dose response for certain end points such as frequency, which could have had high baseline values in this population. Since the data collection for this study, the clinic has initiated standardized pretreatment, ontreatment, and posttreatment assessment of common clinical symptoms; therefore, a more robust data set on which to repeat this analysis will be available in the future. However, lack of sufficient high-toxicity cases for some of the end points, such as nocturia, dysuria, stream, and hematuria, while clinically desirable, will continue to make the dose response of these end points difficult to study in small populations. Therefore, validation of the results of this study will require a larger cohort in addition to knowledge of baseline toxicity grades and longer followup.

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Supplementary data

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References