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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.

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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 an 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.