Introduction

Definitive treatment for cervical cancer most often consists of fractionated external beam radiotherapy combined with multi-fraction intracavitary brachytherapy. CT imaging in gynaecological brachytherapy treatment planning has been widely used in the past decade. With the advantages of image-based treatment planning and the commercial treatment planning software tools available, it is possible to determine the dose received at each voxel of the image for each dose fraction delivered. Recent recommendations for image-based dose recording recognize these capabilities, and a number of dose-volume-histogram (DVH) based parameters have been recommended for dose recording of both tumour/target volumes and organs at risk (OAR) [1, 2, 3].

However, there are two potential drawbacks for using DVH parameters for the hollow elastic OARs surrounding this cancer site, such as bladder and rectum. First, the ability to precisely define cumulative dose received by these highly deformable normal structures is limited due to the large localized variations that can occur in most, if not all, of these structures from one fraction to the next. These variations are caused by factors such as variable bladder, bowel, and rectal filling, tumour regression, and displacement of structures by the intracavitary brachytherapy applicators. Moreover, the current DVH parameters used in practice are usually calculated for the whole volume of the hollow organs, whereas the area of interest is only the wall and not the filling. Therefore, the standard volumetric DVH parameters provide no information on the spatial distribution of the dose within the organ wall in situations of repeated fractions with changes in organ shape or size.

In spite of their limitations, standard volumetric DVH parameters have been used to show that treating with a full versus empty bladder can have a significant effect on the total dose received by the bladder and other surrounding OARs, with no significant difference in the dose distribution delivered to the target volume [4, 5]. At our institution, the practice of alternating the amount of bladder filling in consecutive fractions of high-dose-rate (HDR) brachytherapy for cervical cancer patients has therefore been adopted to potentially change the location of high dose regions and avoid delivering a high dose to the same spot in consecutive fractions. However, tools to calculate the localized cumulative dose and the correlation between this dose and the observed bladder toxicity are not presently available.

Consequently, calculation of cumulative dose for the deformable hollow OARs in the pelvis is an area that still requires more investigation. The aim of this research was to develop methods to more accurately determine geometrically localized, cumulative dose to the bladder wall in intracavitary brachytherapy for carcinoma of the cervix. New cumulative-dose parameters are defined and the correlations between these parameters and the observed bladder toxicity are investigated retrospectively.

Methods

The planning CT scans and treatment plans for five high dose rate (HDR) brachytherapy fractions of each patient included in the study were used as the raw data. The bladder inner and outer surfaces were carefully contoured, using MIM Maestro software (MIM Software Inc. Cleveland, OH). Also, three landmark points were identified on each scan: the points of entrance of the two ureters to the bladder and the point of attachment of the urethra to the bladder (bladder neck). All three landmarks are in the posterior half of the bladder, which is the part of the bladder where high dose regions tend to occur. The bladder wall contours and landmark points of a random selection of patients were reviewed and approved by a radiologist at our centre. The bladder inner and outer contours were exported as 3-dimensional (3D) point clouds and imported into MATLAB (The MathWorks Inc., Natick, MA, version R2013b). In order to fill the space between the inner and outer surfaces, a final bladder wall point cloud was created by linearly interpolating between nearby points in the inner and outer contour point clouds.
In order to accumulate the dose received at different treatment fractions, we need to establish point correspondence across the shapes of bladder at different fractions [6]. A point set registration toolbox for MATLAB, Coherent Point Drift (CPD) [7], was used to non-rigidly transform the bladder-wall points from four of the fractions to the coordinate system of the remaining fraction, which we refer to as the reference fraction. The software outputs a point-correspondence vector (C), which matches the indices of points in the moving structure (Y) to those in the fixed or reference structure (X). The three landmarks were also included in the point sets, and they were used to evaluate the quality and accuracy of the registration by calculating a target registration error (TRE) for each landmark. The TRE was calculated by finding the distance between the position of the matched point in X (based on C) to a landmark in Y and the known position of the corresponding landmark in X.

There are many different parameters that can be adjusted for the point-matching technique, such as the number of points of the target and the moving structures, registration regularization weight (the weight of a prior distribution over the displacements of the points), the width of the Gaussian kernel (smoothness), number of iterations, etc. These parameters were optimized based on the minimization of the average TRE for all three landmarks. For the reference fraction, the “emptiest” bladder was chosen for each patient in order to compare inter-patient tissue volumes that were as anatomically equivalent as possible. The underlying assumptions here are that the cell density is about the same in the unfilled bladder for all patients, and that the number of cells affected correlates with the dose response.

To calculate cumulative dose, the voxel-dose values computed by the BrachyVision Treatment Planning software (Varian Medical Systems Inc.) were exported as a 3D matrix, with a resolution of 2.5 mm by 2.5 mm by 1.25 mm. The point-doses for the wall points used in the deformable registration step for each fraction were estimated by linear interpolation in MATLAB. Given the resolution of the dose matrix, linear interpolation was sufficiently accurate for the dose gradients present in the bladder wall. The resultant point-correspondences between the bladder-wall points from the deformable registration, were used to accumulate the point-doses for all fractions on the points of the reference fraction. In addition, the cumulative biological effective doses (BED) were calculated for each point using the following equation:

\[ cBED = \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 \frac{\alpha}{\beta} \]

where \( d_i \) is the dose received at each point in each fraction. An \( \alpha/\beta \) ratio of 3 was used, based on the standard value for normal tissue as reported in literature [8, 9].

The accumulated point-doses can be analyzed against the toxicity scores using different cumulative-dose parameters. The chosen parameters in this study included the size of hot spot regions at selected absolute dose thresholds, consisting of \( cV_{20Gy} \) (the volume of bladder wall receiving a minimum of 20 cGy cumulative dose), \( cV_{25Gy} \), and \( cV_{30Gy} \). Also measured were the minimum cumulative dose values of the hottest contiguous 1cc and 2cc regions for cumulative dose (\( cD_{1cc} \) and \( cD_{2cc} \), respectively) and for cumulative BED values (\( cBED_{1cc} \) and \( cBED_{2cc} \), respectively). The hottest regions were found approximately by parcellating the bladder-wall mask into contiguous 1cc and 2cc regions randomly, selecting the hottest region and repeating these steps until convergence.

The correlation between the cumulative parameters and the reported toxicity scores based on LENT-SOMA questionnaires for 20 patients treated for cervical cancer with a tandem and ring or tandem and ovoid applicator was studied. Given that toxicity scores are continuous numerical values, they were compared to each of the dosimetric parameters using linear regression analysis.

**Results**

Data for 20 patients were included in this study, with toxicity scores ranging from 0.11 and 3.00. All patients received 5 HDR fractions of 600 cGy. For each patient, the deformable registration was performed from four fractions to the reference fraction using the CPD toolbox. The TRE values were calculated for each registration and the average and standard deviation values were 9.5 and 5 mm, respectively. An example of before and after images for a single registration is shown in Figure 1.
Figure 1. An example of the point-set deformable registration result. The left picture shows the target structure in red and the moving structure in blue. The right picture displays the result of the deformed moving structure superimposed on the target structure for comparison purpose. Note that the algorithm normalizes both point-sets to zero mean and unit variance before registration, hence the scale of the image on the right.

The cumulative doses and cumulative BED’s were accumulated onto the reference fraction. An example of a final result of dose accumulation for both cumulative dose and cumulative BED is shown in Figure 2. Visual inspection of the color-mapped accumulated point dose on the bladder wall indicates that the dose accumulation outputs look as expected, with highest dose values in tissue nearest the HDR source dwell positions for each fraction. Despite the variable filling of the bladder volume across fractions, certain regions of the bladder wall appear to accumulate much higher dosages than other regions.

Figure 2. An example of the cumulative dose (left) and cumulative BED (right) on a reference fraction. The color map shows the accumulated dose values in cGy.

The point dose values together with the bladder-wall masks were used to calculate the defined dosimetric parameters. The mean, minimum, maximum, and standard deviation (SD) values for all the dosimetric parameters and the whole volume of the reference bladder are listed in Table 1. The correlations between each dosimetric parameter and the toxicity scores were studied using the simple linear regression analysis method. No significant correlation between these cumulative dose parameters and the observed bladder toxicity was found.
Table 1. List of the mean, minimum, maximum, and standard deviation values for all determined parameters and the volume of the reference bladder.

<table>
<thead>
<tr>
<th>Statistics</th>
<th>$cV_{20Gy}$ (cc)</th>
<th>$cV_{25Gy}$ (cc)</th>
<th>$cV_{30Gy}$ (cc)</th>
<th>$cD_{1cc}$ (Gy)</th>
<th>$cD_{1cc}$ (Gy)</th>
<th>$cBED_{2cc}$ (Gy)</th>
<th>$cBED_{1cc}$ (Gy)</th>
<th>Bladder Reference Volume (cc)</th>
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<tr>
<td>Average</td>
<td>5.2</td>
<td>2.5</td>
<td>0.77</td>
<td>11.4</td>
<td>16.0</td>
<td>1100</td>
<td>2200</td>
<td>150</td>
</tr>
<tr>
<td>Min</td>
<td>0.0</td>
<td>0.0</td>
<td>0.00</td>
<td>4.7</td>
<td>8.1</td>
<td>100</td>
<td>510</td>
<td>80</td>
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<tr>
<td>Max</td>
<td>12.8</td>
<td>6.6</td>
<td>2.84</td>
<td>19.0</td>
<td>21.8</td>
<td>2500</td>
<td>4900</td>
<td>230</td>
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<tr>
<td>SD</td>
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<td>2.0</td>
<td>0.90</td>
<td>3.8</td>
<td>3.8</td>
<td>680</td>
<td>1100</td>
<td>42</td>
</tr>
</tbody>
</table>

Conclusion

In this study, a method was proposed for measuring accumulated dose in the bladder wall across multiple brachytherapy fractions. Low TRE values and the general appearance of the accumulated dose distributions suggest this is a reasonable approach worthy of further exploration.

Based on this study, no significant correlation was found between the cumulative dose parameters defined and the LENT-SOMA toxicity scores. However, the preliminary patient data set used was small, and we plan to continue this analysis with a larger data set. Clinical factors such as patient age, volume of empty bladder, and baseline (pretreatment) urinary function likely also play a significant role, and will be included in future studies with the expanded data set. Other deformable registration techniques will also be investigated with the larger data set.

References


