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FULL PAPER

Quantification of interobserver variability in image registration using cone beam CT for partial bladder radiotherapy—a comparison between lipiodol and bladder wall surface

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Objective: The use of lipiodol or bladder wall surface (BWS) for image guidance has improved the treatment quality for partial bladder irradiation. Currently, this procedure is manually performed by different users. This study assessed the interobserver variability of using image guidance for partial bladder irradiation.

Methods: 7 observers were prospectively recruited to manually register 5 cone beam CTs (CBCT) from each of 20 bladder cancer patients with lipiodol injected for tumor demarcation. Lipiodol and BWS were used to register the CBCT to pre-treatment reference images, and displacement values in three directions were collected. Mean difference among observers and the 95% limit of agreement were calculated to measure interobserver variability. Margin required and the resultant treatment volume were compared between the surrogates.

Results: A total of 4200 displacement values were collected for analysis. Lipiodol was superior to BWS,

with a mean difference among observers of <2 mm and a 95% limit of agreement of <5 mm in all directions. Of the three directions, greatest variability was observed in the superior-inferior direction for both surrogates, hence requiring a larger margin than the other two directions. After applying the corresponding margin, the mean volume of BWS-planning target volume was calculated to be significantly larger than lipiodol-planning target volume (166 cm³ vs 134 cm³, $p < 0.05$).

Conclusions: The use of lipiodol achieved a higher interobserver agreement than BWS. A larger margin in the superior-inferior direction is recommended due to greater interobserver variability observed in this direction for both surrogates.

Advances in knowledge: The uncertainty associated with the image registration by multiple observers for bladder image-guided radiotherapy is quantified for two surrogates.

INTRODUCTION

Significant improvement in the quality of bladder radiotherapy has been demonstrated with the use of cone beam CT (CBCT) due to its capability in visualizing soft tissue for target localization.¹ It provides important information about the interfraction motion of the bladder and the location of normal critical structures, thus facilitating a reduction in planning target volume (PTV) margins without compromising target coverage.^{2,3} Although various methods to personalize bladder radiotherapy are available,⁴ previous studies have demonstrated the efficacy of using a patient-specific PTV (PS-PTV) derived from the magnitude of bladder volume variation and deformation observed in an individual patient in reducing the irradiated volume for both whole bladder⁵ and partial bladder irradiation.⁶

For partial bladder irradiation, radio-opaque fluid such as lipiodol has been injected around the tumor prior to radiotherapy simulation to aid in volume delineation and image guidance due to difficulty in differentiating the location of the tumor from the normal bladder wall on both the planning CT and CBCT.^{7–10} However, when lipiodol injection was contraindicated, bladder wall surface (BWS) is the preferred non-invasive surrogate for image guidance.¹¹

At the Princess Margaret Cancer Centre, image registration using either the lipiodol or the BWS is performed manually for daily online radiotherapy guidance, and for deriving the PS-PTV. A high degree of consistency among different users is required for adequate geometric coverage

Figure 1. Planning CT in transverse, sagittal and coronal view displaying the outline of the two surrogates of Patient 19. Image registration: using lipiodol by displaying the lipiodol outline (blue) and overlaying it onto the lipiodol visualized on CBCT and; BWS by displaying the CTV outline (red) and aligning it to the bladder wall where the tumor resided. BWS, bladder wall surface; CBCT, cone beam CT; CTV, clinical target volume.

of the target and for minimizing the volume of irradiated normal tissue. One study has reported high interobserver reproducibility using gold markers and orthogonal electronic portal images for prostate image-guided radiotherapy.¹² However, the uncertainty associated with image registration by multiple users using lipiodol or BWS for bladder has not been examined. Unlike a gold marker, which is an unambiguous object that does not change shape, lipiodol can exhibit significant deformation due to changes in bladder filling.¹⁰ It is possible that those changes may increase the subjectivity of the image registration process, and thus it is critical to quantify this uncertainty to ensure that adequate treatment margins are applied. Therefore, the purpose of the study is to quantify and to compare the interobserver variability of using lipiodol or BWS for image registration for partial bladder irradiation.

METHODS AND MATERIALS

Patients

After obtaining approval from the local research ethics board, 20 bladder patients with lipiodol injected into the bladder wall

for target localization were identified. These patients had biopsy proven urothelial carcinoma of the bladder and were reviewed in a multidisciplinary bladder cancer clinic. They were treated with radiotherapy $\pm$ chemotherapy with curative intent between April 2009 and May 2013.

All patients had lipiodol injected to demarcate the edges of the tumor bed prior to CT simulation. They were instructed to have a comfortably full bladder and empty rectum for both planning and treatment. The following regions of interest were delineated: Whole bladder (solid), clinical target volume (CTV), pelvic lymph nodes,¹³ rectal wall, small and large bowel. The lipiodol was also contoured for image registration purposes. A total of 66 Gy was delivered in two phases using a 7-field, step and shoot, inverse planned IMRT technique: 46 Gy in 23 fractions to pelvic lymph nodes and whole bladder during Phase 1, followed by 20 Gy in 10 fractions to the partial bladder PS-PTV alone during Phase 2. Daily CBCT were acquired for online image guidance.

Figure 2. Correlation of displacement values (cm) measured between lipiodol and BWS. AP, anteroposterior; BWS, bladder wall surface; RL, right-left; SI, superior-inferior.

Image registration surrogates

For this study, the first 5 CBCTs acquired during treatment from each of the 20 patients were manually registered to the pre-treatment planning CT using the following two image registration surrogates (Figure 1):

- (1) Lipiodol: The outline of lipiodol from the planning CT was overlaid onto the lipiodol visualized on CBCT. This method required the observer to make a subjective match that resulted in even distribution of overlap/underlap between the outline from the planning CT and the Lipiodol on CBCT in the three major planes.
- (2) BWS: The outline of the CTV from the planning CT was overlaid onto the bladder surface where the tumor resides on CBCT. This method required the observer to make a subjective match that was the “best fit” to minimize the summed distance between the distal borders of the CTV outline and the CBCT bladder surface in that region

Observers

Seven observers were randomly selected from a group of Radiation Therapist volunteers, all of whom had a minimum of 1 year experience with target localization using CBCT and lipiodol. Each observer was instructed to manually register all the CBCTs to the planning CT using the lipiodol for all 20 patients first, then repeat the registration using BWS starting from the first patient. Observers were blinded to the results obtained by other observers. The level/window and contrast/brightness parameters were optimized at the discretion of the individual observers.

Data collection and analysis

The translational displacement data were recorded in three dimensions for each CBCT, each patient, each image registration surrogate, and each observer. The absolute displacements measured using BWS were then compared to those using lipiodol to determine if there was an association. The mean and standard deviation of the absolute difference among observers, and the 95% limit of agreement were calculated for each surrogate to determine interobserver variability.¹⁴ Systematic (Σ) and random (δ) errors were calculated for each surrogate in each direction to calculate the margin necessary to account for interobserver variability ($2.5\Sigma + 0.7\delta$).¹⁵ Lipiodol-PTV and BWS-PTV were generated by applying the corresponding margin to the composite volume of the clinical target volumes from the five CBCTs for comparison.⁶

RESULTS

The manual registration of 100 CBCTs from 20 patients to the corresponding reference CT by 7 observers using lipiodol and BWS resulted in a total of 4200 displacement values for analysis.

The two-dimensional displacements measured by lipiodol were highly correlated with those measured by BWS ($R^2 > 0.99$) (Figure 2). The mean and standard deviation of absolute difference among the seven observers in the three dimensions are summarized in Table 1. Overall, BWS was inferior to lipiodol, as indicated by a larger mean difference among observers and 95% limit of agreement in all directions [4.1 vs 3.2mm in right-left (RL); 5.8 vs 3.6mm in anteroposterior (AP); 6.5 mm vs 4.9 mm

Table 1. Mean, range and SD of absolute difference among observers (mm) in the right-left, anteroposterior and superior-inferior directions for this cohort of 20 patients

	Right-left		Anteroposterior		Superior-inferior	
	Lipiodol	BWS	Lipiodol	BWS	Lipiodol	BWS
Mean	1.1	1.8	1.3	2.0	1.8	2.6
Range	0–13	0–16	0–16	0–30	0–17	0–29
SD	1.6	1.8	1.9	3.0	2.5	3.2

BWS, bladder wall surface; SD, standard deviation.

Figure 3. Limit of agreement plot for displacement values (mm) measured among seven observers (indicated by different symbols) using lipiodol (a–c) and bladder wall surface (d–f) in the right–left, anteroposterior and superior–inferior directions, with the dash lines indicating the 95% upper and lower limit of agreement with the mean.

in superior–inferior (SI)] (Figure 3). This agrees with the significantly larger systematic and random errors calculated for BWS in all three dimensions when compared to lipiodol ($p \leq 0.0002$) (Table 2).

In terms of direction, interobserver variability was the greatest in the SI direction for both surrogates, hence requiring a larger margin to accommodate (Table 2). After applying the corresponding margin, the mean volume of BWS-PTV was calculated

Table 2. Systematic, random error and the PTV margin (mm) of lipiodol and BWS

	Systematic error			Random error			Margin		
	RL	SI	AP	RL	SI	AP	RL	SI	AP
Lipiodol	0.8	1.6	1.1	1.5	2.3	1.7	3	6	4
BWS	1.4	2.2	1.7	2.0	3.0	2.7	5	8	6

AP, anteroposterior; BWS, bladder wall surface; PTV, planning target volume; RL, right–left; SI, superior–inferior.

Figure 4. Absolute difference in 3D displacement among observers (mm) for individual patients. 3D, three-dimensional; BWS, bladder wall surface.

to be significantly larger than lipiodol-PTV (166 cm^3 vs 134 cm^3 , $p < 0.05$).

Figure 4 displays the absolute mean difference in three-dimensional displacement among observers for each individual patient. The degree of variation in image registration differed from patient to patient and this variability was greater for BWS than lipiodol (Lipiodol: 0.7–2.7 mm; BWS: 1.0–3.9 mm). However, no strong association with the tumor volume, planning bladder volume, magnitude of interfractional volume change or the location of the tumor was noted. The mean difference in three-dimensional displacement among observers was clinically significant for 20 and 65% of the cohort when using lipiodol and BWS, respectively. In addition, lipiodol achieved a higher interobserver consistency than BWS for all patients except for Patient 19 and 20.

DISCUSSION

Image guidance for partial bladder irradiation has been manually performed using either the lipiodol or the BWS as the surrogate. We quantified the interobserver variability of this process to calculate the margin required to account for this uncertainty.

Our study demonstrated a higher interobserver agreement achieved by lipiodol vs BWS, with a mean difference among observers of $< 2 \text{ mm}$ in all directions. The use of a radio-opaque marker has been previously shown to be more consistent than soft tissue among observers for prostate image guidance.¹⁶ When comparing lipiodol for bladder and gold marker for prostate, the interobserver variability was greater for lipiodol, with a systematic error (in mm) of 0.8, 1.1 and 1.6 in the RL, AP and SI directions for prostate vs 0.09, 0.28 and 0.36 for bladder. This suggests that subjectivity in image registration may be greater when using lipiodol due to variation in the location and shape of the surrogate induced by bladder filling, as compared to gold markers implanted in the prostate that change very little in location and shape. Gold markers have also been used as a surrogate for bladder image guidance.^{17–20} Similar to lipiodol, it is effective in improving treatment precision. However, data on matching consistency among observers using bladder gold markers are lacking and it would be interesting to know if the interobserver variability is significantly different when several rigid objects are used for bladder image guidance.

This study identified SI as the direction that is subject to the greatest interobserver variability by either of the surrogates, hence requiring the largest margin among the three directions. Bladder wall movement has been reported to be the greatest in

Figure 5. Axial, sagittal and coronal view displaying the lipiodol (blue) on reference CT above and CBCT below. Lipiodol was deformed on CBCT due to a smaller bladder at the time of treatment. CBCT, cone beam CT.

the SI and AP direction²¹ and the relative position of the lipiodol during treatment could vary substantially from the time of planning. Figure 5 displays the bladder at the time of planning and a smaller bladder at the time of treatment. Due to the displacement of the bladder wall in the SI direction, the lipiodol was deformed, thus increasing the subjectivity of the manual registration in this direction. One possible approach would be to align the superior portion of the lipiodol to minimize inclusion of the surrounding organs at risk (e.g. small bowel) in the prescription dose volume, while another would be to align by averaging out the distance between the superior and inferior extent of the outline and the Lipiodol on CBCT. Due to the complexity associated with the various locations of the tumor within the bladder wall and the significant motion and deformation caused by bladder filling in this disease group, very detailed patient-specific image guidance instructions developed by a multidisciplinary team are necessary to improve the quality of the process.

Interobserver variability was greater for some patients than others. However, the magnitude of the variability was not strongly associated with any of the identified factors. In an attempt to understand why BWS was a better surrogate for some patients, we further investigated patients 19 and 20, (Figure 4). Patient 19 had one of the smallest planning bladder volumes (72 cm³) and was noted to have largest interfractional bladder volume changes in the five fractions in this cohort (treatment bladder volume up to 2.5 times larger than planning volume). When comparing the outlines of the two surrogates, the lipiodol outline was more elongated, covering a larger portion of the bladder wall (Figure 1). Since the shape of the lipiodol is stretched by the stretching of the bladder wall during bladder filling,¹⁰ the stretched (deformed) shape of the lipiodol exhibited during treatment could have increased the subjectivity in finding the best fit using the outline delineated based on the planning bladder. For Patient 20, there was also a large interfractional bladder volume change during treatment (up to 1.6 times larger than planning). In addition, the tumor extended over a large portion of bladder wall in the superior-lateral aspect, an area which is prone to increased deformation, and likely exacerbated the difference between the shape of the lipiodol at planning and treatment.

The spectrum of planning bladder volume in this cohort is large, with a range of 66–510 cm³. Despite being given drinking instructions, 30% of the treatment bladders were at least 10% larger than the planning bladder and 13% were less than half of the planning bladder volume. This provides a representative sample of bladder volume variation to quantify interobserver variability for image guidance using surrogates. Nevertheless, there are few limitations in this study. Our data have been collected based on the use of CBCT and the interobserver variability measured herein may not be applicable to two-dimensional orthogonal images, which have been preferred for image guidance as they allow for reduced imaging dose without compromising precision.²⁰ In addition, the outline of the surrogate was generated based on a reference CT acquired with a full bladder in this study. Although interfraction motion of the bladder wall has been shown to be comparable between full bladder and empty bladder,²² it is uncertain how the consistency of image registration would be affected when the surrogate is outlined based on a reference CT acquired with an empty bladder. Lastly, the presence of the lipiodol in the images may have affected the BWS matching in two ways. Firstly, streaking artifacts produced from the lipiodol could obscure the bladder surface and make surface matching difficult. Secondly, the presence of lipiodol could bias the results for the BWS match, making them more similar to lipiodol. Although other authors have reported a novel approach in removing high contrast objects in CBCT,^{16,23} the location of the Lipiodol within the bladder wall precludes this approach.

CONCLUSIONS

A higher interobserver agreement was achieved with the use of lipiodol for image guidance when compared to BWS for partial bladder irradiation. As a result, despite a good correlation between the displacements measured by the two surrogates, a larger PTV margin is required to accommodate interobserver variability when BWS is used. Bladder filling variation can cause substantial variation in the shape of liquid radiopaque markers, such as lipiodol and very detailed patient-specific image guidance instructions developed by a multidisciplinary team are necessary to improve the quality of the process.

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