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Original Article

The dosimetric impact of manual adjustments following automated registration in prostate image-guided radiotherapy

Mohamed Nazmy ElBeltagi[1,2], Dean Harper[1], Lisa Coleman[1]

[1]*St Luke's Radiation Oncology Network, Dublin, Ireland,* [2]*NCI Cairo University, Egypt*

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Abstract

Aim: Although manual adjustment of automatic cone beam computed tomography (CBCT) matching may improve the target coverage in certain points of interest, concerns exist that this may lead to dosimetric uncertainties which would negate the theoretical benefit of this approach. The objective of this study is to evaluate the dosimetric impact of manual adjustments made after automatic bony registration on CBCT in prostate patients.

Methods: A total of 50 CBCT datasets of ten high-risk prostate cancer patients were randomly chosen. Each CBCT dataset was registered three times. Method (A): Automatic registration, Method (M1): Manual adjustment carried out by two experienced radiation therapists, Method (M2): Manual adjustment carried out by different radiation therapists with varying levels of experience. The clinical target volume (CTV), planning target volume (PTV), the bladder and the rectum were subsequently contoured on each CBCT dataset by a radiation oncologist blinded to the registration methods. The absolute difference of various dosimetric parameters were then analysed and compared with the original planning doses. A comparison of the three matching methods employed was also carried out.

Results: There was a statistically significant difference in the magnitude of move taken in the inferior superior direction between M1 and M2 method. There were no significant differences observed in any of the dosimetric parameters examined in relation to the rectum, bladder or CTV. The only significant difference observed was the volume of PTV covered by the prescription isodose (95%) which was statistically significant lower in method A compared with both M1 and M2. There was no difference observed between M1 and M2 methods. The mean duration of the automated registration and subsequent analysis was 64 seconds compared with 91 seconds for automated registrations which included the additional manual adjustment.

Findings: CBCT-based manual adjustments of automated bony-based registrations during the image-guided radiotherapy verification of prostate cancer patients can improve PTV coverage without impacting negatively on the doses received by the organs at risk. This strategy is associated with a small increase in overall treatment time.

Keyword: cone beam computed tomography; image-guided radiotherapy; image registration; prostate cancer

Correspondence to: Mohamed Nazmy ElBeltagi, MBBCh, MSc, PhD, FRCR, Consultant Radiation Oncology, St Luke's Radiation Oncology Network, Rathgar, Dublin 6, Ireland. Tel: 0035 389 460 8541. E-mail: mnazmy@hotmail.com; nazmy.elbeltagi@slh.ie

INTRODUCTION

Intensity-modulated radiotherapy (IMRT) in conjunction with daily image-guided radiotherapy (IGRT) for prostate cancer is currently recommended in worldwide guidelines.[1,2] Daily IGRT for localised prostate cancer optimises normal tissue avoidance while minimising the risk of target misses.[3]

Different IGRT strategies have been proposed for cone beam computed tomography (CBCT)-based verifications, many involving the use of various algorithms developed to automate or accelerate the process such as 3D fully automated bony matching, 3D fully automated soft tissue matching, 3D manual matching[4] or manual anterior rectal wall matching.[5] These studies, however, are mostly concerned with identifying the systematic and random setup error and there is a distinct paucity of data with regards to the dosimetric impact of employing these various image-guided strategies, both to the target and the surrounding critical structures.[4]

Fully automated-based verifications save time whilst simultaneously eliminating the inter-observer variability associated with manual-based verification procedures. Sophisticated computer-based algorithms utilise all the 3D data available to give the best 'match' achievable based on the available correctable parameters, that is translations and rotations.[6]

Currently the host institutions' IGRT protocol for patients undergoing radical radiotherapy to the prostate involves an automatic bony registration. The resulting correction is applied before treatment. To improve the accuracy of the match, a region of interest (ROI) is defined to encompass stable pelvic bony anatomy at the level of the planning target volume (PTV).

When imaging in an online environment, volumetric imaging such as CBCT allows assessment of the clinical target volumes (CTVs) coverage (i.e., prostate ± seminal vesicles (SVs) and in certain instances it may be apparent that the CTV coverage is compromised, for example SVs dropping posteriorly due to reduced rectal volume. As SV's can move independently to the prostate gland it may not be possible to perform an exact soft tissue match but it may be possible to perform a manual adjustment to ensure that the delineated CTV is encompassed within the PTV, which is expected to receive the prescribed dose. Although such manual adjustments would theoretically improve the CTV coverage, it is not currently standard practice at the host institution as concerns exist that it may have a negative impact on the planned dose distribution both to the target (CTV) and the organs at risk (OARs). Furthermore, manual adjustment to the automatic match is likely to be susceptible to inter-observer variability depending on the experience of the radiation therapist doing it and it may also result in an increase to the time which the patient is on the treatment couch.

The aim of this work is to compare different IGRT registration strategies in the verification of high-risk prostate patients undergoing radical radiotherapy under various parameters. The first strategy involves automated CBCT registration which replicates current practice at the host institution and acts as a control dataset. The second strategy involves an additional step whereby manual adjustment of the automated registration by two expert radiation therapists is permitted with the aim of optimising CTV coverage. The third strategy replicates the 2nd strategy, however the manual adjustments are carried out by a number of radiation therapists at the host institution with varying levels of experience. An analysis has been carried out to determine both the dosimetric impact of employing these different strategies on the actual dose delivered to the prostate and organs at risk as well as the impact on the overall verification time. This information will assist in the development of an optimal online IGRT strategy for high-risk prostate patients using an evidenced-based approach.

METHODS

Ten high-risk prostate patients were sampled from the entire population of patients who had received radical radiotherapy to a dose of 74 Gy in 37 fractions using Varian RapidArc® technique (Varian Medical Systems, Palo Alto, CA, USA). For the purpose of this study patients were identified as high risk if they received the prescribed dose to both the prostate and 2 cm seminal vesicles. From the ten patients randomly identified, five CBCT datasets images were then randomly selected from each patient to give a total of 50 CBCT datasets from which the analysis was conducted. This method was chosen to ensure a homogenous inclusion of CBCT datasets images at different time points during the radiotherapy treatment course.

Each CBCT dataset was registered three times.

Method (A): The first registration done using the automatic matching software (Aria Image Registration) as per department guidelines. The ROI includes the sacrum posteriorly, the pubic symphysis anteriorly, laterally includes bony pelvis excluding the femoral head. The ROI should also include superiorly/inferiorly the full extent of the PTV extending as far superiorly to include as much of the sacrum that is visible on the scan.

Method (M1): The second method involved manual adjustment of the initial registration focusing on optimal CTV coverage as perceived by two clinical specialist radiation therapists. The final manually adjusted registration was based on both radiation therapists agreement mimicking practice in an online environment. Both clinical specialist radiation therapists are well qualified with over 20 years' combined experience in a variety of image-guided methods and both are designated IGRT leads in the host institution. Both radiation therapists have also undergone formal training in prostate contouring on computed tomography (CT) but no specific training was given before this study.

Method (M2): In the third method, manual adjustment of the initial registration was again carried out focussed on optimal CTV coverage, but this registration was done by different radiation therapists (16 in total) working at the host institution with varying levels of experience). All radiation therapists have a Bachelor of Science degree (BSc) in Radiotherapy or equivalent. Radiation therapist experience ranged from 1 to 15 years.

Each registration was coded using numbers (1 to 5 in each patient) and letters (A, B and C according to the registration method used A, M1, M2) to blind the radiation oncologist responsible for contouring as to which registration method had been employed. This was done to prevent bias.

As each CBCT was registered three times, a total of 150 CBCT registered datasets images were available for review. Using the contouring tools available in Eclipse planning system (Varian Medical Systems), the bladder and the rectum were contoured on each of the CBCT datasets registered by method A by an experienced radiation oncologist. The upper and lower level of the rectum delineated were not comparable with that delineated on the original planning CT dataset due to the limitation of the CBCT scan range in order to have a valid comparison, the rectum was contoured 5 mm above and below the PTV. This was then replicated on the planning CT scan with the new rectal contour delineated to the same upper and lower extent as the CBCTs. The original planning CT-based prostate and the SV contours (CTV) were copied onto each CBCT dataset and adjusted separately to fit the corresponding structures as visualised on each CBCT dataset and subsequently combined to form CBCT-based CTVs. PTV contours were subsequently generated by applying the same margin to all delineated CTVs according to the institutional guidelines which is 1 cm isotropically except at the posterior aspect where it is 5 mm.

After finishing with all contours on datasets images labelled A, the newly contoured rectum, bladder and CTV were copied and pasted to the registered datasets images labelled B and then moved for best match as perceived by the experienced radiation oncologist. The PTV margin was generated again then the same procedure was repeated for the registered datasets images labelled C.

All volumes were contoured and matched by one experienced radiation oncologist only to avoid any interobserver variability. The same window levels were used to contour volumes in each dataset with a minimal time interval in-between.

The dose volume histograms (DVHs) of the CTV, PTV, rectum and bladder were evaluated for each registration and compared with the original planning DVHs. The parameters evaluated included the maximum difference of: the CTV and PTV minimum dose (CTV_{min}) (PTV_{min}), the PTV mean dose (PTV_{mean}), the CTV and PTV volume covered by 95% of the dose (CTV V95%) (PTV V95%), bladder maximum dose (Bladder-max), Bladder volume receiving 50 Gy (Bladder V50), rectum maximum dose (Rectum-max) and rectum volume receiving 50 Gy (Rectum V50).

Statistical consideration: The Statistical Package for Social Sciences (SPSS) version 21 was used for data analysis. Quantitative data was presented as the mean and standard deviation. To compare quantitative variables between the three methods, one-way analysis of variance was used.

Ethical consideration: This is a retrospective study, all the matching and the volumes were done on a copy of stored images in our planning database of patients who have already completed their course of radiotherapy. No analysis was carried out on any of the actual treatments received. All patients were treated according to the departmental guidelines.

Table 1. *Mean, min and max values for the manual adjustments taken after automatic registration*

	M1	M2	*p* value using paired sample *t*-test
X_{mean}	−0·08 mm	0·05 mm	0·23
$X_{min-max}$	−4·9 and 1·8	−5·2 and 2·2	
Y_{mean}	−2·14 mm	−0·52 mm	0·000
$Y_{min-max}$	−10·4 and 4·1	−9·2 and 5·6	
Z_{mean}	−0·03 mm	−0·25 mm	0·426
$Z_{min-max}$	−9·4 and 4·7	−9·9 and 4·5	

Notes: M1 was carried out by two experienced radiation therapists, M2 was carried out by different radiation therapists with a wide range of experience.
X = medial lateral direction; Y = superior inferior direction; Z = anterior posterior direction.

Table 2. *Number of manual adjustments implemented after automatic registration categorised by magnitude*

	M1	M2
X > 5 mm	0	0
X > 1 mm	11	11
Y > 5 mm	12	5
Y > 1 mm	36	36
Z > 5 mm	2	3
Z >1 mm	12	21

Notes: M1 registrations were carried out by two experienced radiation therapists, M2 were carried out by different radiation therapists with a wide range of experience.
X = medial lateral direction; Y = superior inferior direction; Z = anterior posterior direction.

RESULTS

Difference between M1 and M2 registration

First we assessed whether there was any difference in the manual adjustment registrations carried out by the two experienced radiation therapists (M1) compared with those carried out by the other group of radiation therapists working in the department (M2). Table 1 summarises the manual adjustments that were implemented in each direction X, Y, Z (lateral, longitudinal and vertical, respectively) in each registration method (M1) and (M2). There was no statistically significant difference found in the adjustments made between M1 and M2 methods in either the X or Z direction, however there was a statistically significant difference observed in the Y direction. On average the experienced radiation therapists in method M1 manually adjusted the registration 1·6 mm more inferiorly to improve target coverage.

We also looked at the number and magnitude of manual adjustments implemented post automatic registration and as shown in Table 2, the least number of adjustments were carried out in the X direction, with no adjustment >5 mm observed in this direction in either group. Conversely, the highest number of adjustments implemented were in the Y direction with 36 instances of an adjustment >1 mm recorded in both groups and a further 12 cases requiring an adjustment of >5 mm in the Y direction by the experienced radiation therapists (M1) compared with only five cases observed in the other cohort of radiation therapists(M2).

Time required for registration

The mean duration for the automated registration and associated review was 64 (±8) seconds while it was 91 (±7) seconds for the automated registration followed by manual adjustment and associated review in both the M1 and M2 groups combined. These results show that adding a manual adjustment to optimise CTV coverage increased the mean registration time by just 27 seconds regardless of the level of experience of the radiation therapists carrying out the registration. There was no significant time difference seen between the radiation therapists in M1 or M2.

Effect of different registration methods on dose to the target and organs at risk

The absolute values of the variation observed in several dosimetric parameters compared with the original planning CT values are shown in Table 3. We used the absolute values of the variation to prevent negative and positive values nullifying each other and thus disguising potential dosimetric consequences of manually adjusting automatic bony registrations for target coverage. This was required for all values except the per cent volume of the PTV covered by 95%.

As shown in Table 3, none of the parameters analysed showed any statistically significant difference from those recorded on the original planning CT apart from the volume of the PTV covered by 95% of the prescribed dose. The volume of PTV covered by the 95% isodose was statistically significant less in the bony-based automatic match registrations compared with both methods were manual adjustment were carried out with the aim of improving target coverage. There was no statistically significant difference observed in this parameter between group M1 or M2. For reference, 99% of the PTVs received 95% of the prescribed dose for all cases on their initial plan. Although a statistically significant improvement in PTV dose was witnessed for those registrations involving a manual adjustment of the initial bony automatic registration, this did not translate to any significant change of the CTV_{min} or CTV V95% parameters.

DISCUSSION

This study showed that manual adjustment of CBCT automated registration done by experienced/appropriately trained radiation therapists in prostate cancer IGRT improves PTV coverage without impacting negatively on the dose received by the organs at risk and it was associated with a small increase in overall treatment time.

Table 3. Absolute value of difference in various examined parameters in each of the three matching methods compared with those derived from the planning computed tomography

	Mean	SD	SEM	*p* value
Difference in PTV minimum dose				
Auto match	10·17 Gy	16·99	2·403	0·777
Manual match	8·43 Gy	15·69	2·218	
Manual match	8·02 Gy	15·40	2·178	
Difference in PTV mean dose				
Auto match	0·43 Gy	1·46	0·207	0·227
Manual match	0·14 Gy	0·23	0·032	
Manual match	0·17 Gy	0·51	0·072	
Difference in rectum V50 Gy in cc				
Auto match	9·97 cc	8·28	1·170	0·132
Manual match	7·49 cc	7·62	1·078	
Manual match	10·86 cc	9·82	1·388	
Difference in rectum maximum dose				
Auto match	0·85 Gy	0·54	0·075	0·931
Manual match	0·82 Gy	0·56	0·079	
Manual match	0·80 Gy	0·48	0·068	
Difference in bladder V50 Gy				
Auto match	10·92 cc	7·79	1·102	0·141
Manual match	9·40 cc	7·44	1·053	
Manual match	13·31 cc	13·34	1·887	
Difference in bladder maximum dose				
Auto match	0·63 Gy	0·66	0·093	0·832
Manual match	0·56 Gy	0·50	0·071	
Manual match	0·60 Gy	0·66	0·093	
PTV V95%				
Auto match	97·38%	6·12	0·866	**0·016** SS
Manual match	99·11%	1·45	0·205	
Manual match	99·36%	1·05	0·149	

Abbreviation: PTV, planning target volume; SS, statistically significant.

Prostate cancer patients usually receive long course of radiotherapy of more than 35 fractions with many CBCT datasets taken for each patient during this long course of treatment. To avoid any geometric trends of patient setup error as prostate treatments progress, the five CBCT datasets images of each patient were randomly selected to ensure a homogenous inclusion of CBCT datasets images at different time points during the radiotherapy treatment course. The number of CBCT datasets analysed in each treatment week was too small to draw a valid conclusion on any geometric trends in the setup error.

Several in-room imaging systems facilitate localisation of the prostate or a related surrogate during treatment verification.[7–10] The use of fiducial markers is considered an effective strategy for localising the prostate gland but their insertion is an invasive procedure which carries its own risks such as bleeding and sepsis.[11] The fiducials act as a surrogate for prostate position but provide no information on organ deformation, seminal vesicle motion or changes to the position and shape of adjacent OARs. The potential for marker migration is another drawback which prevents its wide use in many centres.[12] A recent survey on the patterns of practice in IMRT and IGRT conducted in Japan in 2013 showed that 13% used fiducial markers while 47% used bone matching and 40% used prostate matching.[13]

Vendors of IGRT solutions provide software solutions for image registration and matching to reference images tailored to the technical capabilities of the image guidance system. All of these software systems contain a variety of tools to facilitate the registration process and associated review which may be automated in nature or require manual operation. A number of choices or parameters may be available to the user in automated-based registrations which will 'drive' the registration procedure including those based on bony intensity ranges. Other parameters, which can be varied, include the volume or region of interest (ROI) that the registration is performed for a range of Hus to consider for the match, the number of degrees of freedom in the match (translational and rotational), and the centre of rotation. These parameters may have a large influence on the result of the registration and consequently on the setup accuracy. The European Society of Therapeutic Radiology and Oncology-European Institute of Radiotherapy published in 2010 a guide on 3D CT-based in-room image guidance systems and it emphasised on the importance of visual evaluation of the automatic match outcome.[14]

Manual-based registrations, however, are not risk free. In spite of the different tools available for the assessment of a match like spyglass, toggle function, checker board, complementary colours, blending, and measurement tools, concerns exist that adjusting the match in certain point of interest may worsen the whole matching outcome. This process is likely to be very user dependent and the experience and training of the staff carrying out the match cannot be overemphasised.

This study provides an evidence base which supports the use of manual-based adjustments of more traditional bony-based automated registrations aimed at optimising CTV/PTV coverage. The results show, that when such registrations are carried out by experienced/appropriately trained radiation therapists, in the cases of high-risk prostate cancer, the registration outcome is superior to relying on automatic bony matching alone. Our results also appear to indicate that any concerns over manual-based adjustments in terms of negative dosimetric consequences on the overall planned dose distribution both to the CTV and the OARs are unfounded.

Adding to the requirement of experienced/appropriately trained radiation therapists, there are other points that should be taken into account if considering such IGRT strategy in prostate patients such as the low contrast between the prostate and the periprostatic tissues, and the actual clinical significance of this manual adjustment.

The low contrast between the prostate and the periprostatic tissues on conventional planning CT images is well established and as a consequence target delineation/interpretation on CT is known to be a source of uncertainty in radiation treatment planning.[15] The same issues are probably important when interpreting target coverage using CBCT verification in prostate patients. A recent study, however, showed that it is feasible to use the CBCT in an offline adaptive radiotherapy (ART) setting for target definition showing no significant difference between the target volumes defined on CBCTs and Helical CTs.[16] Another study showed some ambiguity in apex and base level definition but overall good inter and intra observer consistency in delineating the prostate on CBCT plus MRI-guided modification without any significant difference from the consistency in defining the prostate on planning CT.[17] Based on these series, CBCT is currently widely acceptable for target definition in the era of ART.[16] In our study, the only significant difference in the adjustments made between M1 and M2 methods was in the Y direction and this is likely related to the known ambiguity in apex and base level definition, with the experienced radiotherapists (M1) leaning more to maximise apex coverage. This difference was less than 2 mm and it did not lead to any significant difference in the dose to the OAR or to the target.

Although the improvement of PTV V95 in the manual-based strategy was statistically significant, the absolute difference was very small, and it did not lead to a significant difference regarding CTV parameters in the context of our current PTV margins (1 cm isotropic expansion of the CTV except posteriorly where it is limited to 5 mm). On the other hand, manual matching took approximately half a minute longer than automatic matching and may take longer or shorter depending on both image quality and the proficiency of the radiation therapists conducting the match. The time span from patient positioning to the completion of a fraction typically varies from 6 to 20 min with IMRT[18] and should be relatively shorter with the use of VMAT techniques. Although the manual-based strategy was more accurate at that point in time, it can be argued that the increase in time although relatively small, could potentially negate the perceived benefits observed with regards PTV coverage in the presence of intra-fractional motion of both patient and target.

In view of this, it is difficult to give firm recommendations as to whether manual adjustments are warranted in every single patient however, we believe that all bony-based automatic registrations should be evaluated by competent and qualified radiation therapists and that manual adjustments can be safely applied if required in order to improve target coverage without significantly increasing the overall treatment time.

CONCLUSIONS

Manual adjustments of automated registrations in prostate cancer IGRT can improve PTV coverage without impacting negatively on the dose received by the organs at risk. This is associated with a small increase in overall treatment time.

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Conflicts of Interest

The authors confirm that there are no actual or potential financial or personal relationships with other people or organisations that could inappropriately influence (bias) this work.

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