Comparison of a simple dose-guided intervention technique for prostate radiotherapy with existing anatomical image guidance methods

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Objectives: A simple dose-guided intervention technique for prostate radiotherapy using an isodose overlay method combined with soft-tissue-based corrective couch shifts has been proposed previously. This planning study assesses the potential clinical impact of such a correction strategy.

Methods: 10 patients, each with 8–11 on-treatment CT studies ($n=97$), were assessed using this technique and compared with no intervention, bony anatomy intervention and soft-tissue intervention methods. Each assessment technique used a 4-mm action level for intervention. Outcomes were evaluated using measures of sensitivity, specificity and dosimetric effect, and compared across intervention techniques.

Dosimetric effect was defined as the change in dosimetric coverage by the 95% isodose from the no intervention case of an evaluation construct called the verification target volume.

Results: Bony anatomy, soft tissue and dosimetric overlay-based interventions demonstrated sensitivity of 0.56, 0.73 and 1.00 and specificity of 0.64, 0.20 and 0.66, respectively. A detrimental dosimetric effect was shown in 7% of interventions for each technique, with benefit in 30%, 35% and 55% for bony anatomy, soft tissue and dosimetric overlay techniques, respectively.

Conclusion: Used in conjunction with soft-tissue-based corrective couch shifts, the dosimetric overlay technique allows effective filtering out of dosimetrically unnecessary interventions, making it more likely that any intervention made will result in improved target volume coverage.

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Image-guided radiotherapy (IGRT) aims to improve treatment delivery accuracy by visualising the patient's anatomy immediately prior to treatment, comparing this with the localisation data, usually a CT scan, and identifying and compensating for inaccuracies in the set up or target position that would compromise treatment efficacy [1]. In cancer of the prostate, potential inaccuracies include misalignments of the patient, *e.g.* caused by pelvic rotation or skin drag against the treatment couch, or changes in internal anatomy as a result of motion caused by bladder or rectal filling.

Planar megavoltage (MV) imaging using electronic portal imaging devices has long been used to verify bony anatomy position [2] and, in recent years, the increased availability of kilovoltage and three-dimensional MV in-room imaging systems has enabled soft-tissue visualisation [3–6]. Image-based correction using translational couch shifts is now routine practice in modern radiotherapy centres, with bony anatomy, fiducial marker and soft-tissue-based assessment protocols being well documented [7–12].

In prostate radiotherapy, moving from bony anatomy to soft-tissue-based assessment and intervention changes the approach from a surrogate for target position to tracking the target itself. Logically this should improve treatment accuracy, since the effect of internal motion on prostate position should be directly taken into account. However, clinical intervention strategies assume that any breach of a defined action level always requires a corrective shift and takes no account of the expected dose distribution in the patient.

Systematic and random error components of the margin between the clinical target volume (CTV) and the planning target volume (PTV) mean that dosimetric coverage of the CTV will not be compromised if, despite changes in position, it remains within the International Commission on Radiation Units and Measurements (ICRU) 50/62-compliant 95% dose “cloud” [13, 14]. In such a case, clinical intervention would not be necessary. Using dose-guided radiotherapy, the coverage of the daily verification CTV (vCTV) could be assessed against the expected daily dose distribution. An informed decision on the need to intervene could then be made based on probable dosimetric coverage, taking account of remaining uncertainties.

Such an online dose-guided technique could be performed using a full dose recalculation based on the daily on-treatment anatomy immediately prior to treatment

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delivery. However, the implementation of any online dose-guided intervention poses a number of logistical problems: it would be time consuming, require prompt access to treatment planning stations, be prone to error because of the short decision time available and is a significant role extension for treatment staff more used to anatomical matching techniques. An alternative technique would be to use a sufficiently accurate surrogate for a full dose calculation, allowing dose-based judgements without the need for a potentially time-consuming calculation while a patient is in the treatment position.

A previous paper proposed a dosimetric overlay method for dose-based assessment in image-guided radiotherapy of the prostate [15]. The technique involved the use of an overlay of the treatment plan 95% isodose over an on-treatment verification CT scan, achieved by a quick CT reference point registration between the verification CT scan and the localisation planning scan. The isodose could then be used in lieu of a full recalculation of the dose distribution on the pre-treatment scan and used to assess the adequacy of CTV coverage on that day. The paper showed that the technique was a feasible and acceptable means of assessment for prostate radiotherapy and that uncertainties between a full recalculation and this overlay isodose for a given patient anatomy were quantifiable and reasonable.

This paper describes a planning study performed to determine the efficacy of the dosimetric evaluation technique described in Smyth et al [15] compared with both existing bony anatomy and soft tissue-matching and intervention protocols. Issues around future clinical implementation of the dosimetric overlay technique will also be discussed.

Methods and materials

Patients received radical radiotherapy for cancer of the prostate on a Siemens CT Vision (Siemens, Concord, CA) combined multimodality linear accelerator and in-room CT on rails, following a local protocol for IGRT. The 10 patients in this study were randomly selected from the subgroup that either had required a clinical bony anatomy-based intervention or had triggered additional imaging sequences during treatment. Local planning and imaging protocols are detailed in the previous paper [15]; however, pertinent points are restated below.

A total of 97 pairs of CT data sets were analysed. Each on-treatment CT data set was assessed against the localisation CT data set using the three techniques described below: bony anatomy, soft-tissue and dosimetric verification. Bony anatomy assessment was performed by treatment radiographers as part of the clinical protocol described below. Soft-tissue matching and dosimetric evaluation, undertaken using both the dosimetric overlay and full recalculation techniques, were performed by a suitably trained physicist.

Local prostate protocol

Patients were localised and treated in a supine position and immobilised using a knee rest and foot stocks.

Planning and treatment verification CT images were acquired with a reconstructed slice spacing of 5 mm. External skin marks defined at the planning CT session and identified by ball bearings during imaging define an internal reference point which is related to the treatment plan isocentre by translational couch shifts. The CTV was defined as the prostate capsule, including seminal vesicles where clinically appropriate. The PTV was grown from the CTV using a uniform 10-mm margin, except in the posterior dimension where the expansion was reduced to 5 mm.

Treatment plans were produced using MasterPlan (Nucletron B.V., Veenendaal, The Netherlands) with a three-field—anterior and two lateral oblique fields—wedged technique. Dose calculation was performed using the pencil beam algorithm on a $5 \times 5 \times 5 \text{ mm}^3$ calculation grid. The Phase 1 dose to the ICRU prescription point was 64 Gy (2 Gy per fraction for 32 fractions) and the PTV was covered by the 95% isodose in all plans, with the exception of 2 patients for whom the clinician made the decision to significantly compromise coverage posteriorly to reduce rectal dose. Only Phase 1 plans were investigated for this study. Treatment delivery was with a Siemens Oncor linear accelerator with 15 MV photon beams and a multileaf collimator (MLC) of 1-cm width at the isocentre.

Each patient had a CT scan for treatment verification on the first three fractions and weekly throughout the remaining course of treatment. Additional three-fraction imaging sequences were triggered if weekly clinical bony anatomy matching results exceeded a trigger level.

Bony anatomy matching protocol

Hard-copy digitally reconstructed radiographs (DRRs) for reference field sizes were produced using MasterPlan. At verification, pre-treatment DRRs for the same reference field sizes were generated using ProSoma virtual simulation software (Medcom, Darmstadt, Germany) from the verification CT scans. Treatment radiographers performed a visual comparison between the two sets of DRRs (*i.e.* hard-copy reference plan DRRs and on-screen verification DRRs) and made couch shift adjustments in ProSoma to align the verification DRRs with the reference field edges. Shifts were recorded and compared with action and trigger levels that guided intervention in normal clinical practice. Image matching was not performed within ProSoma for these patients; however, treatment radiographers had gained experience over a number of years in the hard-copy and on-screen comparison technique described. In the clinical process, systematic error corrections in the X, Y and Z dimensions were performed if the mean shift from a three-image sequence breached a 4-mm action level in that dimension. Weekly imaging sessions triggered additional three-fraction systematic error correction imaging sequences if shifts in any dimension breached a 4-mm trigger level.

In this study, the raw patient shift data were used for each imaging session in isolation; any systematic corrections used clinically were removed from the data to allow a direct comparison between the reference image and a single verification image.

Table 1. Uncertainty components of the dosimetric overlay action level

Uncertainty	Uncertainty detail	Uncertainty (mm)		
		Posteroanterior	Right-left	Superoinferior
Visualised CTV	Imaging error in verification CT	1.2	1.2	0.6
	CTV identification	3.1	2.6	1.5
Overlaid 95% isodose	Uncertainty in CT registration	1.0	1.0	2.9
	Uncertainty in dose overlay	2.5	2.5	2.5
Original CT 95% isodose	TPS planning error	0	0	0
Delivered 95% isodose	Lasers	0.6	0.6	0.6
	Light-radiation coincidence at gantry 0°	0.9	0.9	0.9
	Light-nominal field size at gantry 90° and 270°	1.2	1.2	1.2
Combined error		4.6	4.2	4.5

CTV, clinical target volume; TPS, treatment planning system.

Soft-tissue matching

Planning and verification CT studies were compared within the image fusion module of ProSoma. The studies were initially aligned to the CT reference point on each scan, indicated by the position of the ball bearings on both the planning and verification scans, using the automatic reference point registration in ProSoma. The visualised soft-tissue position of the prostate in the verification scan was then manually aligned with that visualised on the reference planning scan using translational couch shifts. The original CTV structure set was available as a reference to assist matching when necessary.

Shifts measured with this technique were used as the basis for both the soft-tissue matching and dosimetric overlay interventions. Shifts for the soft-tissue intervention were subject to a 4-mm action level for each direction, in line with the intended clinical protocol at this centre. Shifts for the dosimetric verification were applied regardless of size if the dosimetric verification technique, described below, indicated that shifts were required.

Dosimetric verification

Dosimetric overlay

The dosimetric overlay technique was performed using ProSoma. Full details of the workflow can be found in Smyth et al [15] but are summarised as follows: the planning CT data set, its associated structure set, plan and dose distribution were digital imaging and communications in medicine (DICOM) exported from MasterPlan and loaded into ProSoma. The CT reference point position was confirmed, and the dose display adjusted such that 95% of the prescription dose isodose was visible; this forms the reference data set. The verification CT study was then loaded into ProSoma as a "fusion data set" and the CT reference point was defined based on the location of the ball bearings. A point registration was then performed to align the CT reference points defined on the two CT scans. The reference data set image was then faded out using standard image fusion controls, leaving the 95% isodose superimposed on the verification anatomy.

A judgement on whether the prostate visualised on the verification CT lies sufficiently inside the 95% isodose overlay was made based on an action level described below. The evaluation was judged to have failed if, on any single CT slice, the visualised vCTV was not at least

the action level distance within the 95% isodose. In this case, the shifts determined from the soft-tissue matching process would then be applied in full.

Dosimetric evaluation action level

Full consideration of an appropriate action level for the dosimetric evaluation was carried out with reference to a protocol produced by the Working Party of the British Institute of Radiology [16]; its components are summarised in Table 1 and detailed below. For this analysis, breathing motion and intrafractional motion were assumed to be negligible. While this may not always be the case for the prostate, estimation of the uncertainty associated with intrafractional motion is outside the scope of this work.

The error in determining the vCTV position comprises the uncertainties arising during the acquisition of the verification CT data set and visualisation of the vCTV. The imaging error is estimated from quality control tolerances for longitudinal couch calibration and height and width measurements for the CT scanner. The uncertainty in the visualisation of the prostate is based on published values [17] of uncertainty in the clinician's CTV delineation. The uncertainty in visualisation of the prostate by a suitably trained dosimetrist or radiographer could be expected to be of the same magnitude as that of a clinician. The original clinician-outlined treatment planning prostate volumes would be available for reference as part of the clinical process and this could also assist in decision making.

The error in the dosimetric overlay process includes contributions from the uncertainty in registering the two CT data sets and the inherent uncertainty of the isodose overlay compared with a full calculation of the dose on the verification anatomy. The uncertainty in registration is determined by the tolerances in the placement of the ball bearings on the patient's skin and the identification of the ball bearing position on the verification CT. This is estimated to be 1 mm in the anteroposterior and left-right dimensions. In the superoinferior dimension the uncertainty lies in choosing the "correct" CT slice for the reference point placement, again because of determining the location of the ball bearing on the scan, and is estimated from the slice spacing according to the Working Party of the British Institute of Radiology [16]. A previous paper [15] found that the difference in the shape and position of the 95% isodose between a full dose calculation and a dosimetric overlay technique was

generally within the half-voxel size error associated with the dose calculation matrix geometry for the clinical protocol ($5 \times 5 \times 5 \text{ mm}^3$ voxel size), giving an error of 2.5 mm when using the dosimetric overlay. It is not clear how dominant the effect of the dose calculation uncertainty due to voxel size is on the dosimetric overlay uncertainty. A study comparing plans calculated using smaller voxel sizes is needed to determine how the dosimetric overlay uncertainty changes in these cases.

The treatment planning error is determined from the discrepancy between the linear accelerator beam data and the beam model in the treatment planning system. This is quantified by the Working Party of the British Institute of Radiology [16] as the difference between the 90% beam width in the penumbra computed by the treatment planning system and the measured width in the water tank. While this value can be of the order of 1–2 mm, measurements performed locally confirmed that the error was negligible over the range of expected prostate field sizes for the clinical machines in this department. The uncertainty in the delivered 95% isodose has been estimated from linear accelerator quality control tolerances. This uncertainty includes contributions from the laser indication of the isocentre and uncertainty in jaw alignment, with the gantry angle determined from local quality control tolerances.

Combining these errors in quadrature gives results in overall uncertainty of 4.6 mm, 4.2 mm and 4.5 mm in the anteroposterior, left–right and superoinferior directions. This is translated into a practical action level of 4 mm in all dimensions for the dosimetric overlay technique.

Dosimetric recalculation

Dosimetric verification was also undertaken for a full recalculated isodose distribution from MasterPlan to determine whether the use of the dosimetric overlay resulted in discrepancies in evaluation. As the inherent voxel size error in the full dose calculation is of the same magnitude as the uncertainty of the overlay itself, the same 4 mm action level was used for this evaluation.

Coverage evaluation

Each on-treatment CT study was exported to MasterPlan and the Phase 1 vCTV outlined. An evaluation construction called the verification target volume (VTV) was then created by applying a 4 mm margin to the vCTV. The VTV is analogous to the function of the PTV in the original treatment plan: for the vCTV to be adequately covered by the 95% isodose during treatment, taking account of remaining uncertainties, the VTV must be covered by the 95% isodose in the pre-treatment dosimetric evaluation. The margin required to grow from vCTV to VTV is equivalent to the dosimetric verification action level described above.

The treatment plan parameters were imported onto the on-treatment CT study and shifts from the CT reference point to the treatment isocentre applied. For each verification technique, the identified isocentre move couch shifts were applied and a full dose calculation was performed as per the local planning protocol. A full dose calculation, applying the original plan monitor units for each beam, was also performed on each raw

unshifted image to determine the effect of no intervention for that fraction.

For the recalculated plans for each intervention technique and the no intervention situation, the percentage volume of the VTV encompassed by the 95% isodose was determined from the MasterPlan dose volume histogram (DVH). Changes in the dosimetric coverage of the VTV between the no intervention case and each intervention technique under investigation were calculated. Only positive or negative changes in dosimetric coverage of the VTV greater than $\pm 0.5\%$ in volume—equivalent to a change of greater than one scale division on the MasterPlan DVH—were defined as a significant benefit or detriment.

The proportion of interventions deemed “dosimetrically necessary”, as initial coverage of the VTV was less than 99.5% (*i.e.* 100% minus the significance threshold), was determined, giving the positive predictive value for each technique [18]. The proportion of incidents in which a decision not to make an intervention was made and was proved to be correct according to VTV coverage, *i.e.* VTV coverage was already 99.5% or greater, was determined, giving the negative predictive value for each technique [18]. Evaluations of sensitivity, specificity and dosimetric effect were performed for each intervention method and compared [19]. Dosimetric effect was defined as a measure of whether decisions to shift gave a beneficial, detrimental or negligible effect on dosimetric coverage of the VTV.

Results

Dosimetric evaluation

The results of breaches for both dosimetric evaluation methods agreed in all but 7 instances (7.2%), demonstrating the acceptability of the dosimetric overlay technique as a surrogate for a fully recalculated dose distribution. In each of these cases, the dosimetric overlay technique indicated that no shift was necessary whereas the full recalculation indicated that an intervention was necessary. This conflict could be problematic regardless of its low incidence; however, on further analysis of the data, in six of the seven cases the full recalculation intervention made no significant change in VTV coverage. The seventh instance resulted in marginally worse coverage (-0.8%) when the intervention recommended by the full recalculation technique was performed.

Intervention decisions

Figure 1 shows the number of dosimetrically necessary and unnecessary interventions for each of the intervention techniques. The proportion of interventions that are dosimetrically necessary is the positive predictive value of the technique [18]. While the absolute number of correct interventions increases when moving from bony anatomy to soft tissue-based verification, the increased number of interventions carried out overall results in a decrease in the positive predictive value (from 0.53 to 0.40). This may indicate a need to re-appraise

the soft-tissue action level; however, that is beyond the scope of this paper.

The dosimetric overlay technique demonstrates both an increase in the absolute number of dosimetrically necessary shifts and a decrease in the overall number of interventions, with the positive predictive value increasing to 0.68. Compared with the soft-tissue technique, the number of unnecessary shifts made is reduced by 58% whereas the number of necessary shifts is increased by 37%.

Non-intervention decisions

Figure 2 compares the number of non-intervention decisions made for each technique, showing the proportion of those decisions for which it was appropriate to perform no shift and those for which the inappropriate decision was made and dosimetrically the volume of the VTV was not covered by the 95% isodose. The proportion of correct non-intervention decisions is the negative predictive value of the technique [18]. Soft-tissue intervention again demonstrates disappointing results, with a drop in the negative predictive value compared with bony anatomy (from 0.67 to 0.50). The dosimetric overlay technique has a negative predictive value of 1.00.

Sensitivity and specificity

Sensitivity is defined as the proportion of correctly identified true positives and specificity is the proportion of correctly identified true negatives [19]. Results

showed a sensitivity of 0.56, 0.73 and 1.00 and a specificity of 0.64, 0.20 and 0.66 for bony anatomy, soft-tissue and dosimetric overlay interventions, respectively. The dosimetric overlay technique demonstrates a considerable improvement in sensitivity over the other intervention methods, while maintaining the level of specificity of the bony anatomy technique. The relatively poor specificity of the soft-tissue intervention method reinforces the need for further investigation of the implementation of the technique at this centre.

Dosimetric effect

Figure 3 shows the number of interventions made for each technique and the proportion of interventions that resulted in beneficial, detrimental or insignificant changes in dosimetric coverage of the VTV. The results showed a detrimental effect on dosimetric coverage in 7% of interventions for each intervention technique, with an improved dosimetric coverage in 30%, 35% and 55% of cases for the bony anatomy, soft-tissue and dosimetric overlay techniques respectively.

Discussion

The aim of this paper was to determine whether a proposed dose distribution overlay method of verification was capable of accurately identifying patients requiring intervention during treatment verification and whether it had the capacity to reduce the resources required during IGRT processes by effectively filtering

Figure 1. Graph showing the number of dosimetrically necessary and unnecessary interventions for each intervention technique. The proportion of dosimetrically necessary interventions indicates the positive predictive value of the technique.

Figure 2. Graph showing the number of non-intervention decisions made for each technique and the proportion of those that were "correct" ("no-shift correct") and "incorrect" ("no-shift when needed"). The proportion of correct decisions indicates the negative predictive value of the technique.

Figure 3. Graph showing the number of interventions made for each technique and the resulting beneficial, detrimental or insignificant ("no change") effect on dosimetric coverage of the verification target volume.

out interventions that would provide no significant dosimetric improvement. These results demonstrate that the dosimetric overlay technique described in both Smyth et al [15] and this paper is a potentially useful tool in guiding intervention in prostate radiotherapy. The dosimetric overlay technique results demonstrate its potential benefit in ensuring that the decision of whether to intervene is both necessary and more likely to improve dosimetric coverage.

Results for the existing bony anatomy and soft tissue-based techniques are of concern, and clinical protocols at the centre must be examined in light of their relatively poor results. Not only is soft-tissue matching alone worse than bony anatomy at correctly predicting whether an intervention is warranted, but also the majority of interventions would provide no significant benefit to the patient. This is effectively a wasted time resource for treatment staff. It is suggested that improved rectal preparation and bladder management throughout treatment should be considered, since this may improve results for the anatomical techniques. The current clinical protocol is for treatment with an empty bladder; rectal preparation is by dietary advice only.

Clinical implementation

It is intended to implement this technique in the department as part of a clinical pilot study. The proposed workflow for a specific treatment fraction (Figure 4) is sufficiently similar to that intended for soft tissue-based intervention that the additional training and clinical implementation for the isodose overlay aspect is expected to be straightforward. The intended clinical workflow would combine this technique with a systematic error correction strategy similar to the clinical bony anatomy protocol outlined above. The dosimetric overlay technique would be used to determine the need for online corrective shifts on a specific treatment fraction during the initial three-fraction systematic error correction sequence, with offline soft-tissue matching used to determine the systematic error correction, itself subject to no action level. New three-fraction systematic error correction sequences would be triggered if weekly dosimetric overlay verification failed, with online corrective action when necessary.

The dosimetric technique outlined in this paper and in Smyth et al [15] could easily be implemented into any department with the equipment described, provided treatment radiographers had suitable training in soft-tissue matching and prostate visualisation. Further investigation is required to determine the possible processes for other equipment mixes, particularly whether different virtual simulation or verification packages can perform the isodose overlay aspect using their image fusion capability. The use of this technique in departments with different volumetric imaging equipment, for example kilovoltage or megavoltage on-board imaging systems, is theoretically feasible if the system's image quality provides sufficient soft-tissue contrast to accurately visualise the prostate and there is a suitable registration point. With integrated systems, inherent knowledge of the relationship between the imaging and treatment isocentres may make the treatment isocentre a more useful registration point.

Figure 4. Proposed dosimetric overlay clinical workflow on a single treatment fraction. CTV, clinical target volume.

Further investigation

A number of issues require further investigation, including any relationship between the inherent dose calculation error and the error measured for the dosimetric overlay. It may be expected that an increase in the original dose calculation grid size would increase the uncertainty in the agreement between the dosimetric overlay and a full dose calculation. However, it is not clear whether further reductions in calculation grid size would reduce the uncertainty in the dose overlay, since the uncertainties for the overlay also include uncertainties caused by the relative differences in radiological path length between the planning scan and the on-treatment CT scan. Some improvement may be seen with reducing grid size; however, it is likely that past a certain limit the path length differences would become dominant. Therefore, quantification of the overlay discrepancies for smaller voxel sizes than the relatively coarse calculation grid used clinically in this centre should be investigated.

A full investigation into what effect the proposed clinical implementation workflow of a combined dosimetric overlay online corrective action technique and offline soft-tissue systematic error correction would have on the initial CTV to PTV planning margins is also necessary.

It is intended to evaluate this technique for other anatomical sites, where relative changes in radiological path lengths would also be expected to be small between scans, e.g. bladder, female pelvis. Investigation into the

use of such a technique in the lung, coupled with collapsed cone-type dose calculation algorithms, is also planned.

Conclusion

The dose distribution overlay technique described in Smyth et al [15] and this paper is a simple and effective dose-guided intervention technique for prostate radiotherapy. It enables simple assessment of expected dosimetric coverage of the treatment volume prior to delivery of a treatment fraction without the need for a full dose calculation. When used in conjunction with soft tissue-based corrective couch shifts, the dosimetric overlay technique allows effective filtering out of dosimetrically unnecessary interventions, making it more likely that any intervention made will result in improved target volume coverage.

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