Evaluations of an adaptive planning technique incorporating dose feedback in image-guided radiotherapy of prostate cancer

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(Received 28 July 2011; revised 23 September 2011; accepted for publication 12 October 2011; published 9 November 2011)

Purpose: Online image guidance (IG) has been used to effectively correct the setup error and inter-fraction rigid organ motion for prostate cancer. However, planning margins are still necessary to account for uncertainties such as deformation and intra-fraction motion. The purpose of this study is to investigate the effectiveness of an adaptive planning technique incorporating offline dose feedback to manage inter-fraction motion and residuals from online correction.

Methods: Repeated helical CT scans from 28 patients were included in the study. The contours of prostate and organs-at-risk (OARs) were delineated on each CT, and online IG was simulated by matching center-of-mass of prostate between treatment CTs and planning CT. A seven beam intensity modulated radiation therapy (IMRT) plan was designed for each patient on planning CT for a total of 15 fractions. Dose distribution at each fraction was evaluated based on actual contours of the target and OARs from that fraction. Cumulative dose up to each fraction was calculated by tracking each voxel based on a deformable registration algorithm. The cumulative dose was compared with the dose from initial plan. If the deviation exceeded the pre-defined threshold, such as 2% of the D_{99} to the prostate, an adaptive planning technique called dose compensation was invoked, in which the cumulative dose distribution was fed back to the treatment planning system and the dose deficit was made up through boost radiation in future treatment fractions. The dose compensation was achieved by IMRT inverse planning. Two weekly compensation delivery strategies were simulated: one intended to deliver the boost dose in all future fractions (schedule A) and the other in the following week only (schedule B). The D_{99} to prostate and generalized equivalent uniform dose (gEUD) to rectal wall and bladder were computed and compared with those without the dose compensation.

Results: If only 2% underdose is allowed at the end of the treatment course, then 11 patients fail. If the same criteria is assessed at the end of each week (every five fractions), then 14 patients fail, with three patients failing the 1st or 2nd week but passing at the end. The average dose deficit from these 14 patients was 4.4%. They improved to 2% after the weekly compensation. Out of these 14 patients who needed dose compensation, ten passed the dose criterion after weekly dose compensation, three patients failed marginally, and one patient still failed the criterion significantly (10% deficit), representing 3.6% of the patient population. A more aggressive compensation frequency (every three fractions) could successfully reduce the dose deficit to the acceptable level for this patient. The average number of required dose compensation re-planning per patient was 0.82 (0.79) per patient for schedule A (B) delivery strategy. The doses to OARs were not significantly different from the online IG only plans without dose compensation.

Conclusions: We have demonstrated the effectiveness of offline dose compensation technique in image-guided radiotherapy for prostate cancer. It can effectively account for residual uncertainties which cannot be corrected through online IG. Dose compensation allows further margin reduction and critical organs sparing. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3658567]

Key words: adaptive radiation therapy, image-guided radiation therapy, intensity modulated radiation therapy, prostate cancer, inter-fraction motion

I. INTRODUCTION

In modern fractionated radiotherapy (RT) of prostate cancer, advanced technologies, such as three-dimensional radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT), provide the capabilities to deliver highly conformal dose to the target volume while minimizing the

dose to the surrounding normal tissues and critical organs. However, these tailored dose distributions are very sensitive to the patient positioning (setup) errors and internal organ motions during the course of treatment, which typically consists of many fractions and lasts several weeks. As a consequence, large discrepancies between the actually delivered dose and the prescribed dose may occur at the

end of treatment, if these uncertainties are not accounted properly.

Advanced online image guidance (IG) techniques utilizing marker implantation,^{1,2} on-board kV image system,³ or in-room CT-on-rail system⁴ have been implemented in the clinic to measure the setup uncertainties and inter-fractional rigid organ motions. The corrections can be made by adjusting the couch position while patient is on the treatment table. However, geometric variations including rotations, non-rigid organ motion (deformation), and intra-fraction motion cannot be corrected through online IG. These variations and residual errors from the online IG can be either compensated through the use of margins during treatment planning or incorporated into the offline analysis and subsequent plan modifications. Under the condition that target coverage is not compromised, smaller planning margin will definitely lead to lower doses to the surrounding critical organs. Therefore, efforts have been directed at minimizing the effect of uncertainties with offline strategies.

Two types of offline adaptive radiotherapy (ART) strategies have been proposed to manage the inter-fraction motion. One strategy uses the geometric feedback from early measurements while the other uses the dosimetric feedback. The original geometric ART, a pure offline process, was initially introduced by Yan *et al.*,^{5–8} in which image information acquired from first few treatment fractions were used to construct a patient-specific planning target volume (PTV) and a modified plan based on this individualized PTV was used in future treatment fractions. Because of the complexity of the process, this strategy was only successfully implemented in a few clinics. Due to the prevalence of the online IG for prostate cancer in the clinic, naturally a hybrid strategy was recently proposed which combine online IG and offline geometric ART for further margin reduction.^{9,10} An alternative technique to account for the residuals from online correction is the dosimetric ART or dose compensation technique, which was first proposed for image-guided radiotherapy (IGRT) of prostate cancer,^{11,12} and the cumulative dose distribution from early fractions was incorporated into adaptive IMRT inverse re-planning for future fractions. In addition, the dose compensation is the only known technique that can correct mistakes occurred in the online IG.

In the previous proof-of-concept study, offline dose compensation technique was applied to one prostate patient to demonstrate the principle.¹¹ However, there were some limitations of that study and many interesting questions remain unanswered. For example: (1) There was no systematic investigation in that study because only one subject was included for the demonstration; (2) the initial treatment plan was created with 3D-CRT, while currently IMRT is the dominant and state-of-art modality for the prostate cancer radiation therapy. Compared with 3D-CRT, IMRT is more sensitive to the target motion because it provides higher conformal dose distributions to the target and has better critical organs sparing; thus, the effect of dose compensation should be of interest to the radiotherapy community. The purposes of this study are (1) to apply the offline dose compensation technique to a large patient data sample (28 patients) and evaluate the feasibility, effectiveness, and benefit of this

strategy on margin reduction and improvement of dose delivered to organs-at-risk (OARs) (2) to evaluate different dose compensation schedules and delivery strategies.

II. METHODS AND MATERIALS

II.A. Patient data and initial treatment planning

Data from 28 prostate cancer patients were used in the simulation. For each patient, one planning helical computed tomography (HCT) scan and at least 15 HCT scans were acquired with a conventional helical scanner. All CT images were imported into the Pinnacle treatment planning system (Pinnacle v8.0, Philips Radiation Oncology System, Madison, WI, USA) for further processing. To remove the setup error, all treatment CTs of the same patient were rigidly registered to the planning CT based on the bony structures. The slice thickness of the original HCT image was 3 mm in the superior-inferior direction. In order to avoid the round-off error by the CT slice thickness, all CT images and contours were interpolated into 1 mm thick slices so the resolutions in 3D are approximately the same at 1 mm.⁹ All the following studies were based on the interpolated images and contours. The contours for prostate, bladder, and rectum were delineated by experienced planners on each CT slice. The clinical target volume (CTV) was the prostate gland.

A hypofractionation protocol was used to simulate the treatment. The protocol was designed to prescribe 3.9 Gy per fraction to the CTV over 15 fractions for a total of 58.5 Gy in 3 weeks. The initial treatment plan was created with a step-and-shoot IMRT plan using 15 MV photon beams at seven approximately equi-spaced gantry angles. Zero CTV-to-PTV margins were used in the treatment planning in this study to demonstrate the dose compensation technique. A standard set of optimization objectives and constraints were used for all patients. A direct-machine parameter optimization (DMPO) technique was utilized in the plan optimization. The objectives for the PTV include uniform dose and minimum DVH, and the constraints for rectum and bladder include multiple maximum DVH points.

II.B. Online image guidance

The online registration was simulated by matching the center-of-mass (COM) of the prostate from each treatment CT with that from the planning CT.^{9,13} This registration can be used to simulate online IG based on implanted markers in prostate gland. Registration was limited to translations only in this study. The translational components in setup error and organ motion were assumed to be removed after the online correction.

II.C. Offline analysis

II.C.1. Organ deformation and cumulative dose analysis

At each treatment fraction, the isocenter of the treatment plan was shifted according to the online correction, and the dose distribution was recomputed. In order to account for the

inter-fraction non-rigid organ motion and accurately evaluate the dose delivered to the target volume and OARs, deformable organ registration (DOR) was performed. In this study, a DOR based on biomechanical model and finite element analysis (FEM) was performed for each organ to establish a sub-volume mapping between the planning and treatment CTs, and daily and cumulative doses to target and OARs were computed based on these mappings.^{11,13,14} The accuracy of the DOR was systematically investigated on the relationships between achievable registration accuracy and tissue mechanical and organ geometrical properties.¹⁵ It was found that the effect caused by mis-registration is minimal for the treatment evaluation if the entire prostate is the target. The FEM based DOR has also been intensively studied by others and applied to image-guided radiotherapy.^{16,17} We would like to point out that currently the cumulative dose analysis can be only performed offline because many components are not ready for the real-time operation. The dosimetric index used for the evaluation was D_{99} (dose to the 99% of the volume, a representative of minimum dose) for CTV, and generalized equivalent uniform dose (gEUD) for OARs such as bladder and rectum. The parameter of the gEUD was chosen to be 10.

II.C.2. Dose compensation

In the offline analysis, cumulative dose was computed at each fraction of the treatment course. If a discrepancy between the cumulative and prescription dose for the target exceeded the tolerance (or pre-defined criterion), the treatment plan can be modified and the discrepancy can be made up through boost radiation in future treatment fractions. The relative dose difference after fraction k can be written as

$$\frac{D_{99}(CD_k) \times N/k - D_{99}(D_0)}{D_{99}(D_0)} \times 100\%, \quad (1)$$

where D_0 is the dose in the initial optimized plan intended for all fractions, CD_k is the delivered cumulative dose after k fractions, and N is the total number of fractions. The factor (N/k) normalizes the CD_k to the total dose. The pre-defined criterion was chosen to be -2% in this study. The possible causes of the dose deficit could be the use of aggressive zero margin in the initial treatment planning, or significant target deformation during the treatment course, etc.

The dose compensation can be implemented with either 3D-CRT or IMRT techniques. IMRT has the unique capability to incorporate the previous delivered cumulative dose distributions into the plan optimization for future treatment delivery^{18,19} and thus is more suitable for the dose compensation purpose. In this study, dose compensation was achieved by IMRT through adaptive inverse planning. The optimization objective function can be written in the form of

$$f(D_{Rx}, CD_k + FD_{k+1 \rightarrow N}), \quad (2)$$

where D_{Rx} is the prescription dose and $FD_{k+1 \rightarrow N}$ is the dose to be delivered in future fractions. When $k=0$, the plan from Eq. (2) becomes the initial plan. For simplicity, the planning CT and contours were used as the reference for the dose

compensation re-planning, although other treatment CTs and contours could also be used. The objective was to deliver prescribed dose to the prostate in the planning CT by taking the prior cumulative doses into account. Same constraints on target and critical organs were used for both initial and modified plans in this study, although they can be adjusted to suit each patient. To simplify the delivery of dose compensation, beam arrangements were chosen to be the same for the initial and boost plans.

The frequency of dose compensation has been tested in the previous study.¹¹ By taking into account the effectiveness, workload, and efficiency, dose compensation on a weekly basis seems a good choice due to its biologic advantage and more practical implementation in the clinic. Therefore, weekly compensation was chosen as the primary schedule in this work. For one patient with a large discrepancy (more than 10%) between the cumulative and prescription doses at the end of treatment, in addition to weekly compensation, a more frequent schedule (once every three fractions) was also performed to test the effect of dose compensation frequency.

Once the decision was made during offline dose analysis that dose compensation was necessary, the choice of delivering the dose compensation also needs to be selected. The new plan can be delivered in a single fraction or spreading over several fractions or spreading over all future fractions. A single fraction delivery strategy was used in the previous study.¹¹ Despite that a single fraction delivery has the advantage of simplicity and may be more effective to recover the dose deficit immediately, it has some disadvantages. For example, the dose discrepancies may be too big to be delivered in a single fraction; the uncertainty associated with the single fraction delivery can be large, and it cannot compensate for the fraction where the boost dose is delivered. Spreading the boost dose over all (or several) future fractions may be more practical and more beneficial to reduce the execution errors. Two weekly compensation delivery strategies were studied: schedule A: the modified plan will be delivered over all future fractions; schedule B: the modified plan will be delivered over the following week only, with the intention to return to the initial optimal plan. For both types of delivery schedules, a second decision of dose compensation was made at the end of second week. If the dose deficit was found to be within the tolerance, then no more re-planning was necessary for that patient. In that case, for schedule A, the modified plan will be used for treatment delivery for the last week. For schedule B, the initial plan will be used. If the dose deficit exceeded the tolerance again, then a new plan was created based on the dose feedback, schedules A and B were the same since there was only one week in the remaining treatment fractions. Table I summarizes the planning and treatment schedules for online IG and weekly compensation.

III. RESULTS

Figure 1 shows the variation of prostate D_{99} between the cumulative and prescription doses as a function of treatment

TABLE I. Comparison of treatment schedules for online image guidance and weekly compensation. “×” indicates delivery of the initial treatment plan 0; “o” indicates compensation is delivered with modified plan 1; “Δ” indicates compensation is delivered with modified plan 2.

	# of replanning	Treatment week		
		1	2	3
Online IG	0	×	×	×
Schedule A	1	×	o	o
	2	×	o	Δ
Schedule B	1	×	o	×
	2	×	o	Δ

fraction for each patient. For 28 patients we studied, after the ideal COM registrations were performed in the online correction, 17 patients passed the criteria of 2% underdose at the end of treatment course (black star dashed curves). The average dose deficit is -2.1% at the end of the treatment course (see Table II). It is possible that the cumulative dose deficit at the end of week 1 or 2 could be more than 2%, but the final cumulative is still within 2%, see patients 13, 16, and 22 in Fig. 1. However, if that happened, dose compensation was still applied after week 1 or 2 whenever 2% underdose was found. Therefore, the total number of patients needed dose compensation in this study is 14. The rest 14 patients passed the criteria at the end of treatment course as well as at the end of *each treatment week*.

For those 14 patients whose differences in prostate D_{99} exceeded the criterion, the delivered cumulative dose distributions were fed back into the treatment planning system, and new modified plans were created for future treatment delivery. The corresponding D_{99} differences after weekly compensation are shown in Fig. 2 (only patients who need compensation are shown in the figure, including patients 13, 16, and 22). After weekly compensation, ten out of 14 patients (black star dashed curves) passed the 2% underdose criterion at the end of treatment. Only detailed results from schedule A are shown here for demonstration.

If dose compensation was necessary for the second week, it was expected that the dose deficit improvement of schedule B be better than that of schedule A, as shown in Fig. 3(a). This was because schedule B was designed to make up the previous dose deficit in one week, while schedule A intended to achieve the goal in two weeks. However, for a few patients included in the simulation, schedule A showed better dose improvement than schedule B at the end of the second week. A typical patient of this type is shown in Fig. 3(b) for illustration. The possible reason could be due to the anatomy difference between the planning CT and treatment CTs since prostate contours of planning CT were used as reference in the re-planning, and the quality of modified plans could be different.

Figure 4 compares the pass rate at the end of each treatment week for strategies with and without dose compensation.

FIG. 1. Prostate D_{99} differences [Eq. (1)] between the normalized cumulative dose and the initial plan dose as a function of treatment fraction for each patient. The pre-defined criterion (solid horizontal lines) chosen was -2% . Black star dashed curve: patients passed the criterion at the end of treatment course. Open circle solid curve: patients failed. The “#” in each figure indicates the patient ID.

TABLE II. Comparison of CTV dose deficits with and without dose compensation. The dose deficits are expressed as (average $\pm$ stdev) % as defined in Eq. (1). The numbers in parenthesis are the number of patients for the calculation.

	Online IG only	Weekly Comp. (A)	Weekly Comp. (B)
All patients	-2.1 ± 3.2 (28)	-2.0 ± 2.5 (14)	-1.9 ± 2.6 (14)
Patients passed criterion	0.2 ± 0.7 (14)	-1.0 ± 1.0 (10)	-0.9 ± 1.0 (10)
Patients failed criterion	-4.4 ± 3.1 (14)	-4.2 ± 3.8 (4)	-4.4 ± 3.7 (4)

For 10 (9) out of 14 patients studied, schedule A (B) weekly compensation at the second week were not able to reduce the overall dose difference to acceptable level at the end of second week, and another round of re-plannings were still necessary. This could be caused by the deformation occurred at the second week and also residuals from online correction. However, significant dose improvements were still observed during the second week. Another weekly compensation for the last week can reduce the overall dose deficit to pre-defined criterion for majority of patients studied. Without any intervention, the online IG only had the pass rate of about 54% at the end of first treatment week, and then the pass rate gradually increased to 61% at the end of the treatment course. In comparison, the dose coverage to the target with dose compensation improved significantly with time, and the pass rate increased from 54% to about 86% at the end of treatment for both schedules A and B delivery strategies.

To illustrate the differences in prostate dose distribution caused by the inter-fraction organ motion and the improvement of dose compensation technique, example dose-volume

histogram (DVH) at the end of treatment is shown in Fig. 5(a) for one patient (patient 15). “Planned” was for the initial plan; “Cumulative” was the actual cumulative dose distribution delivered to the patient based on the initial plan with online IG only; “Compensation” was the cumulative dose delivered to the patient after performing weekly compensation. For this patient, an underdose of 6% for prostate was observed at the end of treatment if only online correction was performed, mainly due to the aggressive zero CTV-to-PTV margin used in the initial treatment planning and large deformations occurred during the course of treatment. Hot spot of similar magnitude was also present. Both types of weekly compensation can improve the underdose to less than 2% at the end of treatment, with similar improvements on the hot spots. We would also like to point out that if only online IG was performed for this patient, a 2-mm CTV-to-PTV margin was necessary in the initial treatment planning to achieve similar underdose level at the end of treatment. This was an indication that the offline dose compensation can offer additional benefit of margin reduction and thus can improve the critical organs sparing.

The corresponding DVHs of bladder and rectal wall for the same patient are shown in Figs. 5(b) and 5(c), respectively. The changes between the plan and cumulative doses were mainly due to the internal motion of OARs. In this study online correction was based on prostate only, the relative movement of prostate and critical organs were not taken into account, which could be very different from fraction to fraction. During the simulation of online IG by matching the COM of the prostate between planning CT and treatment CTs, the corresponding contours of bladder and rectum were

FIG. 2. Prostate D_{99} differences as a function of treatment fraction after application of weekly dose compensation. The pre-defined criterion (solid horizontal lines) chosen was -2% . Black star dashed curve: patients passed the criterion at the end of treatment. Open circle curve: patients failed. Blank space: patients do not need dose compensation. Only results from schedule A strategy are shown.

FIG. 3. Comparison of two weekly compensation delivery strategies for two typical patients. (a) Schedule A had better dose improvement than schedule B; (b) schedule B had better dose improvement than schedule A.

shifted by the same amount. Furthermore, no special instructions were given to the patients to empty their bladder and rectum before treatment, so the shapes of bladder and rectum at the planning and treatment days were different in general. All these factors could lead to discrepancies between the cumulative and plan doses for critical organs.

In order to have a fair comparison of doses delivered to critical organs for strategies with and without dose compensation, the initial plan doses were used as a reference for each patient. As shown in Fig. 6, the gEUD values of different strategies were expressed as a ratio of plan doses for both bladder and rectal wall. No significant dose changes to bladder and rectal wall were found between the cumulative doses with and without dose compensation using paired student's t-test, this is mainly because the same sets of constraints for the target and critical organs were used in the optimization process for both the initial and modified IMRT planning.

FIG. 4. Pass rate at the end of each treatment week with and without dose compensation.

FIG. 5. Dose-volume histograms (DVHs) comparison of prostate, bladder, and rectal wall for one patient at the end of treatment. Notice that the dose axis for prostate does not start from 0 in order to show the differences among different curves. "Planned" was the initial plan; "Cumulative" was the cumulative dose distribution delivered to the patient based on the initial plan with online IG only; "Compensation" was the cumulative dose after performing weekly compensation.

The average dose deficits are summarized in Table II for treatments with and without dose compensation. For 28 patients included in the simulation, there were four patients (2, 9, 11, and 24) failed the 2% underdose criterion at the end of treatment after weekly compensation, as shown in

FIG. 6. Dose indices (gEUD) of critical organs. The gEUD values are expressed as a ratio of plan doses at zero margins.

Fig. 7. Comparison of different dose compensation schedules for patient 24.

Fig. 2. For three of them (2, 9, and 11), there were notable improvements on the D_{99} , and both types of compensation delivery strategies were able to reduce the overall dose deficit close to the tolerance limit at the end of treatment (-2.7 , -2.4 , -2.1% from schedule A, and -2.1 , -2.9 , -2.4% from schedule B).

For patient 24, no underdose was found at the end of first week. However, significant underdose occurred at fractions six and seven where large changes in prostate shape were observed. Following the weekly compensation protocol, no action was taken for the second week and dose compensation was only scheduled for the third week, as shown in Fig. 7. It should be noted for this patient, results from schedules A and B were same, i.e., it was only done after fraction ten. Dose compensation for the third week could improve the dose difference, but there was still a 10% underdose at the end of the treatment. For this patient, an additional slightly different schedule was attempted, in which the necessity of dose compensation was triggered by the pre-defined criterion in the offline dose analysis, and dose compensation was implemented every three fractions. Also, shown in Fig. 7, the new schedule was able to improve the dose deficit significantly.

We would like to point out that the cumulative underdose is a gradual effect and it cumulates dose from every previous treatment fraction. In other words, daily dose deviation of same magnitude from the plan dose is likely to show up more significant at the early fractions than the late fractions, primarily due to the definition of the normalized total dose in Eq. (1). As an example, Fig. 8 compares the D_{99} differences of daily and cumulative dose from the plan as a function

Fig. 8. Daily and cumulative D_{99} differences as a function of treatment fraction for patient 5.

of treatment fraction for one patient (patient 5). For this patient, two fractions (1 and 6) had larger daily underdose than other fractions, both around 23%. However, only 9% of underdose was observed in the cumulative distribution at fraction 6. In order to better demonstrate this, a simulation was carried out by swapping treatment fractions with $1 \leftrightarrow 11$ and $6 \leftrightarrow 12$, and the result is shown in Fig. 8 as red square curve. In the new arrangement, the largest daily underdose occurred at fractions 11 and 12. However, the effect is barely noticeable for these two fractions in the cumulative D_{99} difference. The two cumulative curves merged into one after fraction 12, as expected. If significant daily underdoses happened at late fractions, large deviations of underdoses may not be observed in the normalized cumulative distribution. This will affect the decision making on whether dose compensation is necessary, and it will also affect the effectiveness of dose compensation because it may be too late to patch up the dose deficit in a few fractions, such as patient 24.

IV. DISCUSSIONS

In prostate cancer radiotherapy, planning margins can be reduced significantly with online IG alone. However, certain margins are still necessary to compensate the uncertainties from contour delineation, organ deformation, intra-fraction motion, and residual errors from online correction. The margin to compensate for each individual uncertainty is usually investigated separately. The overall margin should be the combination of these margins. Offline evaluation and re-planning provides opportunities to further reduce the planning margins, and adaptive re-planning can be implemented through either *geometric* or *dosimetric* feedback. The goal of this study is to evaluate the effectiveness of an offline *dosimetric* adaptive re-planning technique (dose compensation) for prostate cancer. Only uncertainty caused by inter-fraction motion, specifically the deformation, was investigated in this study. A CTV-to-PTV margin is commonly used to account for the uncertainties of inter-fraction motion. In this study, image guidance is investigated to eliminate the CTV-to-PTV margin, thereby reducing the dose to the rectum and bladder while maintaining target coverage. The intra-fraction motion has been extensively studied in detail previously by many investigators,^{20–24} and it was found that a few mm margins are still necessary. This does not contradict with our choice of zero margin in this study, because intra-fraction motion was not modeled in the simulation. Needless to say, the dose compensation technique can also be applied to manage other uncertainties, such as intra-fraction motion and residual errors from online correction, provided they can be measured and recorded during the treatment.

Compared to dose compensation technique, online IG only correction is simpler to implement but requires certain margins. For example, the CTV-to-PTV margin accounting for inter-fraction motion can be reduced to 3 mm with online IG alone,²⁵ and ~ 1 mm with a hybrid strategy combining online and offline adaptive re-planning.^{9,10} Both strategies are geometric in nature. From this study, the margin can be even further reduced if dose compensation is performed in

combination with online correction. Such margin reduction may allow additional increase in dose gradient between prostate and surrounding critical organs, thereby improving the therapeutic ratio.

In addition to offline ART, the benefit of online re-planning has been investigated by a few groups for prostate cancer radiotherapy.^{26–28} However, there are still many hurdles and practical concerns to be addressed for online ART before the clinical implementation. For example, organ contouring, treatment planning including re-optimization, intra-fraction motion, quality insurance, and plan approval, etc.

We used zero CTV-to-PTV margin in this study to demonstrate the dose compensation technique. After the cumulative dose distribution is fed back to the treatment planning system, IMRT inverse planning is capable of depositing additional boost dose to the underdose region, and extracting the “negative dose” from the hot spot in the future fractions. For majority of patients studied, the dose deficiencies from previous fractions can be recovered in future fractions, which is an indication that additional margin reduction is achievable with the combination of dose compensation and online IG.

Since the anatomy changes during the treatment course are different from patient to patient, the decision of whether dose compensation is necessary is a patient-specific decision and should be based on the offline cumulative dose analysis. The application and success of dose compensation depends on the combination of the margins used in the plan and the pre-defined dose criterion. Due to the aggressive zero CTV-to-PTV margins used in the initial treatment planning in this study, the criterion we chose (2%) should be reasonable. The success of dose compensation also depends on many other factors, such as the accuracy of online image registration and the reliability of deformable organ registration. Currently many researches are being carried out to manage these uncertainties, which are beyond the scope of this study.

Dose compensation was not necessary for half of patients (14 out of 28 patients) in this study, indicating that organ deformations were within the estimate at the initial treatment planning stage after ideal COM registration for 50% of the patients. In other words, the magnitudes of organ deformation were within acceptable range throughout the treatment course. For the majority of the other half patients (ten out of 14) who required dose compensation, both types of weekly dose compensations were able to bring the overall dose discrepancies back to tolerant limit at the end of treatment.

The dose differences with weekly compensation did not monotonically decrease as a function of treatment fraction, indicating that the underdose is a gradual effect and cumulates from each fraction. For most of patients (ten out of 14) needing compensation, weekly compensations at the second week alone were not able to reduce the overall dose deficit to the acceptable level. This was caused by the deformation occurred through that week. However, there was still a noticeable improvement over no compensation strategy. At the third week, such effects became smaller and the compensations were able to reduce overall dose deficit.

For a few patients who failed to pass the pre-defined criterion after weekly compensation, some modification in the

work flow may be necessary. For example: (1) adding one more boost dose at the end of treatment; (2) more frequent dose compensation schedule; (3) using non-zero CTV-to-PTV margin in the initial and modified treatment planning; (4) using treatment CT and contours as the reference for the modified plan to remove possible systematic uncertainties (the planning CT may not be a good representative of patient anatomy during the treatment).

Compared with online IG only strategy, both the hybrid and dose compensation strategies are more complex, and significant efforts are needed for the offline analysis and re-planning. The effectiveness and efficiency should be balanced in the clinical implementation. However, all analyses and re-planning of the hybrid and dose compensation strategies are performed offline, thus will not affect online treatment efficiency. Compared with the hybrid strategy, dose compensation requires more efforts for offline dose analysis. The number of re-planning is 1 per patient for the hybrid strategy. For weekly dose compensation, the average number of re-planning is 0.82 per patient for schedule A, and 0.79 per patient for schedule B. Therefore, the number of re-planning for dose compensation is slightly less than those for the hybrid strategy.

Online IG only and hybrid strategies assume that the patient motion characteristics and the treatment process follow a pre-determined population distribution. However, each patient may display very different motion characteristics, and mistakes could also happen during the online treatment. As long as they are recorded by the imaging study and captured by the electronic medical system, the treatment process can be reconstructed through the offline analysis to produce the cumulative dose distributions. Then the dose compensation technique can be applied to incorporate individual patient motion and correct mistakes. In addition, the dose compensation can be implemented together with the hybrid strategy, thus creating an additional safety mechanism to ensure proper dose delivery.

V. CONCLUSIONS

In conclusion, we have demonstrated that the combination of online image guidance and offline dose compensation can effectively patch up the dose deficit occurred at early fractions due to inter-fractional deformation. Compared with the online image guidance alone, dose compensation can further reduce the margin without increasing the dose to critical organs. As a consequence, this allows additional increase of dose gradient between the target and critical organs, thus reduces treatment related complications. Dose compensation at a weekly basis is effective and practical for most patients.

ACKNOWLEDGMENTS

This study is supported by grant CA118037 from the National Institute of Health. The contents are solely the responsibility of the authors and do not necessarily represent the official view of the NIH.

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