Four-dimensional dose distributions of step-and-shoot IMRT delivered with real-time tumor tracking for patients with irregular breathing: Constant dose rate vs dose rate regulation

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Purpose: Dose-rate-regulated tracking (DRRT) is a tumor tracking strategy that programs the MLC to track the tumor under regular breathing and adapts to breathing irregularities during delivery using dose rate regulation. Constant-dose-rate tracking (CDRT) is a strategy that dynamically repositions the beam to account for intrafractional 3D target motion according to real-time information of target location obtained from an independent position monitoring system. The purpose of this study is to illustrate the differences in the effectiveness and delivery accuracy between these two tracking methods in the presence of breathing irregularities.

Methods: Step-and-shoot IMRT plans optimized at a reference phase were extended to remaining phases to generate 10-phased 4D-IMRT plans using segment aperture morphing (SAM) algorithm, where both tumor displacement and deformation were considered. A SAM-based 4D plan has been demonstrated to provide better plan quality than plans not considering target deformation. However, delivering such a plan requires preprogramming of the MLC aperture sequence. Deliveries of the 4D plans using DRRT and CDRT tracking approaches were simulated assuming the breathing period is either shorter or longer than the planning day, for 4 IMRT cases: two lung and two pancreatic cases with maximum GTV centroid motion greater than 1 cm were selected. In DRRT, dose rate was regulated to speed up or slow down delivery as needed such that each planned segment is delivered at the planned breathing phase. In CDRT, MLC is separately controlled to follow the tumor motion, but dose rate was kept constant. In addition to breathing period change, effect of breathing amplitude variation on target and critical tissue dose distribution is also evaluated.

Results: Delivery of preprogrammed 4D plans by the CDRT method resulted in an average of 5% increase in target dose and noticeable increase in organs at risk (OAR) dose when patient breathing is either 10% faster or slower than the planning day. In contrast, DRRT method showed less than 1% reduction in target dose and no noticeable change in OAR dose under the same breathing period irregularities. When $\pm 20\%$ variation of target motion amplitude was present as breathing irregularity, the two delivery methods show compatible plan quality if the dose distribution of CDRT delivery is renormalized.

Conclusions: Delivery of 4D-IMRT treatment plans, stemmed from 3D step-and-shoot IMRT and preprogrammed using SAM algorithm, is simulated for two dynamic MLC-based real-time tumor tracking strategies: with and without dose-rate regulation. Comparison of cumulative dose distribution indicates that the preprogrammed 4D plan is more accurately and efficiently conformed using the DRRT strategy, as it compensates the interplay between patient breathing irregularity and tracking delivery without compromising the segment-weight modulation. © 2012 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4745562>]

Key words: 4D-IMRT, dose-rate-regulated tracking, constant-dose-rate tracking, segment aperture morphing

I. INTRODUCTION

Real-time tumor tracking is one of the promising techniques in dealing with target motion induced by patient respiration. Studies indicate that for patients with thoracic and abdomen tumors, 4D-IMRT that incorporates breathing induced tumor motion revealed by 4D-CT in IMRT planning and treatment delivery, can deliver the tumorcidal dose precisely to the target while allowing further reduction of the internal margin in order to spare the surrounding tissues and critical organs.^{1,2} Among the proposed tracking strategies, dose-rate-regulated tracking (DRRT) approach starts with a preprogrammed MLC sequence based on the patient's regular breath pattern and phase-to-phase tumor motion/deformation. During delivery, the dose rate is modulated to adjust the speed of treatment delivery to adapt to the patient's breathing irregularities revealed by real-time monitoring. This strategy enables temporal modification of the preprogrammed delivery sequence without changing the governing control points, so that real-time tracking delivery is feasible to current linear accelerators equipped with dynamic MLCs.³ Constant-dose-rate tracking (CDRT) is another tracking algorithm that uses dynamic-MLC to continuously reshape the treatment apertures during delivery and compensate the tumor motion acquired through associated real-time monitoring methods.^{4,5} The motion monitoring methods include applications of external fiducials such as RPM (Varian medical Systems, Palo Alto, CA), internal fiducials such as Calypso 4D localization system (Calypso Medical Technologies, Seattle, WA), and fluoroscopic kV-imaging.⁵⁻⁷ Using CDRT strategy, if the target can be treated as a rigid body, each of the MLC leaf pairs optimized on static patient anatomy can be repositioned during treatment to catch up with the target motion.⁸ However, in some thoracic and abdomen cases, significant target deformation such as compression and expansion presents during patient breathing.^{9,10} To take into account both target displacement and target deformation during IMRT treatment delivery, a preprogrammed MLC aperture sequence based on dynamic patient anatomy has to be used regardless of the choice of tracking strategy.

A 4D-IMRT treatment plan for tracking delivery can be generated based on time resolved 4D-CT image data obtained in the planning day, using either "individual phase optimization (IPO)" approach or morphing approaches such as direct-aperture optimization (DAO) or direct-aperture deformation (DAD).^{11,12} The IPO approach should yield a treatment plan that is close to the true optimum because it takes into account the relative position of the dislocated and deformed target and its surrounding organs for each breathing phase. In the absence of the true optimum, it has been used as a gold standard for plan quality evaluation purpose.⁸ However, IPO planning is extremely time consuming and is practically not deliverable due to lack of connection between segment apertures of consecutive phases. These independently optimized plans do not take full advantage of the anatomic relationship between breathing phases, and the mechanical constraints to movement of jaws and MLC leaves associated with the phase-to-phase transition are not incorporated into the optimization.

The direct aperture deformation approach starts with a plan optimized on one single reference phase and then extends the optimized aperture shapes to the remaining phases based on tumor motion and deformation revealed by patient 4D-CT data. If the extension is purely based on the 3D trajectory of tumor centroid but tumor deformation during patient breathing is ignored, the approach results in a "SHIFT" 4D plan, as proposed by Suh *et al.*⁸ On the other hand, based on the planning 4D-CT, tumor deformation between breathing phases can be accounted for using approaches such as segment aperture morphing (SAM) algorithm.¹³ Work has been reported demonstrating that a SAM scheme taking into account the phase-to-phase tumor deformation resulted in 4D-IMRT plans that have plan quality [in measures such as $V_{95\%}$, conformity index, and dose volume histograms (DVHs)] comparable to IPO plans, and better than plans resulted from "SHIFT" scheme.¹⁴

The interplay between the movement of MLC apertures and that of the patient anatomy during irradiation has been shown to potentially create large discrepancy between planned and delivered target dose, but has not been well integrated in 4D-IMRT treatment planning or delivery.¹⁵⁻¹⁷ In plan quality evaluation of proposed 4D-IMRT planning schemes for real-time tumor tracking, single-phase-optimized plans are extended to 4D plans using copying-and-translating or deformable morphing,^{6,12,15} assuming that each of the breathing phases will be treated with a 3D-IMRT plan that is identical in number and weight of beams and segments except for translated/deformed MLC apertures. Dose calculation based on individual set of 4D-CT images is compared to IPO plans either in phase-by-phase fashion or by averaging over all the phases after dose transfer from all the individual phases back to the reference phase via deformable registration. Similar to the case of IPO plans, the dose map of such "identical" plans could only be achieved using gating management by choosing each of the individual phases as the gating window. Due to the interplay effect, significant difference in delivered monitor units (MUs) and resulting dose distribution is expected from phase to phase, and comparison between different tracking methods on each individual phase cannot lead to solid conclusion. However, by using deformable dose summation based on the 4D-CT images, plan quality can be evaluated and compared between delivery methods based on the cumulative results on the reference phase.

Patient breathing irregularity, especially changes in breathing period and amplitude, affects the dose distribution over target and critical organs when real-time tumor tracking method is used for delivery of 4D-IMRT plans. DRRT method is capable of compensating the breathing period variations by adaptively adjusting the dose rate. On the other hand, because constant dose rate is used in CDRT method, the additional interplay effect due to breathing period irregularity will lead to alteration of segments delivered to each individual phase and ultimate decrease of conformity to the cumulative 4D plan. Since the CDRT delivery method is capable of following the real-time tumor centroid movement, it is expected to perform better compensation to the intrafractional variation in patient breathing amplitude than the DRRT delivery.

Studies on technical feasibility and geometric accuracy of dynamic-MLC-based real-time tumor tracking strategies have been well presented in the literature and satisfying dose distribution from tracking algorithms has been demonstrated with 3D dose calculations on individual respiration phases.^{3,5,8,14} However, the 4D dose distribution incorporating the aforementioned interplay effect has not been acknowledged for either CDRT or DRRT methods. This article compares the cumulative dose distribution when dynamic 4D-IMRT plans are delivered using the two tracking methods to compensate patient breathing irregularity. The technical aspects of both methods are based on reports published in the literature to our best knowledge. DRRT strategy compensates the patient breathing irregularity through real-time dose-rate regulation. For CDRT method, several possible strategies to compensate the interplay effect are proposed. We demonstrate that choice of delivery strategy can result in significant difference in dose distribution for target and critical organs and delivery efficiency when interplay between patient breathing and tracking delivery is taken into account.

II. METHODS

II.A. 4D-IMRT planning for real-time tumor tracking

Two lung cancer and two pancreatic cancer cases with maximum motion of GTV centroid greater than 1 cm were selected from a pool of the IRB approved protocol (GCC 0832). Two sets of 4D-CT of different dates for each case are used: one for planning and the other for delivery test. For each case, a step-and-shoot IMRT plan was optimized on the reference phase CT (end of inhale) using 5 to 7 beams, with collimator angles selected so that MLC leaf motion was aligned along the major axis of tumor motion in beam's eye view (BEV), resulting in a single-phase-optimized (SPO) IMRT plan. Direct machine parameter optimization (DMPO) engine of Pinnacle 9.0 (Philips Medical Systems, Cleveland, OH) treatment planning system was used for the IMRT inverse planning. The SAM algorithm was adopted and modified to morph each MLC shape from the reference phase to the nine remaining phases according to both tumor translation and deformation in BEV. Thus for each segment at each beam angle, a deformed aperture shape was generated for each remaining phase. A stable patient breathing curve (constant period and amplitude) is used in generating the 4D segment delivery sequence assuming the plan is delivered at a constant dose rate. Since the DRRT strategy calls for adaptive increase or decrease of dose rate during real-time delivery, the initial constant dose rate for planning has to be less than the maximum value (e.g., 600 MU/min), and longer delivery time is expected. This is one of the disadvantages of DRRT strategy. From a previous study, satisfying tracking accuracy is achievable using DRRT if the variation of breathing period is within 40%.¹⁸ If 20% variation in breathing period is used as the patient-selection criteria, a planning dose rate of 500 MU/min will be sufficient. Due to the interplay between patient breathing and beam/segment sequence in the 3D SPO plan, the beam MU weights (assigned MUs to be delivered for that beam) and the relative segment MU

weights at each beam are determined for each phase, which varies from phase to phase, but the total beam MUs and segment MUs summed over all the 10 phases will be the same as in the SPO plan. Combination of the beam/segment MU weights with the morphed aperture shapes generates 10 temporally and spatially associated 3D-IMRT plans for tracking delivery. Dose distribution for each individual phase is calculated in Pinnacle and the cumulative dose to the target and critical organs is obtained by transferring the dose volume from all the remaining phases back to the reference phase using commercially available deformable image registration (DIR) tool (MIMvista 5.1, MIMvista Corp, Cleveland, OH). Due to mixture of limitations including the morphing algorithm, the finite leaf thickness, and the dose registration, the accumulated 4D dose distribution from the ideal constant-breathing plan is inferior in plan quality compared to the SPO plan, but still good enough to serve as the practical dosimetric goal of 4D delivery using tumor tracking approaches dealing with target motion irregularities. The flowchart of the generation and evaluation of a 4D-IMRT plan is illustrated in Fig. 1. When a 4D-IMRT plan is delivered using tumor tracking methods, the interplay between the patient breathing pattern on the treatment day and the planned segment aperture sequence based on the planning day 4D-CT data may lead to altered beam/segment weights for each phase according to delivery strategy used, as will be discussed in Sec. II.D. Dose distribution is calculated on individual phases of the second set of CT representing patient anatomy on the treatment day. Deformable image registration and dose accumulation on the reference phase of the treatment day CT enable the comparison of delivered plans with the initial 4D plan as well as comparison between tracking methods.

Generating a preprogrammed 4D aperture sequence before the treatment delivery is one of the distinctive features between DRRT and other real-time tumor tracking techniques. This offline planning stage allows the incorporation of phase-to-phase tumor deformation into the design of dynamic apertures. Such deformation is better reflected in the 4D-CT images than any online monitoring techniques currently available. The offline planning strategy reduces the computational burden during tracking delivery, improves the morphing accuracy, enables predelivery check of machine constraints, and allows for 4D plan quality evaluation. Furthermore, a specific study on step-and-shoot IMRT planning reveals that such a predelivery planning scheme permits the resorting and optimization of segment sequencing to significantly reduce the total intersegment time.¹⁹

II.B. Modified SAM algorithm: SAMX

As described in Refs. 12–14, the SAM algorithm compares the location and extension of enveloping rectangles of the old and new target projections in BEV, and for each boundary point determining the MLC aperture shape in the old projection, a unique counterpart is calculated in the new projection. In such approach, the effect of translational motion of tumor is embedded in the deformation, which works best if the deformation can be featured as uniform compression

FIG. 1. Flowchart of transformation from the SPO IMRT plan to a 4D-IMRT plan using SAM algorithm, delivery of the 4D-IMRT plan using DRRT or CDRT tracking methods, and dose registration for plan evaluation and comparison.

or expansion. In this work, we followed the same basic approach as presented by Gui *et al.*¹⁴ but modified the deformation method as follows (dubbed “SAMX”) to improve the morphing for irregular deformation such as nonsymmetric expansion/compression or rotation. First, we separate the tumor deformation from pure translation by matching the target centroids in the old and new projections in BEV. Next, the radial deformation of the tumor at each direction with respect to the centroid is then determined by comparison along the 2D contours of old and new projections, to interpolate the appropriate new radius for each boundary point defined in the old aperture. Finally, the radial deformation combined with the translation determines the location of each boundary point and the entire MLC aperture shape in the new projection. A detailed comparison between our approach and that presented in Refs. 12–14 is discussed in Ref. 20. Phase-by-phase comparison of the SAM and SAMX approaches shows better correlation between MLC shapes and target deformation from the latter approach, and the cumulative dose distribution on the reference phase also indicates noticeably improved planning quality for the latter. Figure 2 compares the DVHs of cumulative dose of a pancreatic case. The SPO plan was generated into 4D-IMRT plans using either SAM morphing (thin lines) or the modified SAMX approach (thick lines). The percentage of PTV volume receiving 95% of prescription dose (V_{95}) was 95% from SAM approach and became 99% from SAMX approach. The target coverage is significantly improved using the SAMX morphing.

FIG. 2. DVH of cumulative dose of a 4D-IMRT plan generated using SAM (thin lines) or modified SAMX (thick lines) morphing approach for a pancreas case. Prescription: PTV mean dose = 50.4 Gy. Target (PTV) coverage is improved with SAMX method.

II.C. 4D plan delivery using DRRT tracking strategy

Change of a patient breathing pattern during a treatment, especially the unpredictable variation in breathing period and amplitude, is the key challenge to tumor tracking. To simulate the dosimetric outcome of tumor tracking methods using DRRT or CDRT strategy in the presence of patient breathing irregularities, breathing patterns were designed with constant amplitude but varying periods representing either faster or slower breathing on the treatment day compared to that on the simulation/planning day. In delivery of an IMRT plan using existing linear accelerators, the MUs to be delivered between any two control points cannot be modified on-the-fly, since other parameters including dose rate and MLC leaf speed are enslaved to the MUs. In DRRT method, we adjust the dose rate by comparing the patient breathing period during delivery with that on the planning day: if breathing becomes slower (faster), dose rate is decreased (increased) to slow down (speed up) the leaf motion, and the synchrony between tumor motion and beam adjustment is maintained.³ In this way, although the cumulative dose as a function of delivery time is altered from the preprogrammed 4D plan, the association between the control points (i.e., MUs delivered) and the temporal-spatial change of the treated target is conserved. The dose-rate control can be realized through an electron gun pulse-rate control interface similar to that of the respiration gating board. Instead of a binary on-and-off toggle, the actual dose rate adjustment can be either continuous or stepwise.¹⁸ The online adjustment of leaf speed is able to adaptively compensate the tumor motion, whether the treatment day breathing is slower, faster, or with any combined pattern.

II.D. 4D plan delivery using CDRT tracking strategy

The CDRT tracking delivery method adaptively relocates and/or reforms the segment apertures according to the real-time position and shape of the target, while keeping a constant dose rate same as in the initial planning. One advantage of this method is that the maximum dose rate can be used and the delivery time is shorter compared to the initial planning for DRRT. How the CDRT strategy compensates the interplay

between breathing period irregularity and the constant-dose rate delivery is not reported in the literature. For fair comparison, we assume the preprogrammed sequence of MLC aperture shapes that reflects both the dislocation and the deformation of target is delivered continuously by applying constant dose rate, but the sequence is terminated if and only if the planned MUs are delivered for each beam. In the case of slower breathing during treatment (i.e., longer phase duration), with constant dose rate, earlier segments in the sequence will receive more dose than planned, and segment(s) at the end of the sequence of each beam will receive partial dose or be completely skipped once the planned MUs for that beam have been delivered. In the case of faster breathing (i.e., shorter phase duration) during treatment, the patient receives less MUs than planned for each breathing phase, hence delivery at a given beam will not be complete when the preprogrammed MLC sequence runs out. To complete the planned MUs, we resynchronize the 4D sequence with patient breathing phases and start that beam from the beginning until planned MUs for that beam are reached. As a result, the first one or several segments will get more dose than planned. In other words, if target deformation is taken into account, thus a preprogrammed aperture sequence has to be used, CDRT delivery has to alter segment weights in terms of assigned MUs. Since the relative segment weight at each beam direction is one of the important modulating and optimizing factors in IMRT, such alteration may lead to deviation of dose distributions from the optimized plan. Alternative strategies to compensate such dosimetric deviation will be proposed later in Sec. III.

II.E. Effect of variation in patient breathing amplitude using tracking strategy

The effect of interfractional amplitude variations is simulated using a second set of 4D-CT to calculate dose distribution of the treatment day. When the preprogrammed aperture sequence is applied to the treatment day CT, DRRT delivery does not alter either the shape or the position of the apertures. To deal with the variation in target motion amplitude, the algorithm triggers beam hold if the target motion exceeds the maximum amplitude in planning CT, and restores delivery once the target gets back within the range.³ This strategy decreases the duty cycle (the ratio of beam-on time over the entire delivery time) and increases geometric and dosimetric error in DRRT delivery. As suggested by Han-Oh *et al.*,¹⁸ tracking error less than 6% of the target motion amplitude is achievable for patients with breathing amplitude variation within $\pm 20\%$. In the simulation of CDRT delivery, the preprogrammed aperture shapes are not altered, but are repositioned for each breathing phase according to the target trajectory in the treatment day CT, reflecting the unique capability of exactly following the target motion using this tracking strategy. Compared to DRRT, the CDRT technique has the potential of adaptively compensating relatively larger interfractional and intrafractional variations in target motion amplitude, as long as the MLC leaf speed is not exceeding the maximum. In cases such that online motion compensation requires exceed-

ing of the maximum leaf speed or leaf motion range, a beam-hold is triggered, and will restore once the anomalous condition stops.⁵

III. RESULTS AND DISCUSSIONS

III.A. DRRT and CDRT delivery dealing with variation in patient breathing period

Cumulative DVHs from delivery of a preprogrammed 4D-IMRT treatment plan using DRRT and CDRT tracking approaches for a pancreatic cancer patient are shown in Fig. 3. Although patient breathing varies both interfractionally and intrafractionally, the breathing irregularities encountered on the treatment day were represented by either 10% shorter or 10% longer breathing period in order to quantitatively assess the dosimetric outcome. The variation is applied in the same manner to both tracking strategies. Previous studies on breathing signals from 23 lung cancer patients under free-breathing showed an average breathing period of 4.4 ± 1.8 s, with intrafractional variation of 0.6 ± 0.2 s.²¹ Thus, the 10% variation in breathing period is a justified choice. A 100 ms time delay was applied to both tracking strategies, corresponding to the time interval between the actual completion of repositioning of the segment and when should be from initial 4D planning. As reported in the literature, the system response time as a combination of acquisition of target motion, computation of tracking algorithm, and exertion of MLC repositioning, can be anywhere from 200 to 450 ms, depending on the motion monitoring techniques.^{22–24} By choosing appropriate prediction/correction models for target motion, satisfying accuracy (i.e., less than 2 mm) is achievable,²⁵ and the 100 ms time delay represents a realistic situation after such correction. In Fig. 3, the thin solid lines represent the DVHs of target PTV and organs at risk (OARs) from the 4D-IMRT plan based on stable patient breathing with a constant period of 4 s and delivery using a constant dose rate. The prescription dose is PTV mean dose = 50.4 Gy. The thin dashed lines represent the delivery using DRRT tracking method. The

FIG. 3. DVHs resulting from DRRT (thin dashed) and CDRT (thick solid; 10% faster breathing; thick dashed: 10% slower) tracking methods in comparison with the initial 4D plan (thin solid) based on constant breathing for a pancreas tumor case (prescription: PTV mean dose = 50.4 Gy). The CDRT delivery led to significant dose increase in target and OARs.

results of breathing scenarios, either 10% slower or 10% faster than that of planning day, overlap with those of the 4D plan, and cannot be distinguished from the thin solid lines. This indicates that the DRRT delivery is highly capable of handling variations in breathing period. As the result, DRRT realizes the dosimetric expectation for both the target and the OARs under such breathing irregularities. The thick lines represent the CDRT tracking results, with patient breathing being 10% faster (thick solid lines) or 10% slower (thick dashed lines). Compared to the 4D plan, the two scenarios showed increase in PTV mean dose by 3% and 6%, respectively. OAR doses from CDRT tracking increase in varying extension: the dose received by 30% of organ volume (D_{30}) increases by 1.3 (left kidney), 1.2 (right kidney), and 0.7 Gy (liver) for the scenario of 10% slower breathing. If the DVH curves are renormalized at the PTV mean dose, the CDRT results are almost identical with the 4D plan and DRRT delivery results. The decrease in PTV D_{95} and increase in PTV D_{10} are less than 1%, indicating that the target dose distribution is less uniform but the overall plan quality is not seriously degraded.

The same trend of dose deviation from CDRT delivery was observed in the other pancreatic and lung cases studied. Table I summarizes the relative deviation of target (PTV) mean dose resulted from DRRT and CDRT deliveries dealing with a 10% change in breathing period, in comparison with that of the initial 4D plan. For all four cases studied, DRRT delivery maintained the dosimetric goals of the 4D plan, but CDRT delivery resulted in varying percentage of increase in PTV mean dose. The average increase in PTV mean dose over the 4 cases was 4.5% for 10% faster breathing and 6.6% for 10% slower breathing.

Figure 4 illustrates the dose distribution on critical organs in concern (liver, kidneys, and stomach) for the second pancreatic case by comparing the percentage of the organ volume to receive 25 Gy (V_{25}) (prescription dose is PTV mean dose = 50.4 Gy) from the SAMX 4D plan and if the plan was delivered using DRRT and CDRT approaches. Same as for the target, the DRRT delivery confirmed the dosimetric goals of the 4D plan, and V_{25} for OARs (dotted and dashed bars) is the same or slightly lower than the 4D plan (solid bars). V_{25} for the same OARs is noticeably higher than the 4D plan from CDRT delivery in both faster (horizontal bars) and slower (grid bars) breathing scenarios.

FIG. 4. Volume percentage of OARs that receives 25 Gy dose (V_{25}) for a pancreas case with a prescription dose of 50.4 Gy to the target mean dose, given that patient breathing on treatment day is either 10% faster or slower than planning day. V_{25} from DRRT (dotted and dashed bars) is the same or slightly lower than the 4D plan (solid bars) but is noticeably higher from CDRT (horizontal and grid bars) in both irregular breathing scenarios.

III.B. Cause of increase in target and organ dose from CDRT delivery

The significant increase in target and organ doses resulted from CDRT delivery is a combined effect of (1) the aperture sequencing algorithm in Pinnacle treatment planning system, and (2) the interplay between patient breathing and the constant-dose-rate tracking strategy. The implementation in Pinnacle planning system for step-and-shoot IMRT plans tends to sequence the optimized apertures in a “large-segment-comes-first” pattern. That is, the segment sequence of each beam starts with one or more large apertures which cover the entire PTV in BEV, followed by smaller, modulating apertures. As described in Sec. II.D, if patient breathing is either slower or faster than the day of 4D-CT imaging, delivery using CDRT method will not exhaust exactly the entire preprogrammed MLC sequence. Instead, the delivery will either cut off at some segment, or repeat one or more segments from the beginning of the sequence in order to deliver the planned MUs for each beam. This alters the plan by shifting more weight (i.e., monitor units) to these leading larger segments from trailing smaller segments. The shift of segment weight increases exposure to the entire target and the surrounding tissues, while losing the modulating effect of the smaller segments.

To illustrate this combined effect, we evaluated the effect of “reweighting” of the segments in two approaches. In the first evaluation approach, a quantitative relation between the dosimetric outcome and the adjustment of segment weights due to change in patient breathing period was established simulating the CDRT delivery. As reported by Han-Oh *et al.*, RPM breathing signals from 24 lung-tumor patients show a range of average breathing period of 2.0–6.6 s, and the breathing period during treatment varies from $\pm 10\%$ up to $\pm 50\%$ of the average.²¹ Figure 5 shows the increase in the target (PTV) mean dose from the SPO plan as the result of weight-shifting between segments under CDRT delivery, averaged over the four cases studied. Changes in breathing period from 50% shorter to 40% longer than the planned normal breathing were

TABLE I. PTV mean dose deviation resulted from DRRT and CDRT deliveries when patient breathing is 10% faster or slower in comparison with the initial 4D plan.

Tracking Method	Treatment Day Breathing Period	Case 1 (Pancreas)	Case 2 (Pancreas)	Case 3 (Lung)	Case 4 (Lung)
DRRT	10% Faster	−0.1%	−0.1%	−0.1%	0.3%
DRRT	10% Slower	−0.1%	−0.1%	−0.1%	0.3%
CDRT	10% Faster	2.8%	8.2%	2.5%	4.3%
CDRT	10% Slower	6.3%	7.5%	6.4%	6.1%

FIG. 5. Relative increase in PTV mean dose compared with optimized plan as a result of the “large-segment-comes-first” aperture sequencing in Pinnacle planning system and breathing period change simulating the CDRT delivery strategy, averaged over the four cases studied.

studied. The left branch of the curve represents the “faster” scenarios. The average increase in PTV mean dose reaches a maximum when the patient breathes 30% faster on the treatment day than on the day of 4D-CT imaging. When breathing period is reaching half of the regular period (i.e., patient breathes two times faster than on the planning day), the segment weights regress to the original SPO result, since each segment is practically delivered twice. The right branch of the curve represents the “slower” scenarios. PTV mean dose increases as breathing period increases, but will come to saturation as the large leading segment for each beam reaches 100% of segment weight. In this case the modulating effect of the trailing segments is totally lost, and the IMRT plan regresses into a multifield conformal treatment plan. The trend shown in Fig. 5 supported the segment reweighting effect from CDRT delivery by relating the dosimetric outcome with change in patient breathing period. Such a quantitative relation could be used as a guide for daily plan evaluation/adjustment for CDRT delivery. Since the variation in breathing period can be determined right before the start of tracking treatment, by carefully adjusting (lowering) the total MUs to be delivered, it is possible to reduce the OAR dose while maintaining satisfying target coverage. Acquisition of the patient breathing pattern for a few breathing cycles before the first beam being turned on is necessary for both CDRT and DRRT methods for initial phase-locking alignment and tumor motion prediction.^{7,13,25}

To determine whether the ordering of segments contributes to the discrepancy in 4D IMRT dose distribution between the planned and delivered doses, the aperture sequence of the initial SPO plan was resorted so that each beam was led by a smaller aperture. Since the same apertures and weights are used, the SPO plan is unchanged. When the resorted SPO plan was expanded to the 4D plan, the dose distribution of the modified plan and the DRRT delivery showed no noticeable difference, but the CDRT delivery for both 10% faster and 10% slower breathing resulted in significant decrease in target dose and noticeable reduction in critical organ doses. This result again supports the “reweighting” observation since

the segment weight was now shifted from larger segments to smaller ones when CDRT delivery strategy was used.

Figure 6(a) shows the MLC shapes in BEV at one beam that contains 6 segments, from the 7-beam IMRT plan for the first pancreatic case discussed above. Figure 6(b) shows the segment delivery time for this beam from the SPO plan, and what will be if DRRT or CDRT tracking strategy is used when the patient breathing becomes 20% faster or slower than on the planning day, and Fig. 6(c) illustrates the delivered segment weights for this beam when the preprogrammed 4D-IMRT plan is delivered using either CDRT or DRRT method for those two scenarios. In Fig. 6(a), segment 1 is the leading aperture in the sequence that covers the entire PTV (wire-frame view) and bears the largest segment weight [Fig. 6(c)]. Segments 2-6 are modulating segments with less weight. As shown in Fig. 6(b), the constant dose rate used in CDRT delivery is the same as in the 4D plan (indicated by the same width of the horizontal bars) in either faster or slower breathing scenario, and when the planned MUs for this beam are delivered, the total delivery time is the same, although MUs delivered for each segment are different from the plan. On the other hand, in DRRT delivery, adaptive dose rate regulation algorithm maintains the synchronization between the delivery of each segment and patient breathing phases. The changes in dose rate compared with the 4D plan are indicated by narrower (for slower breathing) and wider (for faster breathing) bars, respectively. Although the total delivery time will increase (decrease) accordingly if the patient breathing is slower (faster), the MUs delivered to each segment and to that beam will not change. As illustrated in Fig. 6(c), if the patient breathing becomes 20% faster than the planning day, CDRT delivery decreases the weight of segments 2-6 accordingly and adds the remaining weight to segment 1. On the contrary, if the patient breathing becomes 20% slower than the planning day, CDRT delivery adds more weight to segments 1-4. Segment 5 bears the remaining weight for that beam, which is less than its planned weight. The last segment in this sequence is skipped because planned MUs for this beam have been completely delivered already. In both scenarios, the larger leading segment(s) gain even more weight while all or some of the trailing segments lose weight, leading to increased dose to both the target and the surrounding tissues. In comparison, the relative weight of each segment in this beam will not change in either scenario if DRRT delivery is applied, since the DRRT algorithm makes sure that MUs for each phase/segment are delivered as planned.

In order to compensate the reweighting effect due to the interplay between the irregularity of patient breathing frequency and the constant dose-rate delivery, several strategies are proposed here. Besides the approach suggested above, i.e., adjusting the total MUs from the plan before the start of each treatment to obtain the same target coverage, another approach is to abide with the MUs delivered by each segment. For CDRT, this can be realized by starting with a 3D-optimized segment and adaptively reshaping the aperture while tracking the dislocation of the tumor, delivering at a constant dose rate until the planned MUs are complete for

(a)

(b)

(c)

FIG. 6. (a, top) Optimized MLC aperture shapes in BEV at one beam from a 7-beam IMRT plan (pancreatic case 1). Surface view: GTV; frame-wire view: PTV. The sequence is led by two large apertures covering the entire PTV. (b, bottom left) Segment delivery time as planned for this beam and delivered using CDRT and DRRT strategies, when treatment day breathing is either 20% faster or slower. The total delivery time from CDRT is the same as planned since the same constant dose rate is used. The DRRT method adaptively adjust the dose rate, hence the segment delivery time changes to maintain the synchronization between patient breathing and the sequence of MLC apertures in either scenario. The narrower and wider bars in DRRT cases indicate adjusted dose rate according to changes in patient breathing period. (c, bottom right) Segment weights from the SPO plan, from DRRT delivery (no deviation from plan), and deviations due to breathing irregularities during CDRT delivery when patient breathing on treatment day is either 20% faster or slower. Notice the missing of segment 6 in the slower scenario, and the remaining weight being added to segment 1 in the faster scenario.

that segment. This strategy treats the target as a rigid body and the 4D dose distribution may not be as good as the one that considers the tumor deformation, as has been demonstrated by Gui *et al.*¹⁴ On the other hand, if a preprogrammed 4D sequence that includes the tumor deformation is to be used, redundant MLC shapes have to be designed in the planning phase for CDRT delivery, allowing termination of delivery at

a respiration phase different from what has been planned. In this case, beam-hold is triggered if the planned MUs for a given segment have been completed at a certain phase, and the remaining apertures in the sequence for this segment are skipped. Dose distribution from such a strategy should be very close to that of the initial 4D plan because the segment weight is not altered. However, since the MUs delivered to each

respiration phase are different from the initial 4D plan, 4D dose calculation and accumulation for each fraction is needed to verify the delivered plan quality. A drawback of the second strategy is that the ending phase for each segment is not predictable, thus beam-hold is necessary before the start of next segment at the alignment phase. This leads to additional elongation of effective treatment time, and because the ending segment is nonpredictable before delivery, the approach of sequence resorting and optimization cannot be applied to reduce the total intersegment time.¹⁹

III.C. Effect of breathing amplitude variation on DRRT and CDRT delivery

The effect of interfractional variation in patient breathing amplitude on the dose distribution when a 4D plan is delivered using DRRT and CDRT strategies was simulated. The preprogrammed 4D aperture sequences based on planning CT and regular-breathing mode were applied to a second set of 4D-CT representing treatment day situation when significant change in breathing amplitude could be identified. For both DRRT and CDRT deliveries, the variation of target motion amplitude on treatment day compared with that on the planning day was chosen to be within $\pm 20\%$, as suggested by Han-Oh *et al.*¹⁹ The variation in breathing period was again intentionally set as either 10% faster or 10% slower than the planning day. In the DRRT delivery, dose rate regulation is based on the breathing period variation, but can be modified to compensate extreme discrepancies in amplitude variation. In case that the target motion exceeds the maximum amplitude in planning CT, a beam-hold is triggered and maintained until the target returns within the planning range and beam-on is restored. This strategy introduces dosimetric tracking error in DRRT tracking and is subject to improvement. In the CDRT delivery, planned aperture sequence and shapes are delivered as is, but the apertures are repositioned in each phase according to the new location of target in the treatment day CT. The capability of real-time reshaping of the MLC segments enables the CDRT method to compensate the interfractional and intrafractional variations of target motion magnitude. Figure 7 shows the cumulative DVHs for a lung case plan (prescription dose: PTV mean dose = 66.6 Gy) being delivered using DRRT and CDRT methods in comparison with the initial 4D plan. The second set of CT on which the delivered dose was calculated showed a decrease of 23% in tumor motion amplitude compared with the planning set of CT of this patient. The change in tumor motion amplitude for this case is slightly larger than the $\pm 20\%$ criterion, but is selected as an eligible patient for DRRT treatment for evaluation purpose. For the faster and slower scenarios, both tracking deliveries in the new CT showed similar trends as presented in Fig. 3: the CDRT delivery resulted in increased PTV and OAR doses, while the DRRT delivery resulted in dose distribution closer to the 4D plan. If the dose volume histograms of CDRT deliveries are renormalized at the PTV mean dose, the two tracking strategies showed little difference in either target or OAR dose. This result indicates that variations in the patient breathing period play a more critical role than the variation

FIG. 7. 4D cumulative DVHs resulting from DRRT (thin solid) and CDRT (medium solid: 10% faster breathing; medium dashed: 10% slower) tracking methods delivered to a second set of 4D-CT in comparison with 4D plan (thin solid) for a lung tumor case. The treatment day target motion amplitude is 23% less than the planning day for this case.

in breathing amplitude, as long as the latter is within $\pm 20\%$ of the maximum amplitude in planning CT. Compared to the 4D-plan, noticeable decrease in target coverage and increase in lung dose was observed in the DVHs from DRRT delivery and the renormalized DVHs from CDRT delivery. These deviations are attributed to the difference of target size and shapes as well as associated change in the volume of lungs between the two 4D-CT sets used for planning and delivery, respectively. As discussed earlier, the DVHs from CDRT delivery are similar to those from DRRT delivery if they are renormalized to the target mean dose, and can be achieved by using the redundant-aperture strategy or by reducing the fractional MU in the plan using the curves shown in Fig. 5 as a “role-of-thumb” guide.

IV. CONCLUSIONS

We compare the capability of dealing with irregular patient breathing using DRRT and CDRT tracking methods in delivery of preprogrammed 4D IMRT plans. The 4D plans are extended from single-phase optimized step-and-shoot IMRT plans using SAM algorithm based on tumor displacement and deformation revealed by 4D-CT. We simulate lung and pancreatic tumor cases with breathing period during treatment being slower or faster than the stable pattern used for planning, and with patient breathing amplitude being greater or less than planning day. Interplay between patient breathing and tracking strategies are accounted for to determine the monitor units delivered for each segment and on individual phases. Deformable image registration is applied to obtain the cumulative dose on reference phase for comparisons between 4D plan and delivery and that between deliveries using the two tracking strategies. The two tracking methods show significant differences in target and OAR dose distributions when the preprogrammed 4D-IMRT plans are delivered and patient breathing irregularities are compensated in different approaches. For all the cases studied, DRRT tracking realizes the dosimetric goals as expected from the 4D plan because it is able to deliver the planned MLC sequence with the

planned weightings. CDRT delivery shows noticeable dose difference between planned and delivered dose histograms, due to the shifts of segment weights depending on aperture sequencing when the breathing periods are different but beam MUs are conserved. If the total MUs for each treatment fraction can be adjusted, or segment MUs can be conserved using approaches such as the redundant-aperture strategy during constant dose-rate tracking delivery, the 4D dose distribution from these two tracking methods can be compatible. Overall, the DRRT method is more effective and dosimetrically more accurate than the CDRT method in delivering preprogrammed 4D-IMRT plans that are generated from 3D IMRT plans by taking into account both the tumor motion and the tumor deformation.

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