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Four-dimensional planning for motion synchronized dose delivery in lung stereotactic body radiation therapy

Hidehiko Tachibana and Amit Sawant*

University of Texas Southwestern Medical Center, Dallas, USA

Abstract

Background and purpose—To investigate a weighted four-dimensional (W-4D) treatment planning strategy based on the greater clinical advantage of the conformal over the intensity-modulated technique in lung stereotactic body radiotherapy (SBRT).

Material and methods—Two planning strategies (individual-phase 4D [IP-4D] and W-4D) were evaluated in eighteen lung SBRT patients. The IP-4D plan can deliver a constant fluence during whole respiratory phases. The W-4D plan's key concept was to escalate (or reduce) fluence using a 4D optimization algorithm when the tumour target was out-of-line (or in-line) with an organ-at-risk. The fluence was converted to a dynamic multi-leaf collimator leaf sequence for deliverable 4D irradiation.

Results—In all patients, the W-4D plan enabled planning tumour volume conformity comparable to the IP-4D plan. The W-4D plan yielded a significantly lower maximum dose than the IP-4D plan for the spinal cord (−11%; $p < 0.01$), oesophagus (−14%; $p < 0.01$), heart (−22%; $p = 0.01$) and stomach (−23%; $p = 0.07$), and a lower mean dose to liver (−19%; $p = 0.18$) while maintaining the mean dose to lung (−1%; $p = 0.23$).

Conclusions—W-4D is a robust, practical planning approach that achieves significant dose sparing relative to non-time-resolved tracking; it may be of greater clinical benefit in radiotherapy than the spatially intensity-modulated 4D approach.

Keywords

Motion management; Lung; SBRT; Robust 4D treatment

Respiratory motion causes significant geometric and, therefore, dosimetric uncertainties in lung cancer radiotherapy [1,2]. The impact of such uncertainties is amplified in hypofractionated regimens such as lung stereotactic body radiotherapy (SBRT). A variety of techniques for respiratory motion management have been described in the literature [3]. These include defining motion-inclusive margins, target immobilization, respiratory gating and real-time motion tracking. A common theme among these approaches is to treat motion as a hindrance and try to mitigate its effect. The aim of the present study was to present a

*Corresponding author at: University of Texas Southwestern Medical Center, 5641 Southwestern Medical Avenue, Dallas, TX 75235, USA. amit.sawant@utsouthwestern.edu (A. Sawant).

Appendix A. Supplementary data

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novel 4D (3D + time) treatment planning approach that uses respiratory motion to our advantage, as an additional degree of freedom rather than as a constraint.

Investigations regarding 4D planning for multi-leaf collimator (MLC) tracking have been reported by several groups. A number of studies have reported the design and development of a deliverable 4D intensity-modulated radiation therapy (IMRT) planning method [4–6]. Several concepts have been proposed for 4D-volumetric modulated arc therapy (4D-VMAT) planning [7,8]. However, these approaches for 4D-IMRT and 4D-VMAT were not time-resolved. They only considered leaf constraints and accounts of translation and deformation of the tumour target over the respiratory phases. This was because dose optimization was performed using only a representative peak-exhale phase 4DCT, and generated one MLC sequence for the phase. Subsequently the MLC motion sequencer modified the other phase MLC sequences to fit the tumour translation and deformation. Nohadani et al. described a time-resolved 4D IMRT optimization where the fluence map is optimized across all four dimensions simultaneously [9]. However, the deliverability of this method was not verified, i.e., whether it is practically possible to achieve a sequence that can deliver the calculated fluence. In addition, if the complex 4D-MLC sequence can be computed, relative to conformal radiotherapy (CRT) the technique is susceptible to the unexpected event of irregular breathing because of the inherent weakness of intensity modulation. In a comparative study involving CRT, IMRT and VMAT for lung SBRT, CRT showed the best dose sparing for lung and spinal cord, with comparable target coverage for a tumour measuring $<70 \text{ cm}^3$ [10]. Regarding practical 4D irradiation, the CRT technique is robust and can provide more sparing of Organs at risk (OARs) while maintaining target dose coverage.

In the present study, we present a novel practical weighted-4D (W-4D) planning technique for conformal lung radiotherapy, developed around a commercial treatment planning system (TPS).

Materials and methods

Patient cohort

Eighteen lung SBRT patients treated at our institution between July 2008 and December 2012 were chosen based on their residual motion ($\leq 5 \text{ mm}$ after immobilization and/or abdominal compression) as assessed from 4DCT. There were fourteen patients with and four without abdominal compression. All patients were treated with three fractions of 18 Gy to a total dose of 54 Gy. Fig. 1 shows the characteristics regarding Planning Target Volume (PTV) location, tumour target volume and residual motion for all 18 patients. The mean volume was 60 cm^3 ($6\text{--}211 \text{ cm}^3$), and the average amplitude of tumour motion was 1 cm ($0.3\text{--}1.6 \text{ cm}$).

Planning with 4DCT simulation

All patients underwent 4DCT simulation acquired on a sixteen-slice Brilliance CT Big Bore helical scanner in conjunction with the Bellows abdominal pressure belt system (Philips

Healthcare, Andover, MA, USA). The ten individual-phase 4DCT datasets were sent to a dedicated workstation running the Eclipse TPS.

Photon beams (6 MV) directed from nine to thirteen fields were used to create two types of treatment plans, an equally weighted IP-4D and W-4D. All plans were normalized such that 100% of the dose covered 95% of the PTV.

IP-4D and W-4D methods

The two methods had several steps in common and are therefore discussed together. In each method, the gross tumour volume (GTV) was contoured on each of the ten phases of the 4DCT. For each phase, the PTV was defined as a 5-mm uniform expansion of the GTV. The 50% respiratory phase, corresponding to peak exhalation, was chosen as the reference phase on which normal structures were contoured. For each patient, ten separate plans were generated using the Eclipse TPS corresponding to the ten respiratory phases. For each plan, the number of beams and the beam angles were transferred from the corresponding clinically approved plan generated using the common internal target volume-based method. To minimize errors and/or beam holds caused by finite leaf velocity, the collimator angle for each field was set such that MLC leaf travel was parallel to the principal component of tumour motion in the beam's eye view (BEV) [11,12]. The MLC aperture for each field was determined by adding a uniform 5-mm margin to the PTV as seen in the BEV to achieve better conformity and heterogeneity for the PTV at each phase. For each patient, a total of $P \times J$ separate 3D dose distributions were calculated using an anisotropic analytical algorithm, version 10.0.28 (Varian Medical Systems, Palo Alto, CA, USA), where P represents the number of respiratory phases (10) and J is the number of beams (between 9 and 13). These dose distributions were exported from the Eclipse TPS and served as input to our inhouse 4D optimization software. Other inputs included the ten volumes comprising the 4DCT and anatomic structures (exported as DICOM RTStruct) contoured on the reference phase.

The spatial correspondence between the reference phase and the remaining phases was determined by calculating deformation vector fields (DVF) between each phase and the reference phase (end-exhalation) using the NiftyReg deformable image registration (DIR) package, which has been extensively validated in lung DIR studies [13]. Subsequently, the DVFs were used to deform the dose distributions for all other phases to the dose distribution of the reference phase.

For the IP-4D plan, the beam weights for each beam were equal over all respiratory phases; they were calculated as the beam weight derived from the corresponding beam of the clinically approved plan, and divided by ten respiratory phases. For each beam, the dose distribution at the reference phase and the deformed dose distributions at all other phases were scaled with the corresponding beam weights to generate the dose distributions for the individual phases. The dose distributions for all beams were then summed to generate the complete dose distribution for the IP-4D plan, and the summed dose distribution was superimposed on the reference-phase 4DCT with the anatomical structures using the Eclipse TPS.

For the W-4D plan, the beam weights for each beam were variable over all respiratory phases; they were determined using a dynamically penalized likelihood optimization algorithm, which performs an iterative calculation [14]. To perform the spatiotemporal optimization, the reference phase, its associated dose distribution and structures, and the deformed dose distributions from the other nine phases were loaded into our optimization software. Clinically prescribed dose-volume constraints were entered for each structure. The optimizer computed beam weights were used to scale the corresponding dose distributions so that the sum of the weighted dose distributions equalled the overall dose distribution for the W-4D plan. The overall dose distribution was superimposed on the reference-phase 4DCT. As described in the Results section, the optimization of beam weights with respect to spatial direction as well as respiratory phase allows respiratory motion to be exploited as an additional degree of freedom. For a given beam direction and respiratory phase, this strategy reduces (or increases) the beam weight, and therefore the monitor units (MUs), when the target is in line (or out of line) with a critical structure to achieve significant dosimetric advantage.

Leaf sequencing and deliverability

Because only conformal fields were involved, the MLC leaf sequence calculation was carried out independently from the optimization. The planning described above was performed using an ideal leaf sequence; that is, the MLC leaf velocity was assumed to be infinite. However, to practically deliver a 4D plan the leaf sequence needs to account for the mechanical limits of the MLC, which determine the maximum leaf velocity, and the maximum relative speed between the leaves and the tumour target. To generate such a deliverable MLC sequence, Ten DICOM-RT plan files from the ten plans, which included information on MU and leaf positions for each beam, were loaded into an in-house leaf motion calculator (LMC). First, for each beam, the LMC arranged the apertures, along with the associated MU, sequentially from phase 0–90%. Second, the LMC checked and iteratively adjusted the leaf positions such that the amount of travel for each leaf from one phase to the next (i.e., 0% → 10% ... 90% → 0%) lay within the maximum leaf velocity limits. Previously reported values of maximum leaf velocity for the Millennium MLC, $V_{\max}$ 3.5 cm/s, were used [15]. The deliverable leaf positions over all beams and all phases were exported to the Eclipse TPS and the corresponding deliverable dose distributions were calculated.

Statistical analysis

Differences in dosimetric endpoints for the W-4D method with respect to the IP-4D method were assessed using the Wilcoxon signed-rank test. Differences with $p < 0.05$ were considered statistically significant. Pearson's correlation was also applied for assessing the relationship between OAR dose reduction of the W-4D and PTV volume, PTV volume change during respiration and residual motion. All statistical calculations were performed using statistical software (Dr. SPSS II version 11.0.1J: SPSS Inc., Chicago, IL, USA).

Results

As an illustrative example, a comparison between the two planning methods for Patient 3 was performed as shown in Fig. 1. This patient, who had a right-lower-lobe tumour (GTV = 61 cc) and exhibited motion of 15 mm despite abdominal compression, represented the most challenging motion management case within our cohort. The DVH curves showed that both the IP-4D and W-4D methods achieved PTV coverage. The W-4D method achieved superior dose sparing as compared with the other method for serial (spinal cord, oesophagus and heart) as well as parallel (liver and stomach) organs. The use of motion as a degree of freedom in the W-4D method showed that the MUs for each beam varied as a function of the respiratory phase, thus allowing the optimization engine to exploit the temporal dimension and escalate (deescalate) the fluence when critical structures were out of line (or in line) with the beam.

Fig. 2 illustrates the deliverability of the W-4D plan for Patient 3 for three hypothetical situations: (i) an ideal case that assumed infinite MLC leaf velocity, and two realistic cases with a finite leaf velocity (3.5 cm/s); respiratory periods corresponding to (ii) typical breathing (4 s); and (iii) rapid breathing (2 s). As expected, for a given value of maximum leaf velocity, the number of leaves that failed to reach the planned positions increased as breathing became more rapid. However, for this particular patient, even a significant (simulated) increase in the rate of respiration did not appear to have a correspondingly significant dosimetric impact as illustrated in Fig. 2d, which presented DVH curves corresponding to the three cases shown in Fig. 2a–c.

Fig. 3 shows the relative differences with respect to the IP-4D method for the W-4D methods. The W-4D methods showed PTV coverage comparable to the IP-4D method with no significant differences in the conformity indices ($CI = D_{95\%}/D_{5\%}$). The W-4D method exhibited superior dose or volume sparing as compared with the IP-4D method for all normal organs, with the exception of the mean lung dose and V_{20}^{lung} (V_X indicates the % volume that receives a dose X Gy.) The W-4D plan yielded a significantly lower maximum dose than the IP-4D plan for the spinal cord (−11%; $p < 0.01$), oesophagus (−14%; $p < 0.01$), heart (−22%; $p = 0.01$) and stomach (−23%; $p = 0.07$), and a lower mean dose to the liver (−19%; $p = 0.18$) while maintaining the dose to the lung (−1%; $p = 0.23$). Fig. 4 shows another two examples of different MU trends during MLC tracking irradiation. MUs over the phases were stable in the patient whose tumour was located distally to the OARs (Fig. 4a). The tumour was close to several OARs and the intensities during the inspiration phase were higher than those during expiration phases (Fig. 4b). Table 1 details the number of the patients treated using the W-4D method who achieved a >5% dose sparing regarding the OARs. Medially located OARs, such as the heart, oesophagus and spinal cord, benefited significantly from use of the W-4D method.

The relationship between OAR dose reduction using the W-4D method and PTV volume, PTV volume change and residual motion was not statistically significant (Pearson's correlation coefficient < 0.5 ; $p = 0.05$).

Considered overall, more lung sparing was achieved using the W-4D method in patients with medium to large-sized lesions. The W-4D method seemed to show a greater dosimetric benefit relative to the IP-4D method in cases where the PTV was located in proximity to critical structures, across all ranges of motion.

Discussion

Most of the clinically used and investigational strategies for the management of respiratory motion aim to mitigate tumour motion. However, it is not always possible to accomplish this objective. For example, in the present study, despite the use of a state-of-the-art technique such as abdominal compression, tumour motion in the range of 0.5–1.5 cm was observed. In some cases, abdominal compression may not work regarding the limitation of the tumour motion, although of course compression would somewhat reduce this motion. Our results indicate that the W-4D approach would facilitate the compression method in limiting this motion. However, the W-4D method may not require the use of compression because it could cover extensive tumour motion even in the range of 1.5 cm, while maintaining plan robustness in terms of deliverability. A strategy that exploits rather than mitigates motion may achieve significant dosimetric benefits (e.g., >80% dose sparing in serial organs). Beyond these immediate dosimetric benefits, the W-4D approach may serve as an enabling tool for cases where the tumour is close to the OARs and lung SBRT is currently not recommended, such as centrally located tumours.

Currently there are three major tracking irradiation techniques, namely a gimbal based tracking using VERO, robotic based tracking involving the CyberKnife, and MLC tracking, which is a method used for general linacs. The theory of our W-4D technique could be applied to all of these techniques and deliverability using the constraint entailing the MLC motion velocity was demonstrated in our study.

The conformal 4D technique is considered to be robust in dealing with the patient's variable breathing pattern relative to the intensity-modulated 4D technique. Lung SBRT requires not only better tumour coverage, and better dose sparing for OARs, but also greater robustness with a higher feasibility of irradiation that complies with the planned dose distribution. According to several SBRT clinical trials, tumour size for the eligible patients is small within 3 or 5 cm maximum diameter. SBRT using the 3D-CRT method has achieved sufficiently acceptable patient outcomes [16]. The conformal 4D technique will be better concerning the accuracy of radiation delivery because the MLC sequence for the conformal 4D technique is composed of comparatively larger MLC apertures at any phase, and will cover almost the entire tumour volume at any phase. However, the MLC sequence used for 4-D IMRT is composed of small MLC apertures, and the tumour coverage may be susceptible to irregular respiration. This means that the accuracy of delivery would be more affected while small beams irradiate the tumour even with slight geometric variations. The W-4D technique is a practical and reliable method for generating sufficient dosimetric benefit in lung SBRT.

The 4D planning approach developed in the current study needs to be well integrated with real-time beam adaptation strategies such as MLC tracking [11]. The combined 4D planning

plus delivery aims to plan for all anticipated motion and to adapt in real-time (e.g., by interpolating closest apertures) to account for unanticipated motion. Such an approach will ensure that an optimal dose is delivered irrespective of anatomical motion and/or deformation of the tumour and surrounding organs.

While we check for the deliverability of the W-4D plan in terms of leaf velocity constraints, special software/firmware interfaces will have to be developed in collaboration with the linac vendors in order to load and execute an MLC leaf sequence that varies with dose fraction as well as the real-time respiratory phase. The linac delivery system will also need to accommodate some form of real-time dose rate modulation in order to deliver different numbers of MUs as a function of respiratory phase. Such variable dose rate technology is currently used in volumetric modulated arc therapy on the TrueBeam and other platforms from Varian.

We have developed and validated a lung SBRT treatment planning paradigm that uses respiratory motion to optimize the plan along the temporal dimension in addition to the three spatial dimensions. Early results indicate that this strategy can yield significant dosimetric advantages in terms of OAR sparing relative to the no-time-resolved tracking method; it may also be a more practical approach from the viewpoint of robustness of the actual irradiation than intensity-modulated tracking irradiation. Our planning and optimization tools have been developed around a commercial treatment planning platform to facilitate a clear path to clinical translation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Conflict of interest

Amit Sawant receives research support from VisionRT Ltd., London, UK and Varian Medical Systems, Palo Alto, CA, USA.

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Fig. 1.

(a) Dose distributions and (b) dose-volume histograms for nine-field individual-phase 4D (IP-4D) and weighted-4D (W-4D) plans for Patient 3. (c) Number of monitor units (MUs) as a function of phase is shown for each beam for the W-4D plan. The modulation of MUs for the W-4D plan is a result of the optimization process (Eq. (3)), which enables the use of respiratory motion as an additional degree of freedom.

Fig. 2.

Multi-leaf collimator sequence for a weighted-4D (W-4D) plan illustrating (a) an ideal sequence with no leaf velocity constraints, and deliverable sequences for respiratory periods of (b) 4 s and (c) 2 s in Patient 3. The positions of the leaves shown in green represent the ideal positions. The overlaid positions shown in red represent the achievable positions, given the finite leaf velocity and respiratory period. (d) Dose volume histogram curves corresponding to the leaf sequences depicted in (a)–(c). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 3.

Relative dosimetric differences for the weighted-4D (W-4D) method with respect to the individual-phase 4D (IP-4D) method. The data are presented in the form of box-and-whisker plots, where the horizontal line in the centre of each box represents the median. The box extends from the first to the third quartile, and the whiskers extend to cover the minimum and maximum values. Because the liver was involved in only two of the 18 patient cases, the D_{mean} and V20 for the liver are shown as absolute differences. All other values are shown as percentages. The W-4D method shows a significant difference for spinal cord, oesophagus and heart.

Fig. 4.

Comparison of monitor units for the weighted-4D (W-4D) plans of Patient 17 (a) and Patient 10 (b). Tumours located distantly to the organs at risk (OARs) do not require time-resolved intensity modulation; however, in cases where the tumour was located close to the OAR the inspiration phase was effective, because the tumour and the OARs were further away from each other at the inspiration phases than at the expiration phases.

Table 1

Number of patients achieving a >5% dose reduction for the organs at risk.

Dosimetric parameter	Number of patients	Dosimetric parameter	Number of patients
Lung (mean)	3	Heart (mean)	11
Lung (V ₂₀)	0	Liver (mean)	2
Spinal Cord (max)	13	Liver (V20)	1
Oesophagus (max)	14	Stomach (max)	6
Heart (max)	10		11