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Assessing Four-dimensional Radiotherapy Planning and Respiratory Motion-induced Dose Difference Based on Biologically Effective Uniform Dose

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Abstract

Four-dimensional (4D) radiotherapy is considered as a feasible and ideal solution to accommodate intra-fractional respiratory motion during conformal radiation therapy. With explicit inclusion of the temporal changes in anatomy during the imaging, planning, and delivery of radiotherapy, 4D treatment planning in principle provides better dose conformity. However, the clinical benefits of developing 4D treatment plans in terms of tumor control rate and normal tissue complication probability as compared to other treatment plans based on CT images of a fixed respiratory phase remains mostly unproven. The aim of our study is to comprehensively evaluate 4D treatment planning for nine lung tumor cases with both physical and biological measures using biologically effective uniform dose $\overline{D}$ together with complication-free tumor control probability, P_+ . Based on the examined lung cancer patients and PTV margin applied, we found similar but not identical curves of DVH, and slightly different mean doses in tumor (up to 1.5%) and normal tissue in all cases when comparing 4D, $P_{0\%}$, and $P_{50\%}$ plans. When it comes to biological evaluations, we did not observe definitively PTV size dependence in P_+ among these nine lung cancer patients with various sizes of PTV. Moreover, it is not necessary that 4D plans would have better target coverage or higher P_+ as compared to a fixed phase IMRT plan. However, on the contrary to significant deviations in P_+ (up to 14.7%) observed if delivering the IMRT plan made at end-inhalation incorrectly at end-exhalation phase, we estimated the overall P_+ , P_B , and P_I for 4D composite plans that have accounted for intra-fractional respiratory motion.

Keywords

Four-dimensional treatment planning; Biologically effective uniform dose; Treatment planning; Radiobiological objectives; Organ motion

Introduction

With great advances in highly conformal treatment methodologies such as intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT), the most significant problem for today's radiotherapy is management of internal organ motion, which occurs both inter-fractionally and intra-fractionally (1-6). The inter-fractional organ motion can be corrected promptly by aligning the patient position using the bony anatomy and/or internal fiducial markers, which is performed right before the daily treatment. Intra-fractional organ motion, on the other hand, still remains mostly unsolved. Respiratory motion, for example, is one of the most substantial intra-fraction organ motions that introduce undesired error during radiation therapy for lung cancer patients. In current radiation therapy, the practical solution accounting for respiratory motion is to add uniform, population based margins to the clinical target volume (CTV). Expanded margins around the CTV, however, usually result in higher doses to normal tissues close to the target. Consequently, to accommodate respiratory motion with suitable protection to normal tissues around the target, four-dimensional (4D) radiotherapy (7-9) is considered as a feasible and ideal resolution.

The workflow of 4D radiotherapy includes 4D computed tomography (4DCT) acquisition and 4D treatment planning followed by 4D delivery. 4DCT are often obtained while the patient breaths freely and therefore the extent of respiratory motion and deformation is captured. To completely describe tumor movement and deformation from phase to phase, deformable image registration needs to be applied after 4DCT acquisition (10). Deformable image registration enables the mapping of dose from multiple anatomic maps at different instants of time to a common geometry. Then, similar treatment plans for different respiratory phases are created based on contours determined specifically for these phases. After the dose distributions of various respiratory phases are established by the treatment planning system, the final 4D composite dose distribution can be calculated by summing up all dose distributions and applying the proper weighting factors to discrepant phases. Although 4D treatment planning in principle provides more accurate dose calculation when organs move during treatment (10), the biological benefits (such as higher tumor control probability) of developing 4D treatment plans as compared to other treatment plans based on CT images of a fixed respiratory phase remains mostly unproven.

Biologically effective uniform dose ($\overline{\overline{D}}$) was defined as the uniform dose that causes the same tumor control probability or normal tissue complication rate as the actual dose given to the patient (11,12). In contrast to other biological dose indices (*e.g.*, equivalent uniform dose, EUD), $\overline{\overline{D}}$ calculation is not model dependent and can be applied to evaluate plans that have more than one target or organs at risk. $\overline{\overline{D}}$ can be used to estimate the effectiveness of radiation therapy in terms of benefit from tumor control and injury to normal tissues. Furthermore, the $\overline{\overline{D}}$ concept directly associates a dose with treatment outcome in terms of the complication-free tumor control probability (P_+) (12).

The goal of this study is to comprehensively evaluate 4D treatment planning for thoracic tumors with both physical and biological measures using $\overline{\overline{D}}$ together with P_+ . Furthermore, comparisons between the 4D treatment plan and MLC-based IMRT plans for fixed respiratory

phases (*i.e.*, at end-inhalation and end-exhalation) were performed to estimate the benefit of 4D planning using a more clinical outcome related approach.

Materials and Methods

4D CT Image Acquisition

CT images for each patient were acquired by using a GE Lightspeed Qx/i 4-slice scanner (GE Medical systems, Milwaukee, WI) in axial cine mode. Patients were coached to breath freely and quietly. To generate spatial and temporal coincidence image data, patient breathing traces were recorded with the Varian Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA) during CT scanning. In brief, the RPM system acquired respiratory motion information by monitoring the patient's abdominal surface motion (8,9). Then, Advantage 4D software (GE Medical systems, Milwaukee, WI) was used to sort reconstructed axial images into ten respiratory phases according to RPM respiratory data (9). The sorted image sets were labeled by the percentage of the respiratory cycle, in which $P_{0\%}$ corresponded to end-inhalation and $P_{50\%}$ represented end-exhalation. In this study, we chose end-inhalation, $P_{0\%}$, as the reference phase for our 4D treatment plans to avoid motion artifacts on 4D CT images (8,10).

Patients

Eight lung cancer patients were randomly selected as candidates for this study. All patients received a fundamental radiotherapy for lung cancer, and had 4DCT images acquired prior to treatment. For each patient, a radiation oncologist delineated the target and the organs at risk manually on each respiratory phase of the 4DCT data sets (*i.e.*, from $P_{0\%}$ to $P_{90\%}$, in total, 10 phases). The gross target volume (GTV) was expanded by 1.5 cm uniformly to form the planning target volume (PTV) (13). Table I shows for all the patients the gender, age, the exact treatment site, and the PTV volume. Among the nine cases we listed in Table I, Patient 9 represents an anonymised respiration-correlated 4DCT image set created for 4D related image researches (14). This set of 4DCT images is freely available for download (15).

Treatment Planning and Image Registration

For each of the nine patients, ten MLC-based IMRT plans were developed for different respiratory phases using the Philips (ADAC) Pinnacle³ treatment planning system (ADAC Laboratories, Milpitas, CA, v 8.0d). In other words, each lung cancer patient in this study had ten IMRT plans of fixed-phases (from $P_{0\%}$ to $P_{90\%}$) plus a 4D composite plan made with $P_{0\%}$ phase as the reference phase. The general prescription of all plans is to provide 60 Gy to at least 95% of the PTV. Dose constraints to organs at risk are listed in Table II. All plans were created independently, and were designed and optimized according to the same radiation oncologist's recommendations and dose constraints. In cases with larger PTVs, the dose to healthy lungs was of primary consideration. A $1.96 \times 1.96 \times 2.5 \text{ mm}^3$ dose-grid resolution was used to compute dose within the whole volume of 3D image sets for each plan (for each respiratory phase).

For the purpose of image registration, sorted 4DCT image sets of ten respiratory phases were post-processed using an in-house developed software, APT4D (16). In order to save memory space, these CT images were down-sampled by a factor of 2 to a size of 256×256 with a pixel resolution of $1.96 \times 1.96 \text{ mm}^2$, while keeping the cranial-dorsal resolution of 2.5 mm. The deformable image registration method adopted in APT4D was proposed by Thirion (17). The local deformable registrations from CT images of the moving phases to images of the reference phase (*i.e.*, $P_{0\%}$ in our study) were performed iteratively using the demons algorithm (17). As suggested from previous research (16), a total of 150 iterations were sufficient to get optimal convergence of the displacement between the fixed and moving images. From results of

deformable registration, displacement maps of moving phases to the reference phase were recorded as deformation fields accordingly.

Deformation fields of image registrations for nine moving respiratory phases were then applied to transform 3D dose matrices of corresponding IMRT plans. To compose a final 4D dose distribution, registered 3D dose matrices of ten respiratory phases were averaged by applying equal weighting to each phase. For physical dosimetry evaluation, the 4D composite treatment plan of each patient was compared with the IMRT plans of $P_{0\%}$ (reference phase in this study) and $P_{50\%}$ in terms of dose statistics (*i.e.*, maximum, mean, and minimum doses) and dose volume histogram (DVH) for the nine lung cases.

Biologically Effective Uniform Dose Evaluation

The uniform dose that causes the same tumor control probability or normal tissue complication rate as the actual dose given to the patient was evaluated using $\overline{D}$ (11,12). This general definition of $\overline{D}$ can be expressed as the equation below:

$$P(\overline{D}) = P(\vec{D}) \quad [1]$$

The radiobiological model that was used to describe the dose-response relation of tumors and organs at risk was linear-quadratic-Poisson model (18,19):

$$P(D) = \exp \left\{ -N_0 e^{(D/D_{50})(e\gamma - \ln \ln 2)} \right\} = \exp \left\{ -e^{e\gamma - \alpha nd - \beta nd^2} \right\} \quad [2]$$

where the $P(D)$ is the probability to control the tumor or induce a certain injury to an organ that is irradiated uniformly with a dose D . Since this model takes into account the fractionation effects that are introduced by the irradiation schedule, d , (equals to D/n) is the dose per fraction, and n is the number of fractions. D_{50} is the dose which gives a response probability of 50% and γ is the maximum normalized value of the dose-response gradient. Variables α and β are the fractionation parameters of the model and account for the early and late effects expected, respectively. The dose-response parameters of the target and organs at risk used in this study were listed in Table III (20-27).

To evaluate the biological effectiveness of the 4D composite plan, the concept of P_+ and $\overline{D}$ were used (12). P_+ is the probability of achieving tumor control without causing complication to normal tissues. In addition, the probability of obtaining benefit from 4D treatments (*i.e.*, tumor control) is denoted as P_B , whereas the probability of causing severe injury to normal tissue is denoted as P_I . In this study, the main objective of using physical dose indices (*e.g.*, DVHs) for plan evaluation was to estimate the normal tissue tolerance against the optimal target dose needed. The actual probabilities of benefit and injury as well as P_+ were carried out using an in-house developed software. Moreover, comprehensive comparisons of the composite 4D IMRT plan against the IMRT plans of fixed phase, $P_{0\%}$ and of $P_{50\%}$, were conducted physically and biologically.

Results

It should be noted that 4D composite plans, $P_{0\%}$ and $P_{50\%}$ plans compared physically and biologically in this study were all MLC-based IMRT plans.

Physical Dose Analysis: DVH

Figure 1 demonstrates the cumulative DVHs of three representative patients with small (patient 1), medium (patient 8), and large (patient 3) PTV sizes, respectively. Each set of DVH curves of the 4D composite plans and P_{50%} plans were superimposed with the results of the reference-phase, *i.e.* P_{0%}, plans to compare target coverage and normal tissue sparing among these three treatment plans. As shown in Figure 1a, PTV coverage of the P_{50%} plan was inferior compared to both 4D composite and P_{0%} plans while keeping the same protection to normal tissues as the other two. As a result, a part of the PTV volume might be missed if delivering reference-phase plan at other moving respiratory phases. On the other hand, the DVH of the 4D composite plan showed the exact PTV coverage, which is slightly substandard to the reference-phase plan, if we can deliver this 4D composite plan perfectly. The suboptimal DVH curve in PTV of the 4D plan reflected dose perturbations due to respiration as a function of time. In contrast with Figure 1a, Figure 1b illustrated different sparing of the organ at risk, heart, in these three IMRT plans when they had the same optimal PTV coverage. The results in Figure 1b show motion induced effects on the discrepant doses of critical organ(s) proximal to the target during radiation treatments. As shown in Figure 1c, nevertheless, there was no significant difference found in the DVHs of 4D plan, P_{0%} and P_{50%} plans from the patient with large PTV size.

Physical Dose Statistics

Tables IV-VIII summarizes mean, maximum, minimum doses, and standard deviations (SD) in PTV, spinal cord, esophagus, heart, and healthy lung, respectively. Mean doses in PTV of these nine lung patients as shown in Table IV fulfilled prescription dose with some differences among the 4D composite plan, P_{0%} and P_{50%} IMRT plans. The dose variety in the target volume as indicated by the SD in Table IV was quite comparable between the 4D plan and reference-phase, P_{0%} plan, but was slightly larger in some cases of comparisons between the 4D plan and P_{50%} plan (*e.g.*, in patient 6).

In general, the physical dose statistics of the 4D composite plan was similar to that of reference-phase IMRT plan in most of these nine cases. The physical dose results of the 4D plans lied between the P_{0%} IMRT plan and the P_{50%} IMRT plan in most patients. However, comparing the doses of the P_{50%} plans with those of P_{0%}, some differences were found in mean (up to 11 Gy in heart, patient 8), maximum (up to 35 Gy in esophagus, patient 8), and minimum (up to 26.7 Gy in PTV, patient 4) doses as well as in SD (up to 10.3 Gy in esophagus, patient 8) of the target and normal tissues.

Biological dose evaluation: $\overline{\overline{D}}$

Figure 2 shows biological evaluation in PTV using tumor control probability (TCP) as well as $\overline{\overline{D}}$ compared with results of physical dose index, mean dose, for the 4D composite plan, P_{0%} and P_{50%} IMRT plans. Based on mean dose and dose distribution in the PTV along with biological parameters acquired from previous researches, the corresponding uniform dose in terms of $\overline{\overline{D}}$ as well as the TCP could be determined in these lung cancer patients for the different IMRT plans (12). From the results indicated in Figure 2a, the TCPs of these nine patients were relatively high for the dose prescription, which was used in these treatment plans. Comparing the TCPs of the 4D plan with those of the P_{0%} and P_{50%} plans, there was no major difference found for most of the patients. For patient 4 and patient 6, the TCPs of P_{50%} plans were about 4% and 6%, respectively, lower than the TCPs of the 4D and P_{0%} plans. These lower TCPs of P_{50%} IMRT plans might be attributed to larger dose variations in the PTVs.

Figures 3-6 illustrates the biological evaluation in spinal cord, esophagus, heart, and healthy lung, respectively, using normal tissue complication probability (NTCP) as well as $\overline{\overline{D}}$ pared with results of physical dose index, mean dose, for the 4D composite plan, P_{0%} and P_{50%} IMRT

plans. From the results indicated in Figure 3, although mean dose in spinal cord varied from patient to patient, NTCP of all patients were approximately zero calculated with the endpoint of myelitis necrosis in our study. Deviations in mean (and max) doses of the 4D, P_{0%} and P_{50%} IMRT plans resulted in the same $\overline{D}$ and thus the same complication rate (*i.e.*, ~0% in all cases) in spinal cord.

In Figure 4, it is shown that all plans of patient 2 had much higher mean doses in esophagus (up to 35 Gy difference) as compared to other patients. The higher mean dose in esophagus was because the location of tumor in patient 2 was right next to the esophagus, resulting in up to 10 Gy higher $\overline{D}$. Therefore, patient 2 had much higher NTCP (up to 15.7%) than the other patients. When compared NTCP among the 4D, P_{0%} and P_{50%} plans, there was no significant difference discovered for all patients.

Figure 5 demonstrates that patient 2, 6, and 8 had higher mean doses in heart compared to other patients. Patient 8, however, had less deviation in the volume of heart (also from results of Table VI), contributing to less NTCP and thus lower $\overline{D}$. As compared 4D and P_{50%} plans to P_{0%} plan of patient 8, up to 11 Gy difference in mean doses resulted in up to 0.7% deviation, which is negligible, in NTCP.

From the results shown in Figure 6, patient 7 had much higher mean doses (up to 9 Gy higher) in 4D, P_{0%} and P_{50%} IMRT plans as compared to other patients, resulting in a high $\overline{D}$ and, furthermore, up to 50% higher NTCP. This much higher NTCP observed in lung of patient 7 was related to the biological parameters of the early radiological pulmonary complications we applied in this study (26,27).

Biological analyses of the 4D, P_{0%}, and P_{50%} IMRT plans in small (patient 1), medium (patient 8), and large (patient 3) PTV using complication-free tumor control probability, P₊, are illustrated in Figure 7. Based on the physical measures using DVH shown in Figure 1 and the results of Tables IV-VIII plus the dose-response probabilities for the target and normal tissues demonstrated in Figures 2-6, Figure 7 illustrates comparisons of overall clinical effectiveness among the 4D plan, P_{0%} and P_{50%} IMRT plans. In this figure, in addition to P₊, we calculated the probability of obtaining benefit from radiation treatments (*i.e.*, tumor control), P_B, as well as the probability of causing injury to normal tissues, P_I, for the 4D, P_{0%}, and P_{50%} IMRT plans. It should be noted that the $\overline{D}$ on the X axis of Figure 7 represents the biologically effective uniform dose calculated based on the radiological characteristics of the target (usually denoted as $\overline{D}_B$). When using $\overline{D}_B$ on the dose axis, the dose-response curves are normalized to $\overline{D}_B$ forcing the response curves of P_B of these three plans coincide (12). As a result, the plan, which has the highest P₊ and lowest P_I as shown in Figure 7 would be considered superior to the rest of plans. Figure 7a shows results of patient 1 with small PTV. From the DVH diagram shown in Figure 1a, it seemed that P_{0%} plan had better target coverage than the other two. The DVHs of normal tissues in these three plans, on the other hand, were all very close. When evaluating the P₊ of the 4D, P_{0%} and P_{50%} plans for patient 1, it turned out that P_{50%} IMRT plan was slightly superior compared to the other plans, because of the lowest P_I value among these three plans. For patient 8 with medium PTV, all three plans had very close mean doses (4D, 59.7Gy; P_{0%}, 60.0 Gy; P_{50%}, 59.6 Gy) from the results in Table IV. However, as illustrated in Figure 1b and Table VII, the doses in heart from three plans varied considerably (mean dose for 4D, 14.6 Gy; P_{0%}, 6.7 Gy; and P_{50%}, 17.7 Gy). Therefore, the results in Figure 7b showed a lowest P₊ with highest P_I in P_{50%} IMRT plan. Figure 7c demonstrates the results of patient 3 with large PTV. From Figure 1c, the DVH curves of the target and normal tissues for the three plans were very close to each other. In Figure 7c, however, P_{0%} was the best plan with the highest P₊ and lowest P_I. While the physical measures of the three dose distributions were similar, the

substantial changes in P_+ and BEUD indicated significant differences in the clinical effectiveness of these three plans.

Discussion

The present study aims to clinically interpret the value of 4D radiation therapy using biological measures in addition to physical dose statistics. The biologically effective uniform dose that we used in this study converted the information of isodose distribution and DVH into more clinically relevant outcomes, expected benefit of tumor control and possible injury to normal tissues. Comparisons among 4D treatment plan and fixed-phase IMRT plans at end-inhalation ($P_{0\%}$) and end-exhalation ($P_{50\%}$) using $\overline{D}$ allowed us to predict the clinical effectiveness owing to respiratory motion induced dose uncertainty.

Several studies have accurately estimated the effect of motion on lung treatments delivered using conventional imaging and planning (2,3,28). Additionally, investigations have also been done to show improvements achieved when 4DCT and thus 4D treatment planning was incorporated into treatment procedures (5,8-10,29). Flampouri *et al.* (29) has suggested that 4D treatment planning should be performed for patients with tumor motion larger than 12 mm and/or with severe image artifacts in free breathing helical CT. Figure 8 demonstrates the observed volumetric variations of manually contoured PTV for the lung tumor at different respiratory phases for the nine lung patients. The results in this figure implied the rigid and non-rigid tumor motion from phase to phase for these lung cancer patients. Patient 6, for example, had large volume deviation from $P_{0\%}$ to $P_{50\%}$ (25% difference in volume size). From our physical results of Table IV, the mean dose differences among the 4D, $P_{0\%}$ and $P_{50\%}$ plans were not significant (59.7 ± 1.5 Gy, 59.9 ± 1.2 Gy, and 58.0 ± 4.7 Gy, respectively). From the results of Figure 2, however, the $\overline{D}$ of the 4D, $P_{0\%}$, $P_{50\%}$ plans were significantly different (59.1 Gy, 59.7 Gy, and 51.8 Gy, respectively), resulting in 98.8%, 98.9%, and 93.0% tumor control rates, respectively.

Variations in P_+ , P_B , and P_I among the 4D composite plan, $P_{0\%}$ and $P_{50\%}$ IMRT plans were summarized in Table IX for the nine lung cancer patients. In this table, the deviation amongst the 4D plan, $P_{0\%}$ and $P_{50\%}$ IMRT plans is shown quantitatively. Patient 2 among these nine cases had the most significant differences in terms of complication-free tumor control rate when comparing these three plans. From the results of physical dose statistics, the mean doses of the 4D plan, $P_{0\%}$ plan and $P_{50\%}$ plan in the target (59.8 ± 1.0 Gy, 59.6 ± 1.6 Gy, and 58.7 ± 1.3 Gy, respectively) and normal tissues (*e.g.*, in esophagus: 41.2 ± 21.7 Gy, 41.0 ± 22.1 Gy, and 43.2 ± 21.5 Gy, respectively) were very close. Although physically the three dose distributions were similar, the discrepancies of P_+ (8.2%, -6.5%, -14.7% between 4D and $P_{0\%}$, 4D and $P_{50\%}$, and $P_{0\%}$ and $P_{50\%}$, respectively) indicated in Table IX demonstrated that their effectiveness differs significantly.

Major uncertainties involved in the workflow of the 4D treatment planning in this study include variations in contouring of the target (and its margin determination) and organs at risk on 4DCT images, which suffer less from artifact but not artifact-free (29), as well as errors in deformation image registration perform on moving phase images registered to images at reference phase (9). For each of the nine patients in our study, who had ten respiratory phase 4DCT image sets, the GTV and normal tissues were manually delineated and determined by the same oncologist one phase following the other. Contours of normal tissue especially at the boundaries that are generally plagued with motion artifacts, such as the boundary between lung tissue and diaphragm were evaluated by the same physician to minimize errors in delineation. A uniform margin of 1.5 cm around GTV we used for all plans in all nine patients was suggested by Flampouri *et al.* (29). They concluded that no significant improvement on tumor coverage with 0.5 cm increase on the PTV margin (29). As for errors in deformable image registration, to our

best knowledge, there is no perfect image registration algorithm for all anatomical situations. Every deformable registration algorithm has tradeoffs between the accuracy and the computation efficiency. From our previous studies, the deformable image registration algorithm we adapted in the software, APT4D, performed non-rigid registration adequately (16). For lung cancer patients, correlation coefficient calculated after image registration of end-inhalation to end-exhalation 4DCT volumes ranged from 0.992 to 0.999 (16). Concerning variations in the $\overline{D}$ evaluation, the calculation of dose-response probabilities of the tumors and normal tissues was based on recently derived data (26,27). The fact is that the radiobiological parameters used by different models are now more reliable as compared with similar data in the past (30).

Based on the lung cancer patients that were chosen and the PTV margin that was applied, we found similar but not identical curves of DVH, and slightly different mean doses in tumor and normal tissue in all cases when comparing 4D, P_{0%} and P_{50%} plans. When it comes to biological evaluations, Table IX summarizes substantial deviations in P₊ (in patient 2, 3, and 4; up to 14.7%), P_B (in patient 4 and 6; up to 5.9%), as well as in P_I (in patient 2, 3 and 6; up to 14.7%) among 4D, P_{0%} and P_{50%} plans. From nine lung patients' results in our study, based on both physical and biological analyses for a 4D composite plan, and IMRT plans for fixed respiratory phases (at P_{0%} and P_{50%}), it is not certain that 4D plans have better target coverage or higher expected tumor control rate without severe complication to normal tissues. Nevertheless, from the data of Table IX, significant variations (up to 14.7% difference) in P₊ from P_{0%} plan to P_{50%} were found in some patients. These results explained the value of 4D radiation therapy for a consistent P₊ through the whole course of the treatment if we are able to deliver 4D treatment plans precisely. In other word, ΔP_+ , ΔP_B , and ΔP_I during 4D treatment plan delivery would be 0 in contrast to the deviations we estimated from P_{0%} to P_{50%} for these nine patients in Table IX. The accuracy of 4D treatment plan delivery, which depends mainly on the reproducibility of the breathing cycle acquired at the simulation in latter actual 4D treatment was not examined in this study.

The possible reason that no absolutely benefit in complication-free tumor control probability in our assessments for 4D treatment planning might be because these 4D treatment plans were optimized based on the physical dose constraints rather than biological limitations. When converting the optimized physical dose distribution into biological dose for 4D composite plans, resulting complication-free tumor control probability might not necessarily be in the optimal level as observed in our results. Consequently, it might be essential to implement biological optimization in terms of optimal complication-free tumor control rate for 4D treatment planning of lung cancer patients in future studies.

Conclusions

In this study, by applying both physical and biological evaluations, the 4D radiotherapy plan has been evaluated thoroughly with the consideration of tumor control probability and normal tissue injury rate, which appear to be more related to clinical treatment outcomes. When comparing the 4D composite plans with fixed-phase IMRT plans using physical measures alone, it was hard to decide and conclude which plan would be superior. After taking into account the biological characteristics of the target and normal tissues as demonstrated, the complication-free tumor control probability, P₊, determined which plan was better.

Because this study was based on nine patients, it was difficult to make generalized conclusions. From the physical measures of DVH and dose statistics, 4D composite plans provided adequate target coverage and mean dose in PTV and similar sparing to organs at risk as compared to the IMRT plan at reference phase (P_{0%} in our study). From the biological results, P₊ of the 4D composite plans for nine patients differed from case to case due to differences in P_B and/or in

P_I . Technical challenges in 4D treatment planning include requirements for 10-20 times more image space and the associated increase in image processing, registration, and segmentation. Consequently, the use of radiobiological parameters is necessary to justify if 4D treatment planning would increase tumor control rates and/or reduce normal tissue complication.

In our study, we did not observe definitively PTV size dependence in P_+ among these nine lung cancer patients with PTVs of various absolute sizes. When evaluating the clinical benefit by comparing $\overline{\overline{D}}$ and P_+ with fixed-phase IMRT plans of $P_{0\%}$ and $P_{50\%}$, it is not certain that 4D plans had highest expected tumor control probability or lowest normal tissue complication rate. However, if 4D treatment plans can be delivered perfectly, the variations in P_+ , P_B , and P_I because of intra-fractional respiratory motion should be close to 0 in contrast to significant deviations observed if delivering the $P_{0\%}$ IMRT plan at $P_{50\%}$ respiratory phase.

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Abbreviations

IMRT, Intensity modulated radiation therapy

SBRT, Stereotactic body radiation therapy

4D, Four-dimensional

4DCT, 4D computed tomography

BEUD, Biologically effective uniform dose

RPM, Real-time Position Management

$P_{0\%}$, Respiratory phase at end-inhalation

$P_{50\%}$, respiratory phase at end-exhalation

GTV, Gross target volume

PTV, Planning target volume

DVH, Dose volume histogram

SD, Standard deviation

TCP, Tumor control probability

NTCP, Normal tissue complication probability

P_+ , Complication-free tumor control probability

P_B , The probability of obtaining benefit

P_I , The probability of causing severe injury to normal tissue

$\overline{\overline{D}}_B$, Biologically effective uniform dose calculated based on the radiological characteristics of the target

$\overline{\overline{D}}_T$, Biologically effective uniform dose calculated based on the radiological characteristics of normal tissues

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Figure 1.

Cumulative DVHs in PTV (green), healthy lung (red), esophagus (orange), heart (pink), and spinal cord (cyan) of the 4D composite plan (square), and IMRT plans of P₀% (solid line) and P₅₀% (dashed line). Results of three patients with (a) small, (b) medium, and (c) large size of PTVs were presented and compared.

Figure 2. Biological dose evaluations in PTV for the 4D composite plans, P₀% IMRT plans, and P₅₀% IMRT plans of the nine lung cancer patients. Comparisons of **(a)** tumor control probability and **(b)** biologically effective uniform dose ($\overline{D}$) with **(c)** physical dose index, mean dose, were illustrated.

Figure 3. Biological dose analyses in spinal cord for the 4D composite plans, $P_{0\%}$ IMRT plans, and $P_{50\%}$ IMRT plans of the nine lung cancer patients. Comparisons of (a) biologically effective uniform dose ($\overline{D}$) with (b) mean dose in spinal cord were illustrated. Normal tissue probabilities (not shown in this figure) of all nine patients were approximately 0.

Figure 4. Biological dose analyses in esophagus for the 4D composite plans, P₀% IMRT plans, and P₅₀% IMRT plans of the nine lung cancer patients. Comparisons of (a) normal tissue complication probability and (b) biologically effective uniform dose ($\overline{D}$) with (c) mean dose in esophagus were illustrated.

Figure 5. Biological dose analyses in heart for the 4D composite plans, P₀% IMRT plans, and P₅₀% IMRT plans of the nine lung cancer patients. Comparisons of (a) normal tissue complication probability and (b) biologically effective uniform dose ($\overline{D}$) with (c) mean dose in heart were illustrated.

Figure 6.

Biological dose analyses in healthy lung for the 4D composite plans, P_{0%} IMRT plans, and P_{50%} IMRT plans of the nine lung cancer patients. Comparisons of (a) normal tissue complication probability and (b) biologically effective uniform dose ($\overline{D}$) with (c) mean dose in healthy lung were illustrated.

Figure 7.

Biological evaluations on the 4D composite plan, $P_{0\%}$ and $P_{50\%}$ IMRT plans using P_B , P_I as well as P_+ . Results of the same three patients as in Figure 1 with (a) small, (b) medium, and (c) large size of PTVs were presented and compared.

Figure 8. PTV volume changes in lung tumors of nine patients obtained by manual contouring on 4DCT images.

Table I

General information of nine lung cancer patients.

	Gender	Age	Treatment Site	PTV (cm ³)
Patient 1	Male	92	Rt upper lobe	50.8
Patient 2	Male	74	Rt lower lobe	184.5
Patient 3	Male	67	Rt upper lobe	657.6
Patient 4	Female	77	Lt upper & lower lobes	125.1
Patient 5	Female	71	Rt hilum	129.4
Patient 6	Male	77	Rt upper lobe	391.7
Patient 7	Male	67	Lt upper & right upper lobes	699.2
Patient 8	Female	85	Rt upper lobe	235.1
Patient 9	N/A	N/A	Rt upper lobe	50.9

Table II

Dose constraints for organs at risk in IMRT plan optimization.

Organs at risk	Dose constraint
Spinal cord	Maximum dose < 4500 cGy
Esophagus	D _{20%} < 1500 cGy
Heart	D _{15%} < 3000 cGy
Total Lung	D _{25%} < 2000 cGy

Table III

Dose-response parameters used in biological dosimetry evaluation.

	D₅₀ (Gy)	γ	s	Endpoint
Spinal cord	57.00	6.70	1.00	Myelitis necrosis
Esophagus	68.00	2.8	3.40	Clinical stricture / perforation
Heart	70.70	0.96	1.00	Late excess cardiac mortality
Lung	15.90	1.00	0.17	Sever radiation pneumonitis, fibrosis
PTV	40.00	3.00	N/A	Control

Table IV
Physical dose statistics in PTV among the 4D composite plan, P_{0%} and P_{50%} IMRT plans.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Mean Dose (Gy)									
4D (Gy)	59.7	59.8	59.9	59.6	59.8	59.7	59.8	59.7	59.7
P _{0%} (Gy)	60.2	59.6	59.8	59.8	60.0	59.9	59.7	60.0	59.7
P _{50%} (Gy)	59.5	58.7	59.7	59.2	59.7	58.0	58.3	59.6	59.5
Standard Deviation (Gy)									
4D (Gy)	0.8	1.0	0.6	1.2	1.0	1.5	1.3	0.9	0.5
P _{0%} (Gy)	0.7	1.6	0.6	0.8	0.7	1.2	1.4	1.3	0.4
P _{50%} (Gy)	1.6	1.3	0.8	2.7	1.5	4.7	1.3	1.4	0.5
Maximum Dose (Gy)									
4D (Gy)	61.5	63.1	62.9	62.9	64.9	65.4	65.6	68.6	62.1
P _{0%} (Gy)	64.8	65.1	64.2	64.5	65.2	67.1	64.5	71.2	61.8
P _{50%} (Gy)	65.2	63.4	63.3	63.6	65.8	63.4	65.2	69.0	62.1
Minimum Dose (Gy)									
4D (Gy)	51.6	49.0	53.8	45.0	50.1	36.3	43.4	47.1	53.0
P _{0%} (Gy)	56.2	44.7	55.8	52.8	54.1	40.7	45.7	46.4	57.6
P _{50%} (Gy)	42.3	42.1	46.4	26.1	38.7	25.8	42.5	39.2	51.7

Table V
Physical dose statistics in spinal cord among the 4D composite plan, P_{0%} and P_{50%} IMRT plans.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Mean Dose (Gy)									
4D (Gy)	1.7	15.3	6.0	5.5	5.5	10.8	5.8	2.2	3.1
P _{0%} (Gy)	1.7	15.1	6.1	5.5	5.0	9.9	5.8	2.3	3.4
P _{50%} (Gy)	1.7	15.2	5.9	5.7	5.5	11.2	5.5	2.4	3.1
Standard Deviation (Gy)									
4D (Gy)	4.1	13.1	8.7	7.7	9.0	12.5	8.2	4.2	4.6
P _{0%} (Gy)	4.3	13.2	8.8	8.0	8.1	11.8	8.4	4.4	5.1
P _{50%} (Gy)	4.3	13.0	8.6	8.0	9.5	13.0	8.2	4.6	4.6
Maximum Dose (Gy)									
4D (Gy)	18.5	37.8	37.3	39.1	32.6	39.6	39.1	15.5	15.2
P _{0%} (Gy)	20.8	36.8	35.4	39.1	29.9	41.7	41.8	17.6	17.5
P _{50%} (Gy)	19.8	37.8	36.0	44.3	34.3	39.3	39.8	18.0	15.5
Minimum Dose (Gy)									
4D (Gy)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3
P _{0%} (Gy)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3
P _{50%} (Gy)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3

Table VI
Physical dose statistics in esophagus among the 4D composite plan, P_{0%} and P_{50%} IMRT plans.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Mean Dose (Gy)									
4D (Gy)	4.6	41.2	5.7	12.3	8.5	11.2	9.8	9.9	4.1
P _{0%} (Gy)	4.3	41.0	6.0	12.3	8.3	11.0	9.0	4.6	4.3
P _{50%} (Gy)	4.8	43.2	5.5	13.0	7.2	13.2	9.5	11.9	4.3
Standard Deviation (Gy)									
4D (Gy)	4.9	21.7	8.6	13.7	8.6	8.9	9.2	11.6	5.6
P _{0%} (Gy)	4.7	22.1	9.1	14.6	8.2	10.1	9.7	4.6	5.9
P _{50%} (Gy)	5.4	21.5	8.2	14.8	8.4	9.8	8.8	14.9	5.7
Maximum Dose (Gy)									
4D (Gy)	17.9	61.8	44.8	58.4	49.4	57.6	40.4	40.6	22.6
P _{0%} (Gy)	18.9	62.8	43.1	59.7	51.4	61.3	45.4	16.9	24.3
P _{50%} (Gy)	18.9	62.4	42.8	58.7	49.3	58.6	40.8	52.8	22.0
Minimum Dose (Gy)									
4D (Gy)	0.3	0.3	0.3	0.3	0.3	1.0	0.3	0.4	0.3
P _{0%} (Gy)	0.3	1.0	0.3	0.3	0.3	1.0	0.3	0.4	0.3
P _{50%} (Gy)	0.3	0.3	0.3	0.3	0.3	1.0	0.3	0.4	0.3

Table VII
Physical dose statistics in heart among the 4D composite plan, P_{0%} and P_{50%} IMRT plans.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Mean Dose (Gy)									
4D (Gy)	5.5	17.4	0.2	6.3	6.4	14.8	5.6	14.6	1.3
P _{0%} (Gy)	5.1	16.7	0.2	7.4	5.8	14.9	4.9	6.7	1.6
P _{50%} (Gy)	5.8	17.2	0.2	5.1	6.1	12.6	5.4	17.7	1.0
Standard Deviation (Gy)									
4D (Gy)	8.2	14.6	0.2	6.5	10.0	15.2	7.7	8.0	2.0
P _{0%} (Gy)	7.7	14.2	0.2	7.7	9.0	15.5	6.9	3.8	2.6
P _{50%} (Gy)	8.5	14.5	0.2	5.8	9.6	13.3	7.6	9.5	1.7
Maximum Dose (Gy)									
4D (Gy)	51.6	61.8	0.6	44.3	60.5	63.0	48.7	46.7	18.8
P _{0%} (Gy)	53.3	63.1	0.6	52.8	61.5	64.0	46.7	24.4	19.7
P _{50%} (Gy)	52.3	63.1	1	37.5	62.4	62	49.7	55.7	20.4
Minimum Dose (Gy)									
4D (Gy)	0.3	0.7	0.3	0.3	0.3	0.7	0.3	1.4	0.3
P _{0%} (Gy)	0.3	0.7	0.3	0.3	0.3	0.7	0.3	0.7	0.3
P _{50%} (Gy)	0.3	1.0	0.3	0.3	0.3	0.7	0.3	1.8	0.3

Table VIII
Physical dose statistics in healthy lung among the 4D composite plan, P_{0%} and P_{50%} IMRT plans.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Mean Dose (Gy)									
4D (Gy)	10.2	16.7	9.9	9.1	12.8	12.3	18.8	13.4	8.4
P _{0%} (Gy)	10.1	15.2	9.2	9.4	12.8	11.9	18.4	12.9	8.6
P _{50%} (Gy)	10.0	17.6	10.0	8.8	12.8	11.7	18.7	13.5	9.3
Standard Deviation (Gy)									
4D (Gy)	15.5	13.9	19.0	12.9	19.3	19.4	18.9	18.6	14.9
P _{0%} (Gy)	15.4	12.6	18.3	13.2	19.5	19.3	18.5	18.9	14.7
P _{50%} (Gy)	15.5	15.2	19.1	12.8	19.4	18.1	18.8	18.8	15.1
Maximum Dose (Gy)									
4D (Gy)	61.5	60.8	62.9	62.9	64.9	65.4	62.6	68.6	63.1
P _{0%} (Gy)	65.5	60.5	64.2	64.5	65.5	67.1	65.2	71.2	64.0
P _{50%} (Gy)	65.2	62.8	63.6	62.9	65.8	63.4	62.5	69.0	64.1
Minimum Dose (Gy)									
4D (Gy)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3
P _{0%} (Gy)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3
P _{50%} (Gy)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3

Table IX
Deviations of the quantities in P_+ , P_B , P_I , and both $\overline{D}$ calculated in terms of benefit and injury among the 4D plan, $P_{0\%}$ and $P_{50\%}$ IMRT plans.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
ΔP_+ (%)									
P0-4D	0.70	8.20	4.20	-1.90	-0.30	1.20	2.60	1.50	0.70
P50-4D	0.60	-6.50	-1.00	-3.50	0.90	0.60	0.10	-1.30	-0.90
P50-P0	-0.10	-14.70	-5.20	-1.60	1.20	-0.60	-2.50	-2.80	-1.60
ΔP_B (%)									
P0-4D	0.20	-0.10	0.00	0.20	0.10	0.10	0.00	0.10	0.00
P50-4D	-0.20	0.00	-0.10	-3.90	-0.10	-5.80	-0.50	-0.10	0.00
P50-P0	-0.40	0.10	-0.10	-4.10	-0.20	-5.90	-0.50	-0.20	0.00
ΔP_I (%)									
P0-4D	-0.60	-8.20	-4.20	1.90	0.40	-1.00	-2.70	-1.50	-0.70
P50-4D	-0.80	6.50	0.90	-0.50	0.10	-6.50	-0.60	1.20	0.90
P50-P0	-0.20	14.70	5.10	-2.40	-0.30	-5.50	2.10	2.70	1.60
ΔD_B (Gy)									
P0-4D	0.50	-0.40	-0.10	0.45	0.30	0.55	-0.20	0.20	0.00
P50-4D	-0.70	-0.20	-0.20	-6.10	-0.45	-7.35	-1.60	-0.50	-0.20
P50-P0	-1.20	0.20	-0.10	-6.55	-0.75	-7.90	-1.40	-0.70	-0.20
ΔD_I (Gy)									
P0-4D	-0.40	-1.35	-0.80	0.60	0.10	-0.15	-0.50	-0.25	-0.20
P50-4D	-0.45	1.10	0.15	-0.15	0.05	-1.05	-0.10	0.20	0.25

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
P50-P0	-0.05	2.45	0.95	-0.75	-0.05	-0.90	0.40	0.45	0.45

P_{+} , complication-free tumor control probability; P_B , tumor control probability; P_I , normal tissue complication probability; $\overline{\overline{D}}_B$, biologically effective uniform dose calculated based on the radiological characteristics of the target; $\overline{\overline{D}}_I$, biologically effective uniform dose calculated based on the radiological characteristics of normal tissues.