Feasibility of Four-dimensional Adaptation of Volumetric Modulated Arc Therapy Based on Volumetric Modulated Arc Therapy-computed Tomography

Xiaodong Zhao[1], Rui Zhang[2,3]

[1]Department of Radiation Oncology, Washington University in St. Louis, St. Louis, Missouri, [2]Department of Physics and Astronomy, Louisiana State University, [3]Department of Radiation Oncology, Mary Bird Perkins Cancer Center, Baton Rouge, Louisiana, USA

Abstract

Purpose: Volumetric modulated arc therapy (VMAT) has been increasingly used for cancer patients due to the fast delivery and improved dose conformity. Adaptive radiotherapy (ART) can significantly decrease dose to normal tissues and allow for dose escalation. However, current imaging techniques cannot provide four-dimensional (4D) patient anatomy or dose information during VMAT, which is critical for ART that involves respiratory motion. A novel imaging tool named VMAT–computed tomography (VMAT-CT) has the potential to reveal intra-fractional patient information. The goal of this study was to evaluate the feasibility of 4D adaptive VMAT based on 4D VMAT-CT. **Materials and Methods:** A commercial QUASAR respiratory phantom and an in-house deformable lung phantom were used in this study, and lung VMAT plans, including 4D union plan and 4D ART plan, were generated for the phantoms. A real lung patient's plan was also used in this feasibility study. ART plans based on 4D VMAT-CT were created for the phantoms and the real patient when planning goals were not met. Dose escalation plan based on 4D VMAT-CT was also created for the real patient. **Results:** Planning target volume (PTV) coverage for the QUASAR phantom was 85.5% after breathing pattern being changed, and went up to 95% after adaptive re-planning. PTV coverage for the deformable phantom was 93% after deformation and breathing pattern being changed, and went up to 95% after re-planning. Re-planning and dose escalation were feasible and can spare normal tissues for the real patient. 4D ART plan based on 4D VMAT-CT required smaller margins than 4D union plan while maintaining the same prescription dose coverage. **Conclusions:** ART based on 4D VMAT-CT is feasible and would potentially facilitate re-planning and PTV dose escalation for VMAT patients who have the motion issue.

Keywords: Adaptive radiotherapy, computed tomography, four-dimensional, volumetric modulated arc therapy

INTRODUCTION

More than half of cancer patients receive radiotherapy (RT) during their course of illness.[1] For lung and upper abdominal cancer patients whose treatments involve the motion issue, current RT planning usually requires a generous margin around the tumor. This target margin can account for possible geometric and dosimetric uncertainties, but limits the total dose that can be safely delivered and causes adverse effects.[2-6] Radiation dose escalation has been shown to significantly improve local control and survival for lung cancer patients,[7-12] for example, the 5-year overall survival of inoperable non-small cell lung cancer patients increased from 4% to 28% when patient dose increased from 63 - 69 Gy to 92–103 Gy,[8] and survival of extensive-stage small cell lung cancer patients at 1 and 2 years for >45 Gy arm was 58.1% and 25.2% compared to 43.8% and 15.1% for <45 Gy arm.[12] However, the benefits of dose escalation can be hampered by increased normal tissue toxicities, mainly due to the size of the target volume.[5,6,13] Recently, stereotactic body RT (SBRT) has been used to escalate dose successfully and is one of the most significant advances in treating medically inoperable non-small cell lung cancer,[14-16] but it also faces the challenges of multiple adverse effects.[17-20]

Address for correspondence: Dr. Rui Zhang, Department of Physics and Astronomy, Louisiana State University, Baton Rouge, Louisiana, USA. E-mail: rzhang@lsu.edu

Access this article online

Quick Response Code:

Website: www.jmp.org.in

DOI: 10.4103/jmp.jmp_24_23

Advanced RT techniques, such as intensity-modulated RT and volumetric modulated arc therapy (VMAT), allow more efficient delivery of radiation to achieve dose escalation while minimizing normal tissue doses. Among various techniques, VMAT has been increasingly used and shows specific advantages for lung and upper abdominal cancers,[21-25] and is considered the best way to deliver SBRT because of its short treatment time and improved dose conformity.[26-28] However, as VMAT contains a high degree of complexity, the need for accurate monitoring and verification also increases, especially for hypo-fractional treatment such as SBRT, since dosimetric errors that occur in one fraction can have a significant impact.[29]

Adaptive RT (ART) holds the potential to compensate for errors or uncertainties and reduce target margin in RT by changing treatment plans based on patient-specific variation in a treatment session.[30] This is particularly helpful for cancer sites that involve complex uncertainties such as patient motion, tumor regression, and migration. Numerous studies have shown ART can significantly decrease the dose to normal tissues and allow for dose escalation.[30-34] Accurate tracking of the treatment, patient anatomy, and dose will significantly help determine when an ART is needed. Mid-treatment or weekly ART is performed in most current ART studies, although the literature has shown daily ART will offer the largest benefit.[31,35] Computed tomography (CT) or cone beam CT (CBCT) is the most commonly used imaging technique for ART.[30-32,36,37] In many clinics, three-dimensional (3D) or four-dimensional (4D) CBCT is performed both before and after SBRT to help with patient setup and determine the patient's final position for dose estimation.[38,39] However, CT or CBCT allows only a snapshot of the patient before or after RT, and introduces excessive dose and extra treatment cost, especially when ART is performed frequently. ART based on these images may remedy inter-fractional changes but not intra-fractional errors, and the actual patient dose, which is critical for ART, remains unknown.

The concept of utilizing therapeutic beams in VMAT to reconstruct 3D VMAT-CT was proposed in 2010.[40] It does not introduce extra dose or cost, and can potentially reveal patient information during treatment, but it did not gain popularity due to multiple limitations and technical challenges. Our group extended the concept of VMAT, and showed the feasibility of 3D[41] and 4D VMAT-CT[42] based on the latest linear accelerator (linac) and real clinical plans. The goal of this study was to adapt VMAT plan involving tumor motion based on 4D VMAT-CT. We will focus on lung cancer in this study, although our methods can also be used for other cancer sites that involve target movement.

MATERIALS AND METHODS

Treatment planning and data collection

A QUASAR™ programmable respiratory motion phantom (Modus Medical Devices Inc., London, Ontario, Canada) and an in-house deformable lung phantom[41,42] were used in this study. The QUASAR phantom has a wood cylinder mimicking the lung and the cylinder contains a 3 cm diameter ball mimicking a tumor. The deformable phantom has a balloon filled with gel mimicking a tumor, and the balloon is tied with a string that can be attached to the QUASAR phantom to deform the tumor and drive the tumor with desired breathing patterns. 4D cine planning CT of the phantoms and a respiratory signal were acquired, a probability density function (PDF) of tumor position versus time was obtained, and the mean position of the PDF was calculated. The gross tumor volume (GTV) was delineated on all four phases of 4D planning CT, and one phase's data set was chosen as the mean position planning CT (MPPCT) if that phase's GTV was closest to the mean position.[31]

For the phantoms, we created the 4D union plan which is the standard of care for lung cancer in our clinic and many other clinics.[31] This technique utilizes the contour of the maximum intensity projection of the target and encompasses all possible tumor locations. We also created the initial 4D ART plan similar to the technique proposed by Harsolia et al.[31] mean position GTV in MPPCT was expanded by 0.5 cm as the clinical target volume (CTV) and a static plan was generated first based on this mean position CTV. The static dose was then convolved with the PDF obtained from 4D planning CT to determine the effect of respiratory motion and to find out the necessary initial margin (CTV to planning target volume [PTV]) to ensure the target coverage.

For a real lung cancer patient who has a malignant neoplasm on the lower left lobe, the clinical nonadaptive VMAT plan (P_N) was a 4D union VMAT plan with 50 Gy/5 fraction dose prescription and was created by the dosimetrist in our clinic. An initial 4D ART plan was also created by us for this patient based on planning CT using the method described above.

All VMAT Plans were created in Pinnacle v9.10 treatment planning system (TPS) (Philips Medical Systems, Fitchburg, WI) with two full 6 MV arcs, 45° (clockwise arc) or 135° (counterclockwise arc) collimator angle, 50 Gy/5 fraction heterogeneous dose prescription, 3 mm × 3 mm × 3 mm dose grid, 1800–2000 total Monitor Units per fraction. All plans were delivered through Elekta Versa Linac (Elekta Oncology Systems, Crawley, UK).

The details of respiratory signal extraction based on the normalized cross-correlation (NCC) method,[43] reconstructions of 4D VMAT-CT, 4D VMAT-CT+, and 4D dose can be found in our previous study.[42] Briefly, the respiratory signal was quantified by computing the NCC matrices of the same rectangular area in consecutive portal images. A time-based sorting method was used to split the collected portal images into four phases, and 4D VMAT-CT image sets were created by reconstructing 3D VMAT in each phase. Rigid and deformable registrations were performed to register VMAT-CT in each phase to MPPCT to generate 4D VMAT-CT+. The respiratory signal based on the NCC method was also applied to the linac log file to generate 4-phase beam delivery files, and the dose

was calculated in each phase based on the beam delivery file and VMAT-CT+ images. Note the conceptual difference between VMAT-CT+ and simulated CT proposed by Varian Ethos™ (Varian Medical Systems, Palo Alto, CA, USA): Both planning CT and daily CBCT have a full or large field of view, so the generation of simulated CT only involves deformable registration and is relatively straightforward; in contrast, VMAT-CT is limited to the target area, so the generation of VMAT-CT+ involves local registration that extracts the position and anatomy information from VMAT-CT, and also expands VMAT-CT to a larger field of view.

Adaptive radiotherapy based on four-dimensional volumetric modulated arc therapy-computed tomography

When the PTV coverage did not meet the prescription goal, we performed adaptive re-planning and re-optimization based on 4D VMAT-CT+. For 4D ART plans, daily VMAT-CT was used to form updated PDF and new PTV margins. Harsolia *et al.*[31] used daily fluoroscopy and reported daily 4D ART plan can significantly decrease dose to normal tissues and allow for dose escalation. In this study, we wanted to investigate if VMAT-CT can provide sufficient image information for adaptive correction as daily fluoroscopy.

For the QUASAR phantom, the planning CT captured the original breathing pattern [input signal 1 in Figure 1]. When the phantom was on the treatment couch, we changed the breathing pattern (both time period and amplitude) [input signal 2 in Figure 1] to mimic a change from treatment simulation, took CBCT of the phantom as the ground truth (CBCT$_{ground}$), and delivered the VMAT plan to the phantom with the new breathing pattern. For the deformable phantom, the planning CT captured the original phantom geometry and breathing pattern. When the phantom was on the treatment couch, we changed both the deformation of the phantom and the breathing pattern, took CBCT$_{ground}$ and delivered the VMAT plan.

For the real patient, we tracked geometry and dose changes based on 4D VMAT-CT+, and compared the delivered dose and planned dose to evaluate the necessity of re-planning. Simulated adaptive plans (P$_A$), including both 4D union and 4D ART plans, were created when target coverage or organs at risk (OAR) dose exceeds constraints. Each P$_A$ plan was planned using target and OAR constraints that were scaled to 5 fractions, and was deemed acceptable when OAR constraint compliance was met. In addition, we tried to escalate the PTV dose to 60 Gy (12 Gy/fraction) if more favorable daily OAR anatomy was observed, i.e., the distance between the target and normal tissue increased, since the benefits of dose escalation have been well established for lung cancer.

RESULTS

For both phantoms, VMAT plans based on both 4D union and 4D ART plans were investigated, but only results based on the 4D ART plan were shown in this paper because of the similarity. Figure 2 shows dose calculation and adaptive re-planning for the QUASAR phantom. 4D VMAT-CT + can track the change of respiratory pattern correctly compared to the ground truth (100% 3D Gamma passing rate with an acceptance criterion of 3% and 3 mm.[44]) The PTV coverage of the prescription dose in the original 4D ART plan was 95%, dropped to 85.5% after the breathing pattern being changed because the prescription dose line did not cover the superior part of PTV completely, but went up to 95% after re-planning. The new margin of the PTV compared to the old margin showed a 1.6-mm shrinkage in the superior direction, which is a combined result of the change of breathing pattern, re-optimization with the new static mean position CTV, and convolution of dose with the new PDF.

Figure 3 shows dose calculation and adaptive re-planning for the in-house deformable phantom. VMAT-CT can track the phantom's deformation and change of respiratory pattern correctly compared to ground truth (100% Gamma passing rate with an acceptance criterion of 3% and 3 mm). The PTV coverage of the prescription dose in the original 4D ART plan was 95%, dropped to 93% after phantom deformation and respiratory pattern being changed, but went up to 95% after re-planning. New margin of the PTV compared to the old margin showed a 1-mm expansion in the superior direction
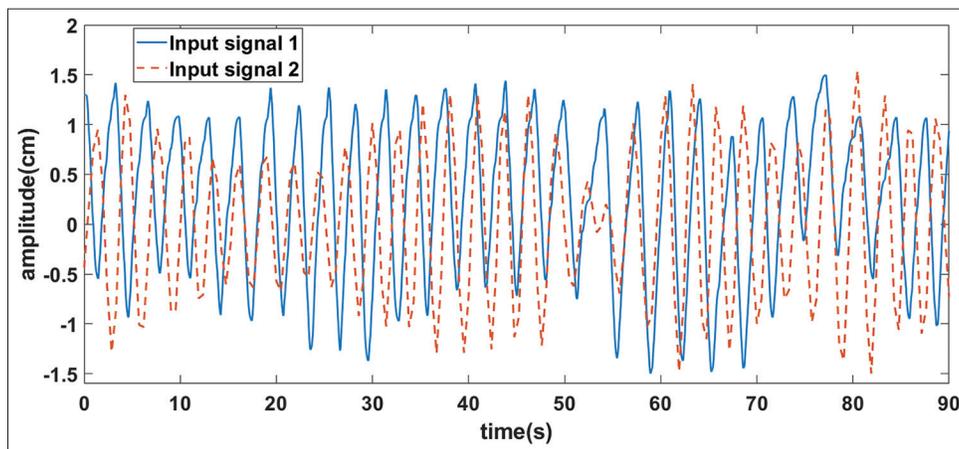
Figure 1: Breathing patterns used in this study. Both signals were from a real lung cancer patient
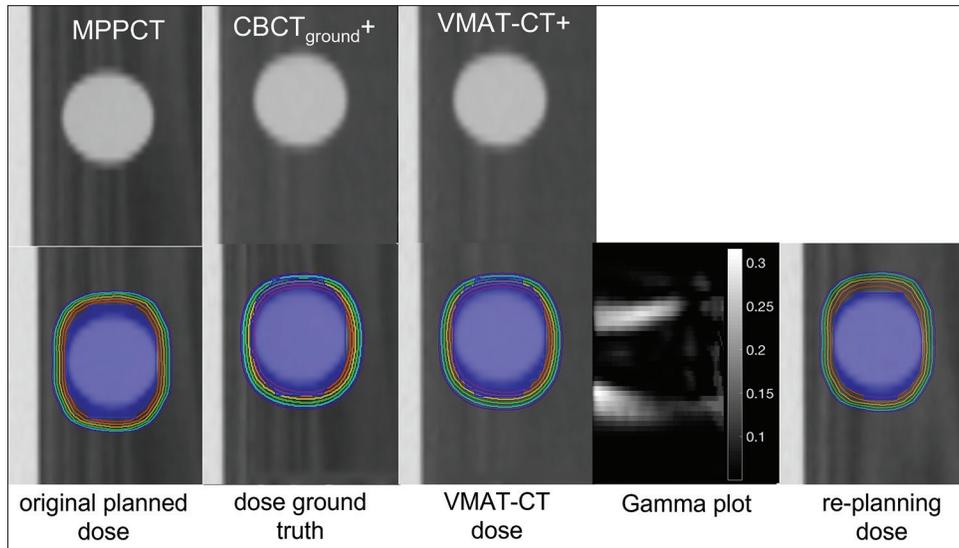
Figure 2: ART demonstrated on a QUASAR phantom. (From left to right) (top row) comparison of MPPCT, CBCTground+ (MPPCT registered to CBCTground), VMAT-CT+; (bottom row) dose distributions in the original plan, dose ground truth which is dose based on CBCTground + after change of breathing pattern, dose based on VMAT-CT+ after change of breathing pattern, Gamma plot comparing VMAT-CT dose and dose ground truth, re-optimized dose based on VMAT-CT+. The blue shaded area is the original or new PTV contour. Y-axis is the direction of breathing motion, and difference in the target height means the difference in breathing magnitude. ART: Adaptive radiotherapy, MPPCT: Mean position planning computed tomography, VMAT-CT: Volumetric modulated arc therapy-computed tomography, PTV: Planning target volume
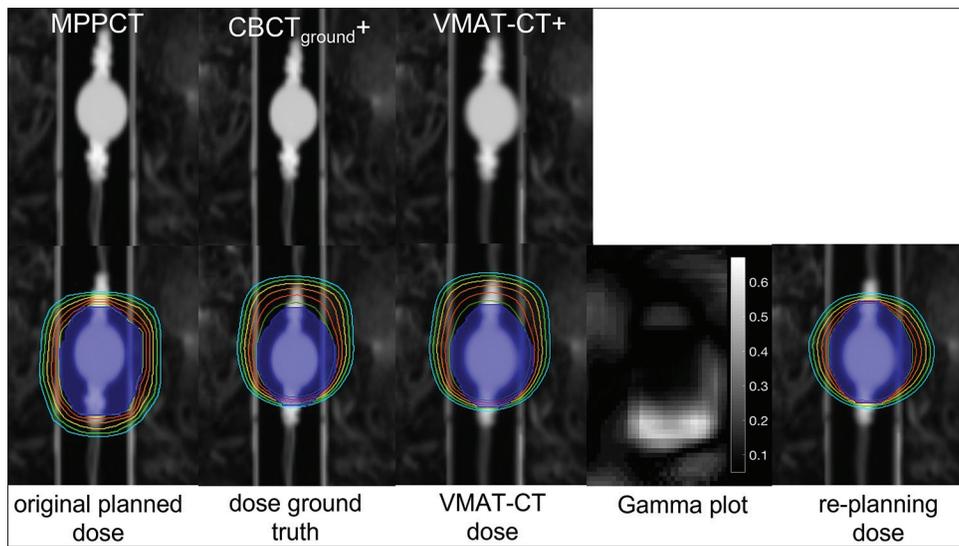
Figure 3: ART demonstrated on an in-house deformable phantom. (From left to right) (top row) comparison of MPPCT, CBCT$_{ground}$+ (MPPCT registered to CBCT$_{ground}$), VMAT-CT+; (bottom row) dose distributions in the original plan, dose ground truth which is dose based on CBCT$_{ground}$ after change of deformation and breathing pattern, dose based on VMAT-CT+ after change of deformation and breathing pattern, Gamma plot of comparison between VMAT-CT dose and dose ground truth, re-optimized dose based on VMAT-CT+. The blue shaded area is the original or new PTV contour. Y-axis is the direction of breathing motion, and difference in the target height means the difference in breathing magnitude. MPPCT: Mean position planning computed tomography, VMAT-CT: Volumetric modulated arc therapy-computed tomography, PTV: Planning target volume, ART: Adaptive radiotherapy, CBCT: Cone beam computed tomography

and 1-mm shrinkage in the inferior direction, which is again a combined effect.

Figure 4 shows the result of the geometry change and dose calculations for the real lung patient. The PTV coverage in the original 4D union plan was 95.8%, while VMAT-CT+ showed PTV had a 2-mm shrinkage in the superior direction and a 5-mm shrinkage in the inferior direction after the treatment fraction. The PTV coverage was 96.2% when P_N was transferred to VMAT-CT+, but the surrounding normal tissues received higher exposure as the prescription dose lines penetrated more into the diaphragm. To spare normal tissues, we reoptimized the 4D union plan. Finally, we escalated the PTV dose to 60 Gy successfully without violating any OAR constraint by
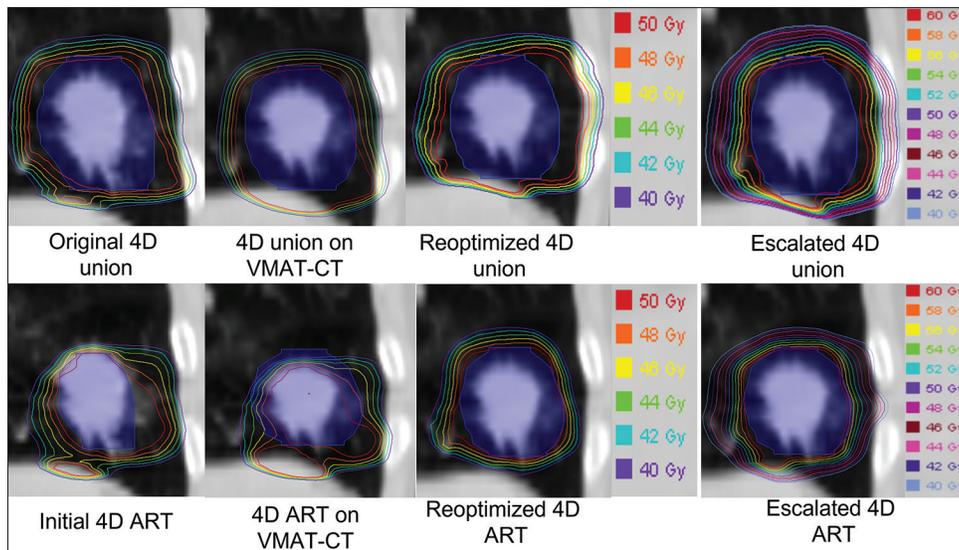
Figure 4: (Top row) dose distributions in the original 4D union plan, dose based on 4D VMAT-CT+, reoptimized plan and dose-escalation plan based on VMAT-CT+; (bottom row) dose distributions in the original 4D ART plan, dose based on 4D VMAT-CT+, reoptimized plan and dose-escalation plan based on VMAT-CT+. The blue shaded area is the original or new PTV in 4D union or 4D ART plans. VMAT-CT: Volumetric modulated arc therapy-computed tomography, PTV: Planning target volume, ART: Adaptive radiotherapy, 4D: Four-dimensional

following Radiation Therapy Oncology Group (RTOG) 0813 SBRT protocol.[45] For this patient, we also evaluated 4D ART plans [Figure 4]. We created an initial 4D ART plan based on the initial breathing PDF collected during planning CT, and the PTV was much smaller than the PTV in 4D union plans and had 95% coverage. VMAT-CT + showed PTV coverage dropped to 35% after the treatment fraction. We then reoptimized the 4D ART plan based on VMAT-CT + to restore PTV coverage to be above 95%, and escalated PTV dose successfully without violating any OAR constraint.

Discussion

We demonstrated the feasibility of 4D adaptive VMAT based on 4D VMAT-CT, which has never been investigated before. Harsolia et al.[31] used daily fluoroscopy for ART plans and obviously fluoroscopy will introduce significant imaging dose,[46] while our method does not introduce any extra dose since VMAT-CT comes directly from treatment beams.

For real patients, we determined microscopic disease (MD) associated with the shrinking tumor will not be underdosed in adaptive plans based on VMAT-CT. Currently, there is no imaging technique that can image MD beyond the tumor boundary, and the extent of MD can be calculated using special probability models. Guckenberger et al.[47] evaluated doses to MD in ART for lung cancer, and studied two situations, including synchronous shrinkage of MD and GTV and stationary MD despite GTV shrinkage, and showed dose coverage of MD was not compromised in either situation. Sonke and Belderbos.[32] suggested the dose required for MD beyond the visible tumor can be significantly lower than the GTV dose. Our study prescribed 100% dose to 95% of the PTV in P_A plans, and over 95%

coverage was achieved on the PTV, which indicates a good coverage of MD.

The real patient was treated with 4D union SBRT in our clinic, so the VMAT-CT was based on the delivery of 4D union plans. We did not have 4D ART plans in the clinic and did not have portal images of the patient based on the delivery of 4D ART plans. However, we do not consider this as a serious limitation of this simulated ART study because the location of the target area would be the same for 4D union and 4D ART plans; just the size of the PTV is different. 4D union plan usually has a larger coverage area, but 4D ART plan can still reveal the target [Figure 5]. To obtain Linac log files without causing any damage to the patient, we delivered all 4D ART plans to the air without any patient in the treatment room. Creating and delivering 4D ART plans for real patients will be performed in the future study.

The change in a patient's breathing pattern could have an impact on the quality of 4D ART plans. Due to the limitation of computation speed, real-time VMAT-CT is not feasible currently and is a future direction that we are actively pursuing. Offline ART based on VMAT-CT, although not as effective as online ART, can still catch and compensate for possible errors without introducing any extra dose or cost, and it is well accepted that offline ART is highly beneficial to patients.[30,48] However, if a patient has drastic changes in breathing baseline and amplitude compared to the last fraction, it is possible that offline ART plans could underdose the target or overdose the surrounding OARs. This is an inherent drawback of offline adaptation, and the drastic change requires onsite decision-making. A potential solution to this type of urgent situation in the clinic is to create multiple 4D ART plans before the treatment. These plans are based on the patient's
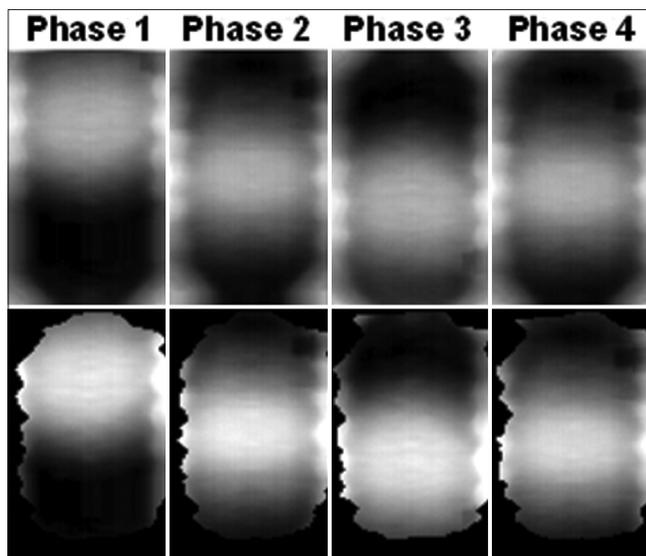
Figure 5: VMAT-CT based on 4D union plan (top row) and 4D ART plan (bottom row) of a QUASAR phantom with a ball insert. VMAT-CT: Volumetric modulated arc therapy-computed tomography, ART: Adaptive radiotherapy, 4D: Four-dimensional

latest anatomy revealed by the latest VMAT-CT, and cover all possible breathing patterns for the patient based on recorded patterns from previous fractions. The plan that utilizes the breathing pattern closest to the pattern of the day will be used for the treatment.

Our study was performed using the copies of the patients' treatment plans and no modification was made to the clinical plans. Evaluation of our imaging tool via randomized trials and patient follow-up will be carried out in a future clinical study, which will allow us to prospectively adapt cancer patients' plans and escalate dose based on VMAT-CT + if possible after each treatment fraction, explore further if the image guidance based on VMAT-CT can reduce normal tissue toxicity, improve tumor control and patient satisfaction. In the future, we plan to include more patients and ultimately incorporate the workflow into daily clinical routines. With more patient data, we will be able to determine what type of patients will be subject to most movement or geometry change during VMAT, and benefit most from our study.

Conclusions

In this study, we demonstrated 4D adaptive VMAT can be generated based on 4D VMAT-CT. Both the 4D union plan and 4D ART plan can be adapted, and the 4D ART plan required smaller margins while maintaining the target coverage. Overall, 4D VMAT-CT can be a very promising imaging tool for VMAT plan adaptation without introducing any extra dose or cost, considering daily ART will offer the largest benefit for patients whose treatments involve the motion issue.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

References

1. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: Estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005;104:1129-37.
2. Cannon DM, Mehta MP, Adkison JB, Khuntia D, Traynor AM, Tomé WA, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol 2013;31:4343-8.
3. Lee CB, Stinchcombe TE, Moore DT, Morris DE, Hayes DN, Halle J, et al. Late complications of high-dose (>/=66 Gy) thoracic conformal radiation therapy in combined modality trials in unresectable stage III non-small cell lung cancer. J Thorac Oncol 2009;4:74-9.
4. Salama JK, Stinchcombe TE, Gu L, Wang X, Morano K, Bogart JA, et al. Pulmonary toxicity in Stage III non-small cell lung cancer patients treated with high-dose (74 Gy) 3-dimensional conformal thoracic radiotherapy and concurrent chemotherapy following induction chemotherapy: A secondary analysis of cancer and leukemia group B (CALGB) trial 30105. Int J Radiat Oncol Biol Phys 2011;81:e269-74.
5. Yorke ED, Jackson A, Rosenzweig KE, Braban L, Leibel SA, Ling CC. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. Int J Radiat Oncol Biol Phys 2005;63:672-82.
6. Belderbos J, Heemsbergen W, Hoogeman M, Pengel K, Rossi M, Lebesque J. Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. Radiother Oncol 2005;75:157-64.
7. Mehta M, Scrimger R, Mackie R, Paliwal B, Chappell R, Fowler J. A new approach to dose escalation in non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2001;49:23-33.
8. Kong FM, Ten Haken RK, Schipper MJ, Sullivan MA, Chen M, Lopez C, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys 2005;63:324-33.
9. Belderbos JS, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. Final results of a Phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 2006;66:126-34.
10. Yamamoto N, Miyamoto T, Nakajima M, Karube M, Hayashi K, Tsuji H, et al. A dose escalation clinical trial of single-fraction carbon ion radiotherapy for peripheral stage I non-small cell lung cancer. J Thorac Oncol 2017;12:673-80.
11. Brower JV, Amini A, Chen S, Hullett CR, Kimple RJ, Wojcieszynski AP, et al. Improved survival with dose-escalated radiotherapy in stage III non-small-cell lung cancer: Analysis of the national cancer database. Ann Oncol 2016;27:1887-94.
12. Hasan S, Renz P, Turrisi A, Colonias A, Finley G, Wegner RE. Dose escalation and associated predictors of survival with consolidative thoracic radiotherapy in extensive stage small cell lung cancer (SCLC): A national cancer database (NCDB) propensity-matched analysis. Lung Cancer 2018;124:283-90.
13. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187-99.
14. Ricardi U, Badellino S, Filippi AR. Stereotactic radiotherapy for early stage non-small cell lung cancer. Radiat Oncol J 2015;33:57-65.

15. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, *et al.* Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan clinical oncology group study JCOG0403. Int J Radiat Oncol Biol Phys 2015;93:989-96.

16. Hiraoka M, Matsuo Y, Takayama K. Stereotactic body radiation therapy for lung cancer: Achievements and perspectives. Jpn J Clin Oncol 2010;40:846-54.

17. Dunlap NE, Cai J, Biedermann GB, Yang W, Benedict SH, Sheng K, *et al.* Chest wall volume receiving>30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;76:796-801.

18. Stephans K. Stereotactic body radiotherapy for stage I non-small cell lung cancer. Cleve Clin J Med 2012;79 Electronic Suppl 1:S26-31.

19. Thompson M, Rosenzweig KE. The evolving toxicity profile of SBRT for lung cancer. Transl Lung Cancer Res 2019;8:48-57.

20. Kalman NS, Hugo GD, Mahon RN, Deng X, Mukhopadhyay ND, Weiss E. Diabetes mellitus and radiation induced lung injury after thoracic stereotactic body radiotherapy. Radiother Oncol 2018;129:270-6.

21. Bree Id, van Hinsberg MG, van Veelen LR. High-dose radiotherapy in inoperable nonsmall cell lung cancer: Comparison of volumetric modulated arc therapy, dynamic IMRT and 3D conformal radiotherapy. Med Dosim 2012;37:353-7.

22. Valakh V, Chan P, D'Adamo K, Micaily B. Early-stage central lung cancer and volumetric modulated arc therapy: A dosimetric case study with literature review. Anticancer Res 2013;33:4491-5.

23. Teoh M, Beveridge S, Wood K, Whitaker S, Adams E, Rickard D, *et al.* Volumetric-modulated arc therapy (RapidArc) versus conventional fixed-field intensity-modulated radiotherapy for ¹⁸F-FDG-PET-guided dose escalation in oropharyngeal cancer: A planning study. Med Dosim 2013;38:18-24.

24. Münch S, Aichmeier S, Hapfelmeier A, Duma MN, Oechsner M, Feith M, *et al.* Comparison of dosimetric parameters and toxicity in esophageal cancer patients undergoing 3D conformal radiotherapy or VMAT. Strahlenther Onkol 2016;192:722-9.

25. Scorsetti M, Bignardi M, Clivio A, Cozzi L, Fogliata A, Lattuada P, *et al.* Volumetric modulation arc radiotherapy compared with static gantry intensity-modulated radiotherapy for malignant pleural mesothelioma tumor: A feasibility study. Int J Radiat Oncol Biol Phys 2010;77:942-9.

26. Sapkaroski D, Osborne C, Knight KA. A review of stereotactic body radiotherapy – Is volumetric modulated arc therapy the answer? J Med Radiat Sci 2015;62:142-51.

27. Ong CL, Verbakel WF, Cuijpers JP, Slotman BJ, Lagerwaard FJ, Senan S. Stereotactic radiotherapy for peripheral lung tumors: A comparison of volumetric modulated arc therapy with 3 other delivery techniques. Radiother Oncol 2010;97:437-42.

28. Rossi MM, Peulen HM, Belderbos JS, Sonke JJ. Intrafraction motion in stereotactic body radiation therapy for non-small cell lung cancer: Intensity modulated radiation therapy versus volumetric modulated arc therapy. Int J Radiat Oncol Biol Phys 2016;95:835-43.

29. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, *et al.* Stereotactic body radiation therapy: The report of AAPM task group 101. Med Phys 2010;37:4078-101.

30. Li XA, editor. Adaptive Radiation Therapy. Boca Raton, FL: CRC Press; 2011.

31. Harsolia A, Hugo GD, Kestin LL, Grills IS, Yan D. Dosimetric advantages of four-dimensional adaptive image-guided radiotherapy for lung tumors using online cone-beam computed tomography. Int J Radiat Oncol Biol Phys 2008;70:582-9.

32. Sonke JJ, Belderbos J. Adaptive radiotherapy for lung cancer. Semin Radiat Oncol 2010;20:94-106.

33. Brock KK, Dawson LA. Adaptive management of liver cancer radiotherapy. Semin Radiat Oncol 2010;20:107-15.

34. Hawkins MA, Brooks C, Hansen VN, Aitken A, Tait DM. Cone beam computed tomography-derived adaptive radiotherapy for radical treatment of esophageal cancer. Int J Radiat Oncol Biol Phys 2010;77:378-83.

35. Dial C, Weiss E, Siebers JV, Hugo GD. Benefits of adaptive radiation therapy in lung cancer as a function of replanning frequency. Med Phys 2016;43:1787.

36. Duffton A, Harrow S, Lamb C, McJury M. An assessment of cone beam CT in the adaptive radiotherapy planning process for non-small-cell lung cancer patients. Br J Radiol 2016;89:20150492.

37. Ding GX, Duggan DM, Coffey CW, Deeley M, Hallahan DE, Cmelak A, *et al.* A study on adaptive IMRT treatment planning using kV cone-beam CT. Radiother Oncol 2007;85:116-25.

38. Purdie TG, Bissonnette JP, Franks K, Bezjak A, Payne D, Sie F, *et al.* Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: Localization, verification, and intrafraction tumor position. Int J Radiat Oncol Biol Phys 2007;68:243-52.

39. Lambrecht M, Melidis C, Sonke JJ, Adebahr S, Boellaard R, Verheij M, *et al.* Lungtech, a phase II EORTC trial of SBRT for centrally located lung tumours – A clinical physics perspective. Radiat Oncol 2016;11:7.

40. Poludniowski G, Thomas MD, Evans PM, Webb S. CT reconstruction from portal images acquired during volumetric-modulated arc therapy. Phys Med Biol 2010;55:5635-51.

41. Zhao X, Zhang R. Feasibility of 3D tracking and adaptation of VMAT based on VMAT-CT. Radiother Oncol 2020;149:18-24.

42. Zhao X, Zhang R. Feasibility of 4D VMAT-CT. Biomed Phys Eng Express 2022;8:065018.

43. Kida S, Saotome N, Masutani Y, Yamashita H, Ohtomo K, Nakagawa K, *et al.* 4D-CBCT reconstruction using MV portal imaging during volumetric modulated arc therapy. Radiother Oncol 2011;100:380-5.

44. Wendling M, Zijp LJ, McDermott LN, Smit EJ, Sonke JJ, Mijnheer BJ, *et al.* A fast algorithm for gamma evaluation in 3D. Med Phys 2007;34:1647-54.

45. Bezjak A, Paulus R, Gaspar LE, Timmerman RD, Straube WL, Ryan WF, *et al.* Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG oncology/RTOG 0813 trial. J Clin Oncol 2019;37:1316-25.

46. Mahesh M. Fluoroscopy: Patient radiation exposure issues. Radiographics 2001;21:1033-45.

47. Guckenberger M, Richter A, Wilbert J, Flentje M, Partridge M. Adaptive radiotherapy for locally advanced non-small-cell lung cancer does not underdose the microscopic disease and has the potential to increase tumor control. Int J Radiat Oncol Biol Phys 2011;81:e275-82.

48. Bertholet J, Anastasi G, Noble D, Bel A, van Leeuwen R, Roggen T, *et al.* Patterns of practice for adaptive and real-time radiation therapy (POP-ART RT) part II: Offline and online plan adaption for interfractional changes. Radiother Oncol 2020;153:88-96.