Recent Advances and Challenges in Adaptive Radiotherapy for Patients with Locally Advanced NSCLC

Hualiang Zhong[1]* and Jian-Yue Jin[2]

[1]Department of Radiation Oncology, Henry Ford Health System, USA

[2]Department of Radiation Oncology, Indiana University, USA

Abstract

Patients with locally advanced Non-Small Cell Lung Cancer (NSCLC) often show significant tumor regression and anatomical changes during the course of radiation treatment. As reaction to these changes, planned treatment parameter will be modified multiple times so that the overall treatment can be optimized. This is termed as Adaptive Radiotherapy (ART). While significant progress has been made in the past few years for development of different ART techniques, challenges still exist in implementation of this treatment modality in clinic. In this topical review, techniques used in different ART components will be briefly reviewed, and strategies to maximize the efficacy of adaptive treatment will also be discussed.

Introduction

Lung cancer is the leading cause of cancer death worldwide; it is responsible for over 1.6 million deaths a year [1]. Most patients with Non-Small Cell Lung Cancer (NSCLC) are treated either with Radiotherapy (RT) alone or by a combination with chemotherapy [2]. Technique development in radiotherapy has made significant progress in the past two decades. For example, Intensity-Modulated Radiotherapy (IMRT) has a better sparing of critical organs than 3D conformal treatment [3]; On-Board Imaging (OBI) enables real-time corrections of patient setup errors [4,5], facilitating Stereotactic Body Radiotherapy (SBRT). These techniques have increased the efficiency of radiation treatment, reduced radiation toxicity to surrounding normal tissues [6] and improved clinical outcomes for patients with early stage NSCLC [7-9].

Although the underlying mechanisms of the SBRT approach are not fully understood, the success of this regimen is likely a result of the significantly higher dose (BED's >100 Gy) delivered in a highly focused way to the tumor [10-12]. For patients with locally advanced cancer, the ability to escalate dose significantly, however, is often limited by the increased risk of normal tissue complications due to the large size of the tumor [13-15]. On the other hand, investigators have observed a significant reduction in tumor volume during fractionated radiotherapy. One study showed that the tumor volume decreased by ~41% (range: 32.9% to 49.6%) and the metabolic activities decreased by 69% on average (range: 62.2% to 76.8%) [16]; other studies reported tumor volume regression of ~1.2% daily and ~52% by the end of treatment [17,18]. The reduction in tumor volume makes it possible to use a carefully validated ART paradigm to reduce normal tissue toxicity, enable iso-toxic dose escalation to the residual tumor target, and consequently improves treatment outcomes for these patients.

Advances in Development of ART Techniques

Adaptive radiotherapy consists of multiple steps: developing an initial treatment plan for the first few fractions, evaluating treatment response using CT, CBCT or PET images, updating Gross Tumor Volume (GTV) and Planning Target Volume (PTV) based on the measured treatment response, revising the original prescription on the target volume according to an adaptive protocol such as the principle of iso-toxic dose escalation, and developing an adaptive plan through re-contouring, dose accumulation, and plan re-optimization. Because tumor and patient anatomy may change significantly after a few fractions of treatment, Deformable Image Registration (DIR) is required to help perform these tasks.

Deformable image registration

DIR plays a key role in implementation of adaptive radiotherapy. Development of an accurate, robust DIR algorithm has been an active area of research. Optical flow-based "demons" and B-spline-

based free form are two most popular registration algorithms used in clinical RT planning systems. In the past two decades a variety of modifications have been applied to improve the performance of these algorithms. For example, the original "demons" [19] has been enhanced to be efficient [20], inverse consistent [21] and diffeomorphic [22,23]; the B-spline-based algorithm [24] has been extended to be hierarchical [25] and diffeomorphic [26], or have non-uniform knot placements [27] and simplified regularization forms [28]. Furthermore, these registration methods have been integrated with mechanical models to improve their performance in regions with low contrast intensity gradients [29] and for cross-modality deformable image registration [30]. The technical developments have greatly improved the efficiency of contour propagation [6,31,32] and dose accumulation [33,34], and advanced the research of adaptive radiotherapy.

Contour propagation

Updating an initial RT plan multiple times may help maximize the ART benefits [35]. However, it is time-intensive to contour tumor target and Organ at Risk (OAR) for each of these plan adaptations [36]. To address this issue, DIR algorithms were employed to propagate OAR contours automatically from the original planning CT images to during-RT images [37,38]. Due to limited contrasts and gradients in during-RT images, the registrations could have large errors, and the propagated volumes should be thoroughly assessed [6]. Also to minimize the influence of tumor regression on the registration of surrounding structures, it was recommended that the registration's displacements in the tumor region be corrected with a mechanical model [33] or alternatively, image information in regions nearby the tumor be excluded from the registration [39].

Dose accumulation

Optimization of an adaptive plan requires radiation dose delivered to each image voxel to be accumulated appropriately over the course of treatment. The accuracy of dose accumulation depends on the DIR and dose mapping methods used. Currently most registration algorithms could be accurate within 2 mm to 3 mm on average [40-42], which is comparable to the resolution of dose grids often used in clinic [43,44]. The spatial uncertainties may result in dose mapping errors up to 3 Gy/mm [45], but in clinical scenarios the impact of these errors could be limited [46]. On the other hand, even with a correct registration map, dose interpolation methods still have inherent errors in regions of high dose gradient [47]; also Deformable Dose Accumulation (DDA) can be compromised by changes in the mass and volume of solid tumors and/or normal tissues over the course of treatment. To address these issues, 4D Monte Carlo-based methods such as Voxel-Warping Method (VWM) [48], Energy-Mass Congruent Mapping (EMCM) [49] and energy-conserved registration methods [33,50] were proposed to help improve the quality of dose accumulation.

Quality assurance

Adaptive treatment planning involves multiple computational tasks such as 3D dose calculation, DIR, dose warping and accumulation. Ideally these tasks could be separately verified for each patient. Unlike 3D dose calculations which can be verified with homogeneous and heterogeneous do simetric phantoms during the commissioning of treatment planning systems, the actual dose delivered to deforming organs over the treatment course is difficult to verify [51]. Since there is a lack of a gold standard to evaluate the DIR and DDA operations directly, alternative verifications must be performed.

Landmark and contour comparisons and Dice similarity coefficients are often used as criteria to evaluate the performance of DIR in various applications including contour propagation [41,52-54]; the self or inverse consistency of deformation maps also can be used to help evaluate the accuracy of the registration [21,55,56]; computational phantoms offer another option to verify the accuracy of displacements directly at each voxel. The phantom's deformation can be simulated using different mathematical formulae [20], and the realism of the deformation can be enhanced with patient-specific deformable models [57]. Different from computational phantoms, physical phantoms may help measure the delivered dose to verify dose accumulation operations. However, these phantoms are limited in simulation of mass changes in tumor and other organs during the course of treatment, and also do not have realistic organ deformation and mass heterogeneity as patients [58-60]. Therefore, further improvement of these phantoms is required, and the phantom-based evaluations should be supplemented by other verification methods such as the energy conservation criterion that can be applied to both deformed anatomical structures and regress tumor volumes [33,50].

Response assessment

In clinic tumor response is evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), based on changes in measured tumor volumes [61]. Note that tumor volume may increase during the course of treatment, for example, due to internal hemorrhage, necrosis, or metabolically non-viable tumor cells mis-counted in the measured volume. Also there are uncertainties when only CBCT images were used for the volume measurement [18]. Since FDG-PET images can show metabolic activities in addition to the tumor size, it has been recommended that both CT and PET images be used for measurement of mid-treatment tumor response for adaptive RT [62,63]. It should be mentioned that the Standardized Uptake Value (SUV) of PET images could be influenced by many factors [64-66], and also changes in region-specific SUVs cannot be quantified until correct deformation maps are applied [66-68]. Methods for quantitative assessments of tumor response are worth further investigations.

Prescription for adaptive planning

It has been reported that for locally advanced NSCLC, dose regimens in the range of 60 Gy to 66 Gy produce 5-year overall survival rates of 10% to 15% [69]. Although a randomized trial did not show superiority at a dose of 74 Gy *vs.* 60 Gy [15], the reasons for the under performance of the higher dose arm are still unclear [70-72]. Many technical factors such as respiratory motion management, treatment planning margins, type of delivery (IMRT *vs.* 3D-CRT), use of FDG-PET and image guidance in the treatment planning and delivery process could be further analyzed [70,73]. With improved RT planning and delivery techniques, it is possible to have the normal lung and heart better spared from radiation, and dose-intensified RT schedules safely administered [69]. It has been found that for patients with locally advanced NSCLC, ART may increase radiation dose to the residual tumor target up to 80 Gy on average, without increasing dose to normal tissue [74,75]. However, more clinical data should be collected to evaluate the impact of ART on normal tissue dose reduction.

For patients with locally advanced NSCLC, it has been reported that increasing dose from 60 Gy to 74 Gy results in predictable, deleterious effects on quality of life [76]. For these patients, RT-

induced adverse events may include pneumonitis, esophagitis and pericarditis [77], and therefore radiation dose to these organs should be minimized. Compared to dose escalation, it is of equivalent importance to develop effective treatment strategies to mitigate normal tissue toxic effects for these patients.

Decision for plan adaptation

For patients with NSCLC, initial plans were suggested to be updated if tumor regression is up to 30% within the first 20 fractions [78]. With a single adaptation at mid-treatment, approximately 65% of the potential dose escalation can be achieved [35]. Since tumor may continuously shrink during the course of treatment, there is a tradeoff between the amount of the reduced tumor volume and the number of the remaining fractions [79]. It has been reported that plan adaptation performed around fraction 15 and fraction 20 is most diametrically efficient for concurrent and sequential chemo-radiotherapy, respectively [79]. Based on iso-toxic Mean Lung Dose (MLD), re-planning twice at weeks 2 and 4 may achieve an average escalation of 13.4 Gy [75], and at weeks 3 and 5 may have an average increase of 7 Gy or a reduction in MLD of approximately 8% [12]. Since tumor shrinkage depends on many factors such as tumor histology, location, stage and imaging modality used in the volume measurement, the optimal time point for plan adaptation and its dosimetric gain could be different for individual patients.

Challenges

Adaptive radiotherapy holds great clinical promise in iso-toxic escalation of radiation dose to target structures and also in reduction of normal tissue complications [80]. Tremendous progresses have been made in development of deformable dose accumulation and re-planning techniques in the past years. However, some critical issues remain to be addressed before this treatment modality is accepted generally in clinic for treatment of NSCLC patients [81].

Since tumor response is not uniform, survived tumor cells may exist sporadically. The CTV margin required for the adaptive plan could be different from that used in the original plan where the margin was designed to cover sub-clinical disease spread from the original gross tumor volume [82]. While PET images, after appropriate registrations, may help measure region-specific tumor response, the resolution of these images is limited, and the survived tumor cells cannot be detected effectively. Also as tumor response to radiation is patient dependent, it is not clear what is the optimal dose required to eliminate the remaining tumor cells, and how much doses should be delivered by the adaptive plan, respectively, to the remaining tumor and to those regions where the tumor is no longer visible from the during-RT images [70].

The accuracy of DIR remains the major concern in the clinical implementation of ART. It has been illustrated that intensity-based DIR algorithms are prone to have errors in regions with low image contrasts [40,42,83], and consequently, errors in dose reconstruction and response assessment may exist in these regions. Also due to the lack of knowledge on the pattern of tumor regression, how to deform the anatomical structures near by the tumor is still unclear [74,80]. Despite some improvements being made using mechanical models, the parameters and constraints of these models remain to be optimized and the accuracy of these algorithms in clinical settings needs to be further evaluated.

Conclusions

Patients with locally advanced NSCLC often have tumor regression during the course of fractionated radiotherapy. Updating an initial RT plan at multiple time points may help spare normal tissue and enable dose escalation to the residual tumor target. With more clinical trials, adaptive strategies can be further optimized to improve clinical outcome for these patients, and consequently help migrate the modality of adaptive radiotherapy into general use in clinic.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.

2. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64(4):252-71.

3. Webb S. Conformal intensity-modulated radiotherapy (IMRT) delivered by robotic linac--testing IMRT to the limit? Phys Med Biol. 1999;44(7):1639-54.

4. Jaffray DA, Siewerdsen JH. Cone-beam computed tomography with a flat-panel imager: initial performance characterization. Med Phys. 2000;27(6):1311-23.

5. Yan D, Ziaja E, Jaffray D, Wong J, Brabbins D, Vicini F, et al. The use of adaptive radiation therapy to reduce setup error: a prospective clinical study. Int J Radiat Oncol Biol Phys. 1998;41(3):715-20.

6. Hardcastle N, van Elmpt W, De Ruysscher D, Bzdusek K, Tomé WA. Accuracy of deformable image registration for contour propagation in adaptive lung radiotherapy. Radiat Oncol. 2013;8:243.

7. Rosenzweig KE, Fox JL, Yorke E, Amols H, Jackson A, Rusch V, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. Cancer. 2005;103(10):2118-27.

8. Bezjak A, Papiez L, Bradley JD, Gore E, Gaspar L, Kong FM, et al. Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients. RTOG 0813 Protocol; 2013.

9. Matsuo Y, Chen F, Hamaji M, Kawaguchi A, Ueki N, Nagata Y, et al. Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: A propensity score matching analysis. Eur J Cancer. 2014;50(17):2932-8.

10. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys. 2014;88(2):254-62.

11. 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(2):324-33.

12. Guckenberger M, Wilbert J, Richter A, Baier K, and Flentje M. Potential of adaptive radiotherapy to escalate the radiation dose in combined radiochemotherapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2011;79(3):901-8.

13. Movsas B, Raffin TA, Epstein AH, Link CJ. Pulmonary radiation injury. Chest. 1997;111(4):1061-76.

14. Yamashita H, Takahashi W, Haga A, Nakagawa K. Radiation pneumonitis after stereotactic radiation therapy for lung cancer. World J Radiol. 2014;6(9):708-15.

15. Bradley JD, Moughan J, Graham MV, Byhardt R, Govindan R, Fowler J, et al. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell

lung cancer: phase I results of RTOG 0117. Int J Radiat Oncol Biol Phys. 2010;77(2):367-72.

16. Kong FM, Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys. 2011;81(5):1442-57.

17. Kupelian PA, Ramsey C, Meeks SL, Willoughby TR, Forbes A, Wagner TH, et al. Serial megavoltage CT imaging during external beam radiotherapy for non-small-cell lung cancer: observations on tumor regression during treatment. Int J Radiat Oncol Biol Phys. 2005;63(4):1024-8.

18. Lim G, Bezjak A, Higgins J, Moseley D, Hope AJ, Sun A, et al. Tumor regression and positional changes in non-small cell lung cancer during radical radiotherapy. J Thorac Oncol. 2011;6(3):531-6.

19. Thirion JP. Image matching as a diffusion process: an analogy with Maxwell's demons. Med Image Anal. 1998;2(3):243-60.

20. Wang H, Dong L, O'Daniel J, Mohan R, Garden AS, Ang KK, et al. Validation of an accelerated 'demons' algorithm for deformable image registration in radiation therapy. Phys Med Biol. 2005;50(12):2887-905.

21. Yang D, Li H, Low DA, Deasy JO, and El Naqa I. A fast inverse consistent deformable image registration method based on symmetric optical flow computation. Phys Med Biol. 2008;53(21):6143-65.

22. Vercauteren T, Pennec X, Perchant A, Ayache N. Diffeomorphic demons: efficient non-parametric image registration. Neuroimage. 2009;45(1):S61-72.

23. Yeo BT, Sabuncu MR, Vercauteren T, Ayache N, Fischl B, Golland P. Spherical demons: fast diffeomorphic landmark-free surface registration. IEEE Trans Med Imaging. 2010;29(3):650-68.

24. Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. IEEE Trans Med Imaging. 1999;18(8):712-21.

25. Klein S, Staring M, Murphy K, Viergever MA, Pluim JP. elastix: a toolbox for intensity-based medical image registration. IEEE Trans Med Imaging. 2010;29(1):196-205.

26. Rueckert D, Aljabar P, Heckemann RA, Hajnal JV, Hammers A. Diffeomorphic registration using B-splines. Med Image Comput Comput Assist Interv. 2006;9(2):702-9.

27. Jacobson TJ, Murphy MJ. Optimized knot placement for B-splines in deformable image registration. Med Phys. 2011;38(8):4579-82.

28. Chun SY, Fessler JA. A simple regularizer for B-spline nonrigid image registration that encourages local invertibility. IEEE J Sel Top Signal Process. 2009;3(1):159-69.

29. Zhong H, Kim J, Li H, Nurushev T, Movsas B, Chetty IJ. A finite element method to correct deformable image registration errors in low-contrast regions. Phys Med Biol. 2012;57(11):3499-515.

30. Zhong H, Cai J, Glide-Hurst C, and Chetty IJ. An adaptive finite element method to cope with a large scale lung deformation in magnetic resonance images, In: 2014 IEEE 11th International Symposium on Biomedical Imaging (ISBI); 2014 April 29 - May 02; IEEE: Beijing; 2014. p. 770-3.

31. Chao M, Schreibmann E, Li T, Wink N, Xing L. Automated contour mapping using sparse volume sampling for 4D radiation therapy. Med Phys. 2007;34(10):4023-9.

32. Mencarelli A, Van Kranen SR, Hamming-Vrieze O, Van Beek S, Nico Rasch CR, Van Herk M, et al. Deformable Image Registration for Adaptive Radiation Therapy of Head and Neck Cancer: Accuracy and Precision in the Presence of Tumor Changes. Int J Radiat Oncol Biol Phys. 2014;90(3):680-7.

33. Zhong H, Chetty IJ. Adaptive radiotherapy for NSCLC patients: utilizing the principle of energy conservation to evaluate dose mapping operations.

Phys Med Biol. 2017;62(11):4333-45.

34. Li HS, Zhong H, Kim J, Glide-Hurst C, Gulam M, Nurushev TS, et al. Direct dose mapping versus energy/mass transfer mapping for 4D dose accumulation: fundamental differences and dosimetric consequences. Phys Med Biol. 2014;59(1):173-88.

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(4):1787.

36. Kumarasiri A, Siddiqui F, Liu C, Yechieli R, Shah M, Pradhan D, et al. Deformable image registration based automatic CT-to-CT contour propagation for head and neck adaptive radiotherapy in the routine clinical setting. Med Phys. 2014;41(12):121712.

37. Lu W, Olivera GH, Chen Q, Chen ML, Ruchala KJ. Automatic re-contouring in 4D radiotherapy. Phys Med Biol. 2006;51(5):1077-99.

38. Shekhar R, Lei P, Castro-Pareja CR, Plishker WL, D'souza WD. Automatic segmentation of phase-correlated CT scans through nonrigid image registration using geometrically regularized free-form deformation. Med Phys. 2007;34(7):3054-66.

39. Guckenberger M, Baier K, Richter A, Wilbert J, Flentje M. Evolution of surface-based deformable image registration for adaptive radiotherapy of non-small cell lung cancer (NSCLC). Radiat Oncol. 2009;4:68.

40. Yeo UJ, Supple JR, Taylor ML, Smith R, Kron T, Franich RD. Performance of 12 DIR algorithms in low-contrast regions for mass and density conserving deformation. Med Phys. 2013;40(10):101701.

41. Castillo R, Castillo E, Guerra R, Johnson VE, Mcphail T, Garg AK, et al. A framework for evaluation of deformable image registration spatial accuracy using large landmark point sets. Phys Med Biol. 2009;54(7):1849-70.

42. Zhong H, Kim J, Chetty IJ. Analysis of deformable image registration accuracy using computational modeling. Med Phys. 2010;37(3):970-9.

43. Rosu M, Chetty IJ, Balter JM, Kessler ML, McShan DL, Ten Haken RK. Dose reconstruction in deforming lung anatomy: dose grid size effects and clinical implications. Med Phys. 2005;32(8):2487-95.

44. Park JY, Kim S, Park HJ, Lee JW, Kim YS, Suh TS. Optimal set of grid size and angular increment for practical dose calculation using the dynamic conformal arc technique: a systematic evaluation of the dosimetric effects in lung stereotactic body radiation therapy. Radiat Oncol. 2014;9:5.

45. Salguero FJ, Saleh-Sayah NK, Yan C, Siebers JV. Estimation of three-dimensional intrinsic dosimetric uncertainties resulting from using deformable image registration for dose mapping. Med Phys. 2011;38(1):343-53.

46. Roussakis YG, Dehghani H, Green S, Webster GJ. Validation of a dose warping algorithm using clinically realistic scenarios. Br J Radiol. 2015;88(1049):20140691.

47. Siebers JV, Zhong H. An energy transfer method for 4D Monte Carlo dose calculation. Med Phys. 2008;35(9):4096-105.

48. Heath E, Seuntjens J. A direct voxel tracking method for four-dimensional Monte Carlo dose calculations in deforming anatomy. Med Phys. 2006;33(2):434-45.

49. Zhong H, Siebers JV. Monte Carlo dose mapping on deforming anatomy. Phys Med Biol. 2009;54(19):5815-30.

50. Zhong H, Chetty IJ. Caution Must Be Exercised When Performing Deformable Dose Accumulation for Tumors Undergoing Mass Changes During Fractionated Radiation Therapy. Int J Radiat Oncol Biol Phys. 2017;97(1):182-3.

51. Jaffray DA, Lindsay PE, Brock KK, Deasy JO, Tome WA. Accurate accumulation of dose for improved understanding of radiation effects in normal tissue. Int J Radiat Oncol Biol Phys. 2010;76(3):135-9.

52. Kaus MR, Brock KK, Pekar V, Dawson LA, Nichol AM, Jaffray DA. Assessment of a model-based deformable image registration approach for radiation therapy planning. Int J Radiat Oncol Biol Phys. 2007;68(2):572-80.

53. Lu W, Chen ML, Olivera GH, Ruchala KJ, Mackie TR. Fast free-form deformable registration via calculus of variations. Phys Med Biol. 2004;49(14):3067-87.

54. Kim J, Hammoud R, Pradhan D, Zhong H, Jin RY, Movsas B, et al. Prostate localization on daily cone-beam computed tomography images: accuracy assessment of similarity metrics. Int J Radiat Oncol Biol Phys. 2010;77(4):1257-65.

55. Christensen GE, Johnson HJ. Consistent image registration. IEEE Trans Med Imaging. 2001;20(7):568-82.

56. Zhong H, Peters T, Siebers JV. FEM-based evaluation of deformable image registration for radiation therapy. Phys Med Biol. 2007;52(16):4721-38.

57. Stanley N, Glide-Hurst C, Kim J, Adams J, Li S, Wen N, et al. Using patient-specific phantoms to evaluate deformable image registration algorithms for adaptive radiation therapy. J Appl Clin Med Phys. 2013;14(6):4363.

58. Zhong H, Adams J, Glide-Hurst C, Zhang H, Li H, Chetty IJ. Development of a deformable dosimetric phantom to verify dose accumulation algorithms for adaptive radiotherapy. J Med Phys. 2016;41(2):106-14.

59. Yeo UJ, Taylor ML, Supple JR, Smith RL, Dunn L, Kron T, et al. Is it sensible to "deform" dose? 3D experimental validation of dose-warping. Med Phys. 2012;39(8):5065-72.

60. Niu CJ, Foltz WD, Velec M, Moseley JL, Al-Mayah A, Brock KK. A novel technique to enable experimental validation of deformable dose accumulation. Med Phys. 2012;39(2):765-76.

61. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

62. Kong FM, Machtay M, Bradley J, Ten Haken R, Xiao Y, Matuszak M, et al. RTOG 1106/ACRIN 6697, Randomized Phase II Trial of Individualized Adaptive Radiotherapy Using During-Treatment FDG-PET/CT and Modern Technology in Locally Advanced Non-Small Cell Lung Cancer (NSCLC). RTOG 1106 Protocol; 2013.

63. Feng M, Kong FM, Gross M, Fernando S, Hayman JA, Ten Haken RK. Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. Int J Radiat Oncol Biol Phys. 2009;73(4):1228-34.

64. Callahan J, Binns D, Dunn L, Kron T. Motion effects on SUV and lesion volume in 3D and 4D PET scanning. Australas Phys Eng Sci Med. 2011;34(4):489-95.

65. Pan T, Mawlawi O, Nehmeh SA, Erdi YE, Luo D, Liu HH, et al. Attenuation correction of PET images with respiration-averaged CT images in PET/CT. J Nucl Med. 2005;46(9):1481-7.

66. Biehl KJ, Kong FM, Dehdashti F, Jin JY, Mutic S, El Naqa I, et al. 18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: is a single standardized uptake value threshold approach appropriate? J Nucl Med. 2006;47(11):1808-12.

67. Lu W, Wang J, Zhang HH. Computerized PET/CT image analysis in the evaluation of tumour response to therapy. Br J Radiol. 2015;88(1048):20140625.

68. Zhong H, Brown S, Chetty I. Voxel-based tracking of 18f-fdg pet images for evaluation of treatment response for NSCLC patients. In: International Conference on Molecular Targets and Cancer Therapeutics. Boston, MA: AACR; 2015. p. A88.

69. Kong FM, Zhao J, Wang J, Faivre-Finn C. Radiation dose effect in locally advanced non-small cell lung cancer. J Thorac Dis. 2014;6(4):336-47.

70. Kong F, Haken RKT, Schipper M, Hayman J, Ramnath N, Hassan KA, et al. A phase II trial of mid-treatment FDG-PET adaptive, individualized radiation therapy plus concurrent chemotherapy in patients with non-small cell lung cancer (NSCLC). J Clin Oncol. 2013;31(15):7522.

71. Cox JD. Are the results of RTOG 0617 mysterious? Int J Radiat Oncol Biol Phys. 2012;82(3):1042-4.

72. Thomas CR. The Importance of quality of life assessment. JAMA Oncol. 2016;2(3):367-8.

73. Movsas B, Hu C, Sloan J, Bradley JD, Kavadi VS, Narayan S, et al. Quality of life (QOL) analysis of the randomized radiation (rt) dose-escalation nsclc trial (RTOG 0617): The Rest of the Story. Int J Radiat Oncol Biol Phys. 2013;87(2):S1-S2.

74. Zhong H, Siddiqui SM, Movsas B, Chetty IJ. Evaluation of adaptive treatment planning for patients with non-small cell lung cancer. Phys Med Biol. 2017;62(11):4346-60.

75. Weiss E, Fatyga M, Wu Y, Dogan N, Balik S, Sleeman W, et al. Dose escalation for locally advanced lung cancer using adaptive radiation therapy with simultaneous integrated volume-adapted boost. Int J Radiat Oncol Biol Phys. 2013;86(3):414-9.

76. Movsas B, Hu C, Sloan J, Bradley J, Komaki R, Masters G, et al. Quality of life analysis of a radiation dose-escalation study of patients with non-small-cell lung cancer: a secondary analysis of the radiation therapy oncology group 0617 randomized clinical trial. JAMA Oncol. 2016;2(3):359-67.

77. Bentzen SM, Parliament M, Deasy JO, Dicker A, Curran WJ, Williams JP, et al. Biomarkers and surrogate endpoints for normal-tissue effects of radiation therapy: the importance of dose-volume effects. Int J Radiat Oncol Biol Phys. 2010;76(3):145-50.

78. Woodford C, Yartsev S, Dar AR, Bauman G, Van Dyk J. Adaptive radiotherapy planning on decreasing gross tumor volumes as seen on megavoltage computed tomography images. Int J Radiat Oncol Biol Phys. 2007;69(4):1316-22.

79. Berkovic P, Paelinck L, Lievens Y, Gulyban A, Goddeeris B, Derie C, et al. Adaptive radiotherapy for locally advanced non-small cell lung cancer, can we predict when and for whom? Acta Oncol. 2015;54(9):1438-44.

80. Sonke JJ, Belderbos J. Adaptive radiotherapy for lung cancer. Semin Radiat Oncol. 2010;20(2):94-106.

81. Schultheiss TE, Tome WA, Orton CG. Point/counterpoint: it is not appropriate to "deform" dose along with deformable image registration in adaptive radiotherapy. Med Phys. 2012;39(11):6531-3.

82. Burnet NG, Thomas SJ, Burton KE, Jefferies SJ. Defining the tumour and target volumes for radiotherapy. Cancer Imaging. 2004;4(2):153-61.

83. Liu F, Hu Y, Zhang Q, Kincaid R, Goodman KA, Mageras GS. Evaluation of deformable image registration and a motion model in CT images with limited features. Phys Med Biol. 2012;57(9):2539-54.