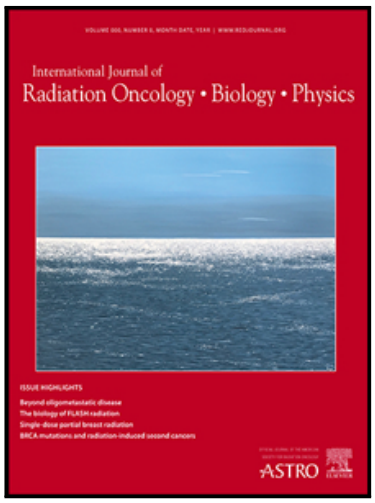

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4-Dimensional Computed Tomography Ventilation Image-Guided Lung Functional Avoidance Radiotherapy: A Single-Arm Prospective Pilot Clinical Trial

Short running title: Lung functional avoidance RT pilot trial

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Conflict of interest: Dr. Yamamoto received an equipment loan (research version of the Pinnacle^3 treatment planning system) from Philips Radiation Oncology Systems. Drs. Kabus and Bal are employees of Philips. Dr. Keall is an inventor on US patent 7,668,357 CT Pulmonary Function test. This patent and associated intellectual property have been exclusively licensed by the University of Sydney to 4DMedical Limited.

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Abstract

Purpose: The primary objective of this prospective pilot trial was to assess the safety and feasibility of lung functional avoidance radiotherapy (RT) with 4-dimensional (4D) computed tomography (CT) ventilation imaging.

Methods and Materials: Patients with primary lung cancer or metastatic disease to the lungs to receive conventionally fractionated RT (CFRT) or stereotactic body RT (SBRT) were eligible. Standard-of-care 4D-CT scans were used to generate ventilation images through image processing/analysis. Each patient required a standard intensity-modulated RT plan and ventilation image-guided functional avoidance plan. The primary endpoint was the safety of

functional avoidance RT, defined as the rate of grade ≥3 adverse events (AEs) that occurred ≤12 months after treatment. Protocol treatment was considered safe if the rates of grade ≥3 pneumonitis and esophagitis were <13% and <21%, respectively for CFRT, and if the rate of any grade ≥3 AEs was <28% for SBRT. Feasibility of functional avoidance RT was assessed by comparison of dose metrics between the two plans using the Wilcoxon signed-rank test.

Results: Between May 2015 and November 2019, 34 patients with non-small cell lung cancer were enrolled, and 33 patients were evaluable (n=24 for CFRT; n=9 for SBRT). Median follow-up was 14.7 months. For CFRT, the rates of grade ≥3 pneumonitis and esophagitis were 4.2% (95% confidence interval, 0.1%-21.1%) and 12.5% (2.7%-32.4%). For SBRT, no patients developed grade ≥3 AEs. Compared with the standard plans, the functional avoidance plans significantly (p<0.01) reduced the lung dose-function metrics without compromising target coverage or adherence to standard organs at risk constraints.

Conclusions: This study, representing one of the first prospective investigations on lung functional avoidance RT, demonstrated that the 4D-CT ventilation image-guided functional avoidance RT that significantly reduced dose to ventilated lung regions could be safely administered, adding to the growing body of evidence for its clinical utility.

Introduction

Thoracic radiotherapy (RT) is limited by toxicities, including pulmonary toxicity (1,2). Pulmonary toxicity diminishes quality of life, which is a significant, independent prognostic factor for survival in non-small cell lung cancer (NSCLC) (3). Common pulmonary toxicities include radiation pneumonitis, difficulty breathing (dyspnea) and lung function loss (1). In particular, pneumonitis is potentially fatal and associated with poor survival (4). The rate of symptomatic pneumonitis reported in published studies (2,5,6) ranges from approximately 16% to 37% in patients with lung cancer who received conventionally fractionated RT with or without chemotherapy. Pneumonitis is also one of the most common toxicities after stereotactic body RT (SBRT) (7),

with an incidence of symptomatic pneumonitis of approximately 9.5% (8). Moreover, immunotherapy (which has been incorporated into the current standard-of-care for locally advanced NSCLC) also causes pulmonary toxicity (9). A recent study has shown a significantly higher incidence of severe pneumonitis in patients with lung metastases treated with SBRT and concurrent immunotherapy than those treated with SBRT alone (11% vs. 0%) (10). As the number of lung cancer patients receiving RT continues to grow (11) and immunotherapy is rapidly adopted into clinical practice, the importance of addressing pulmonary toxicity increases.

Functional avoidance RT is a strategy that preferentially avoids irradiating normal (ventilated or perfused) lung regions, which may reduce pulmonary toxicity compared to standard RT. This strategy was proposed a few decades ago (12) and has been investigated mainly with nuclear medicine imaging methods (13), such as ^{99m}Tc-macroaggregated albumin (MAA) single-photon emission computed tomography (SPECT). A method based on 4-dimensional (4D) computed tomography (CT) and image processing/analysis (henceforth referred to as 4D-CT ventilation imaging) was developed relatively recently (14,15) and has been validated through animal and human studies (16-18). Compared to other functional imaging methods, including SPECT and magnetic resonance imaging (MRI), 4D-CT ventilation imaging provides several advantages: 1) higher spatial resolution; 2) lower cost; 3) greater availability; and/or 4) no extra scans or contrast agents required (because ventilation computation only requires a standard-of-care 4D-CT scan and image processing/analysis), and hence has been commonly used in recent studies (13). Accumulating evidence indicates that pulmonary toxicity is more strongly associated with dose-function (ventilation or perfusion) data compared to standard dose-volume data (19-21).

Functional avoidance RT involves substantial dose redistribution in and around the lungs, which may lead to increased dose to organs at risk (OARs) and increased maximum dose to the planning target volume (PTV) as reported in previous planning studies (22-24), raising safety

concerns. To prospectively investigate these concerns, we initiated a single-arm prospective pilot clinical trial (ClinicalTrials.gov number, NCT****omitted for blind review****) to assess the safety and feasibility of functional avoidance RT with 4D-CT ventilation imaging. The primary outcome measure of this trial was the safety of 4D-CT ventilation image-guided functional avoidance RT, which was defined as the rate of grade ≥3 adverse events (AEs).

Methods and Materials

Patients

In this pilot clinical trial approved by the institutional review board (NCT****omitted for blind review****), we recruited patients at ****omitted for blind review****. Inclusion criteria included: 1) primary lung cancer or metastatic disease to the lung to be treated with either conventionally fractionated RT (CFRT) or stereotactic body RT (SBRT); 2) ≥18 years of age; 3) life expectancy of ≥6 months in the estimation of the treating physician; 4) Zubrod performance status score of ≤2; and 5) adequate marrow and hepatic function. Patients with prior thoracic RT leading to overlap with planned RT fields were excluded. For patients undergoing CFRT, distant metastatic disease was not allowed. For those undergoing SBRT, early-stage primary lung cancer and limited metastatic disease to the lung were allowed; however, oligometastatic disease should have a controlled primary and no more than one other involved organ system. All patients provided written informed consent to participate in this trial.

Imaging

All patients underwent the standard RT planning procedures, including planning 3D CT and 4D-CT scans during free breathing. For patients undergoing SBRT, two 4D-CT scans were performed with abdominal compression to reduce respiratory tumor motion for treatment and without abdominal compression (free breathing). The free-breathing 4D-CT image datasets were used for ventilation computation through deformable image registration (DIR) for spatial

mapping of the end-inhalation CT (moving) to the end-exhalation CT image datasets (fixed) and image analysis for quantifying the regional volume change as a surrogate for ventilation using the Hounsfield unit (HU) change-based metric (14,25), which is one of the most commonly used metrics to quantify ventilation (18). The DIR algorithm used in this study has been previously evaluated in detail (26,27) and demonstrated to achieve sub-voxel accuracy (26). See Appendix E1 for further details on the HU change-based ventilation metric. The calculated ventilation values were converted into percentile values for RT treatment planning.

Physiological assessments

Patients underwent baseline physiological assessments, including pulmonary function tests (PFTs) (*i.e.*, spirometry, lung volumes and diffusing capacity), 6-min walk test (28), and BODE index, which is composed of the body-mass index (BMI) (B), the degree of airflow obstruction (O) and dyspnea (D) and exercise capacity (E) (29). PFTs were performed in the Pulmonary Function and Exercise Testing Lab at ****omitted for blind review****. Each PFT parameter was expressed as a percentage of the predicted normal value. Six-minute walk test and BODE index assessment were conducted during clinic visits at ****omitted for blind review****. BODE index point allocation for each variable was 0 to 3 points for forced expiratory volume in 1 second (FEV_1) (% predicted), 0 to 3 points for the 6-min walk distance (6MWD), 0 to 3 points for dyspnea (Modified Medical Research Council scale), and 0 to 1 point for BMI. The points for each component were added to obtain the total BODE index score, ranging from 0 (best) to 10 (worst). The BODE index has been extensively studied in chronic obstructive pulmonary disease (COPD) (29) and its prognostic value has been previously validated in inoperable NSCLC (30).

RT

Radiation dose was prescribed to the planning target volume (PTV) and was given using intensity-modulated RT (IMRT) with ≥6 MV photon beams and daily cone-beam CT image guidance. Patients received 60 Gy in 2 Gy fractions daily (CFRT), 54 Gy in 18 Gy fractions (SBRT for peripheral tumors), or 55 Gy in 11 Gy fractions (SBRT for centrally located tumors). The RT plan was normalized such that ≥95% of the PTV received the prescribed dose. The radiation oncologist determined the gross tumor volume (GTV), clinical target volume (CTV) (only for CFRT), internal target volume (ITV), and PTV per standard of care. The organs at risk (OARs) included the lungs, spinal cord, heart, esophagus, brachial plexus, proximal bronchial tree, trachea, great vessels and/or skin.

Each patient required a standard RT plan created without a ventilation image as well as a functional avoidance RT plan created with a ventilation image. Functional avoidance RT plans were designed to preferentially avoid irradiating ventilated lung regions without compromising target coverage or adherence to standard constraints of OARs (see Appendix E2). IMRT optimization of functional avoidance RT plans was performed with standard dose-volume objectives and lung dose-function objectives incorporating percentile ventilation values on a voxel-by-voxel basis using linear weighting, which was implemented in a research version of the Pinnacle^3 treatment planning system (Philips Radiation Oncology Systems, Fitchburg, WI) (31). The functional mean dose and percentage lung function receiving ≥20 Gy (fV_{20}) were chosen as dose-function constraints for IMRT optimization based on a previous study showing that these dose-function metrics were more strongly associated with pneumonitis compared to corresponding dose-volume metrics, *i.e.*, the mean dose and percentage volume receiving ≥20 Gy (V_{20}) (19). Additionally, beam angles were also optimized manually to avoid passing through ventilated lung regions. Further details of the functional avoidance RT planning approach have been previously described in the paper reporting on the first patient treatment (32). Per-protocol (acceptable) PTV coverage was achieved when the maximum dose to the PTV was ≤115%

(≤120%) of the prescribed dose and the minimum dose was ≥90% (≥85%) of the prescribed dose for CFRT, and when 99% of the PTV received ≥90% of the prescribed dose for SBRT. Both plans were reviewed and clinically approved by the radiation oncologist. The functional avoidance RT plan was used for treatment for all patients.

Systemic therapy

Systemic therapy was delivered at treating physician discretion. Patients with locally advanced NSCLC were treated with standard-of-care systemic therapy with platinum doublet chemotherapy. Following FDA approval of durvalumab for locally advanced NSCLC in February 2018, consolidation immunotherapy was offered to eligible patients for up to 12 months. SBRT patients did not receive systemic therapy.

Outcomes

The primary outcome measure of this trial was the safety of 4D-CT ventilation image-guided functional avoidance RT, which was defined as the rate of grade ≥3 AEs that occurred ≤12 months after treatment defined as definitely, probably, or possibly related to protocol treatment. During RT, patients were evaluated weekly by the treating radiation oncologist for AEs. After RT, clinical follow-up and contrast-enhanced thoracic CT imaging were performed every three months for 24 months, and at treatment physician discretion beyond 24 months (typically every 6 months year 3-5). All AEs were graded with the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The secondary outcome measures included long-term toxicity and the changes from baseline in the PFT parameters, 6MWD, and BODE index at 6 months after treatment.

Statistical analysis

This pilot trial was designed to assess the safety and feasibility of 4D-CT ventilation image-guided functional avoidance RT. Protocol treatment was considered safe if the rate of grade ≥3 pneumonitis was <13% and the rate of grade ≥3 esophagitis was <21% for CFRT, and if the rate of any grade ≥3 AEs was <28% for SBRT. These criteria were determined based on historical data of NSCLC patients treated with CFRT (5,33) and SBRT (34). A sample size of 34 would yield probabilities of 94%, 99% and 99% to observe AEs with true rates of 13%, 21% and 28%, respectively, in at least one patient. Minimum sample sizes of 17, 10 and 7 would be required to yield probabilities of ≥90% to observe those respective AEs in at least one patient. The AE rates would be estimated with standard errors of 6.7%, 8.1% and 15%, respectively. AE data from more recent studies were also used for comparison. The AE rates are reported with exact 95% confidence intervals (CIs). Descriptive statistics were generated for the patient and treatment characteristics, dose metrics of the standard and functional avoidance RT plans, and changes from baseline in the PFT parameters, 6MWD, and BODE index at 6 months after treatment. We also performed the Mann-Whitney U test and Fisher's exact test (for continuous and categorical variables, respectively) to compare distributions of patient and treatment characteristics between patients who had pneumonitis and those who did not. Moreover, we calculated curves of freedom from pneumonitis using the product-limit method of Kaplan and Meier for patient subgroups defined by patient/treatment characteristics. The time to pneumonitis was measured from start of RT and censored at last follow-up for patients not experiencing this endpoint (including death). For continuous variables, patients were divided by the median value into two subgroups. We compared the resulting curves using the log-rank test. Dosimetric feasibility of functional avoidance RT was assessed by comparison of the dose metrics between the standard and functional avoidance RT plans using the Wilcoxon signed-rank test.

Results

Between May 2015 and November 2019, 34 patients with NSCLC were enrolled: 25 and 9 patients to receive CFRT and SBRT, respectively, and the trial reached its accrual goal. One patient with stage III NSCLC died from rapid disease progression after enrollment and prior to initiating planned CFRT, and was excluded from the analysis. Patient and treatment characteristics are shown in Table 1 for 33 evaluable patients (CFRT, n=24; SBRT, n=9). The majority of patients treated with CFRT (n=23, 96%) had stage III NSCLC. All patients treated with CFRT received concurrent chemotherapy. Four patients treated with CFRT (17%) also received consolidation immunotherapy (durvalumab). The majority of patients treated with SBRT (n=8, 89%) had stage I NSCLC.

The median follow-up for the 33 evaluable patients was 14.7 months (range, 1.6 – 62.4 months). Twenty-one patients (CFRT, n=13; SBRT, n=8) completed the full 12-month follow-up and 12 patients (CFRT, n=11; SBRT, n=1) died before completing the 12-month follow-up. All the 33 patients received full dose (CFRT 60 Gy in 2 Gy fractions; SBRT 54 Gy in 18 Gy fractions or 55 Gy in 11 Gy fractions), except for one patient who chose to discontinue CFRT due to grade 4 esophagitis. Of the 24 patients who received CFRT, five patients (20.8%; 95% CI, 7.1% – 42.2%) developed grade ≥3 AEs. Three and one patients developed grade 2 and 3 pneumonitis, respectively, and the rate of grade ≥3 pneumonitis was 4.2% (95% CI, 0.1% – 21.1%). The patient who developed grade 3 pneumonitis also had grade 3 dyspnea. The results of univariate analyses of patient and treatment characteristics for grade ≥2 pneumonitis are shown in Appendix E3. Kaplan-Meier curves of freedom from grade ≥2 pneumonitis along with the log-rank statistics are shown in Appendix E4. Ten, one and two patients developed grade 2, 3 and 4 esophagitis, respectively, and the rate of grade ≥3 esophagitis was 12.5% (95% CI, 2.7% – 32.4%). One of the two patients who developed grade 4 esophagitis also had grade 3 dysphagia. One patient had grade 3 altered mental status possibly related to protocol treatment. Of the 9 patients who received SBRT, no patients (0%; 95% CI, 0% – 33.6%) developed grade

≥3 AEs. One patient developed grade 2 pneumonitis. A summary table of all grades 2-4 AEs definitely, probably, or possibly related to protocol treatment is shown in Table 2.

Figure 1 shows a comparison of isodose distributions between the standard and functional avoidance RT plans of a representative case who received CFRT. The 10- and 20-Gy isodose curves are pushed away from well-ventilated regions (denoted by red arrows) in the functional avoidance RT plan compared to the standard RT plan. Compared with the standard RT plans, the functional avoidance RT plans significantly (p<0.01) reduced the lung dose-function metrics, including the mean dose, fV_{10}, and fV_{20}, for both CFRT (Table 3) and SBRT (Table 4). For example, the median absolute reduction in fV_{20} was 3.4% (relative reduction, 12.5%) for CFRT and 1.3% (relative reduction, 19.2%) for SBRT. For CFRT, there was no significant (p=0.16) difference in fV_5 between the standard and functional avoidance RT plans. Functional avoidance resulted in decreased fV_5 in 14 patients (absolute difference range, -9.1% – -0.1%) and increased fV_5 in 10 patients (absolute difference range, 0.3% – 4.8%). Per-protocol or acceptable PTV coverage was achieved for all patients, except for two challenging cases with stage III NSCLC (both the standard and functional avoidance RT plans had unacceptable variations in the maximum or minimum dose to the PTV). The standard constraints of OARs were met for all patients.

Data to assess the changes from baseline in the PFT parameters, 6MWD and BODE index at 6 months after treatment were available for 11, 10 and 8 patients who underwent CFRT, respectively, and 8, 6 and 6 patients who underwent SBRT. Data were missing for the other patients, largely due to disease progression or patient refusal. Table 5 shows the change from baseline in each parameter at 6 months after treatment. The median absolute change in FEV_1 was -1% (range, -16% – 10%) for CFRT and 6% (range, -2% – 23%) for SBRT. The median absolute change in the 6MWD was 9.3 m (range, -69.5 – 105.1 m) for CFRT and -5.3 m (range,

-93.9 – 204.2 m) for SBRT. The median absolute change in the BODE index was -1 point (range, -2 – 1 points) for CFRT and -1 point (range, -3 – 0 points) for SBRT.

Discussion

This trial represents one of the first prospective investigations assessing the safety and feasibility of lung functional avoidance RT and reports on the first prospective clinical implementation of functional avoidance SBRT. There are three key findings from this trial: 1) the safety criteria were met for both CFRT and SBRT; 2) functional avoidance RT plans significantly reduced the lung dose-function metrics compared with the standard RT plans, while maintaining PTV coverage (except for challenging cases) and meeting the standard OAR constraints; and 3) declines in the physiological measurements (including the PFT parameters, 6MWD, and BODE index) after functional avoidance RT appeared to be small.

The safety criteria were met for both CFRT and SBRT. For CFRT, the rates of grade ≥3 pneumonitis and esophagitis were 4.2% and 12.5%, respectively, which were lower than the criteria used in this study (pneumonitis, 13%; esophagitis, 21%). For SBRT, the rate of any grade ≥3 AEs was 0%, which was also lower than the criteria (28%). Given that there are differences in patient and treatment characteristics between the historical data (5,33) used to determine the safety criteria and our study, we also compared the AE rates of our trial with data from more recent studies with more similar characteristics. Jiang *et al.* reported an 18% rate of grade ≥3 esophagitis in 165 patients with stage I-IV NSCLC who received CFRT (median prescribed dose, 66 Gy; range, 60-76 Gy) with or without chemotherapy (5). The Radiation Therapy Oncology Group (RTOG) 0617 trial reported a 6.9% rate of grade ≥3 pneumonitis and a 7.4% rate of grade ≥3 esophagitis in patients with stage III NSCLC who received standard-dose CFRT (60 Gy) with concurrent chemotherapy (6). The esophagitis rate of our study was higher than that of RTOG 0617 (6) but comparable to its upper bound of the 95% CI (11.6%).

The maximum dose constraint to the esophagus was met in all the three patients who developed grade ≥3 esophagitis in our study. The mean dose constraint (not required but recommended) was met in two patients, but not in one patient who developed grade 4 esophagitis and chose to discontinue treatment. For SBRT, Zhao *et al.* reported a 1.8% rate of grade ≥3 pulmonary toxicity (including pneumonitis and pulmonary fibrosis) in a pooled analysis of 88 studies on SBRT for patients with early-stage NSCLC or metastatic disease to the lung (8), while no patients who underwent SBRT developed grade ≥3 AE in our trial. Although these findings should be interpreted with caution due to low AE rates and a limited sample size, this study demonstrated the safety of 4D-CT ventilation image-guided functional avoidance RT that significantly reduced dose to ventilated lung regions without compromising target coverage or adherence to standard OAR constraints.

Compared with the standard RT plans, the functional avoidance RT plans significantly reduced the lung dose-function metrics for both CFRT and SBRT (except for fV_5 in CFRT), while maintaining PTV coverage (except for challenging cases) and meeting the standard OAR constraints. There was no significant difference in fV_5 between the standard and functional avoidance RT plans in CFRT because the functional mean dose and fV_{20} were used as dose-function constraints for IMRT optimization. Faught *et al*. (21) demonstrated that fV_{20} was more strongly associated with pneumonitis compared to fV_5 and fV_{10}, supporting the planning approach used in this trial. We noted considerable variability in the difference in the lung dose-function metrics between the standard and functional avoidance RT plans. For example, the absolute reduction in fV_{20} ranged from 0.2% to 14.3% for CFRT. Functional avoidance RT planning could offer limited dosimetric benefit to patients with lung regions of relatively low ventilation or uniform ventilation distributions near the PTV, allowing little room for further reduction of dose-function metrics or dose redistribution. In an attempt to select patients

suitable for functional avoidance, two recent functional avoidance RT trials employed inclusion criteria based on ventilation heterogeneity (35) or ≥10 pack-year smoking history (likely to have heterogeneous ventilation distributions) (36); however, the dosimetric benefit was limited in a subset of patients. Future work to identify the characteristics of patients who benefit the most from functional avoidance is needed.

Declines in the physiological measurements after functional avoidance RT appeared to be small. Post-treatment changes in PFT parameters (particularly FEV_1) have been studied extensively for both standard CFRT (37-39) and SBRT (40,41). In general, these parameters show progressive declines after RT. The mean absolute change in FEV_1 was -0.8% (decline) (relative change, -0.1%) for CFRT in our study, which was consistently smaller compared to the changes reported in previous studies (at 3-6 months after treatment) (37-39). For example, a mean relative change of -6% at 3-4 months after 3D conformal CFRT has been previously observed in 82 patients with NSCLC. For SBRT, the median absolute change in FEV_1 was 6% (increase) in our study, while declines were reported in several earlier studies (at 3-10 months after treatment) (40) and a similar increase (at 6 months) was reported in one study (41). Data on post-treatment changes in 6MWD are scarce and the BODE index has not been studied. The median change in 6MWD was 9.3 m for CFRT in our study, whereas a median change of -46 m after CFRT has been previously observed in 53 patients with lung cancer (42). For SBRT, the median change of -5.3 m was observed in our study, while no significant differences between baseline and post-treatment results have been reported (43). It is difficult to compare the results of our study with previous studies due to a limited sample size of our study (along with missing data) and heterogeneity in patient/treatment characteristics, time points of measurements and data reporting. Nevertheless, declines in these physiological measurements after functional avoidance RT appear to be smaller or comparable to those after

standard RT. Further investigation is needed to directly compare the changes in physiological measurements between standard RT and functional avoidance RT.

The results of two functional avoidance RT clinical trials have recently been published (35,36). Vinogradskiy *et al.* reported the results of the first single-arm phase 2 trial of 4D-CT ventilation image-guided functional avoidance CFRT, showing a 4.5% rate (95% CI upper bound, 11.2%) of grade ≥3 pneumonitis and a 7.5% rate (95% CI upper bound, 15.1%) of grade ≥3 esophagitis in 67 patients with stage I-IV lung cancer (NSCLC or small cell lung cancer) (35). They also reported a 6.0% rate of grade ≥3 dyspnea and a 3.0% rate of grade ≥3 fatigue. Yaremko *et al*. reported the results of the first randomized trial of hyperpolarized ^{3}He MRI ventilation image-guided functional avoidance CFRT (which was closed before reaching its accrual goal), showing a 6.3% rate of grade ≥3 pneumonitis in the functional avoidance arm (16 patients with stage III-IV NSCLC) (36). No other clinician-reported toxicity was reported. There are two differentiating features of our study from these two functional avoidance RT trials. First, our study reports on the first prospective clinical implementation of functional avoidance SBRT. Functional avoidance RT has been extensively studied for CFRT, while data on SBRT are scarce. Dosimetric benefit of functional avoidance SBRT has been demonstrated by Kadoya *et al*. (44) and their results are in line with our study. Binkley *et al*. (45) have shown that dose to well- and poorly-ventilated lung regions is associated with worsened and improved post-SBRT global pulmonary function, respectively, suggesting potential clinical benefit of functional avoidance SBRT. Future work investigating the efficacy of functional avoidance SBRT is needed. The second differentiating feature is that our study employed IMRT optimization incorporating ventilation values on a voxel-by-voxel basis, while the two studies used segmented normal (ventilated) lung regions assuming uniform ventilation distributions within those regions. Lung dose-function metrics defined with the voxel-by-voxel approach have been previously shown to have similar predictive performance for pneumonitis to those defined with the segmentation-

based approach (21). Although it is difficult to compare the dosimetric results between our study and the two studies due to different definitions of dose-function metrics (dose-function data of the whole lung vs. dose-volume data of the segmented ventilated lung), the voxel-by-voxel approach theoretically provides increased degrees of freedom for IMRT optimization, particularly in patients with heterogeneous ventilation distributions near the PTV, and thereby may offer flexibility in functional avoidance RT planning. Current clinically available treatment planning systems do not have capability to incorporate image values into IMRT optimization on a voxel-by-voxel basis. Addition of such a capability, which would require effort by a treatment planning system vendor, might facilitate clinical translation.

Limitations of this pilot study include a limited sample size, missing data of the secondary outcome measures, heterogeneity in immunotherapy, changes in ventilation distributions during a course of treatment, and technical limitations of 4D-CT ventilation imaging. First, this study is a single-institution trial with a limited sample size, hampering the generalizability of the results. Nevertheless, the AE rates for CFRT observed in our study (grade ≥3 pneumonitis, 4.2%; grade ≥2 pneumonitis, 16.7%; grade ≥3 esophagitis, 12.5%; grade ≥2 esophagitis, 54.2%) compare favorably with the two recent functional avoidance RT trials reported in Vinogradskiy *et al*. (grade ≥3 pneumonitis, 4.5%; grade ≥2 pneumonitis, 14.9%; grade ≥3 esophagitis, 7.5%; grade ≥2 esophagitis, 49.3%) (35) and in Yaremko *et al*. (grade ≥3 pneumonitis, 6.3%; grade ≥2 pneumonitis, 12.6%) (36). Second, missing data of the secondary outcome measures (PFT parameters, 6MWD, and BODE index) also make the results difficult to interpret as discussed earlier. Third, durvalumab received FDA approval during our trial accrual period, and hence only eligible patients enrolled after February 2018 received consolidation durvalumab, leading to heterogeneity in treatment characteristics and imbalance with the historical data used to determine the safety criteria. Consolidation durvalumab increases pulmonary toxicity as reported in the PACIFIC study (9). In our trial, there was no significant (p=0.11) difference in

the distribution of consolidation durvalumab between patients who had grade ≥2 pneumonitis (n=4) and those who did not (n=20) according to the Fisher's exact test (Appendix E3). Consolidation durvalumab approached significance (p=0.08) according to the log-rank test comparing the Kaplan-Meier curves of freedom from grade ≥2 pneumonitis, with those who received durvalumab showing a lower rate of freedom from pneumonitis (Appendix E4). The pneumonitis rate would likely be higher if all patients received consolidation durvalumab. Fourth, our trial did not account for changes in ventilation distributions during a course of treatment for all patients, except for 1 patient who had a collapsed ipsilateral lung before treatment which re-expanded due to tumor shrinkage during treatment. Tumor shrinkage during a course of RT is common in patients with lung cancer (46) and a substantial increase in regional ventilation and perfusion has been previously reported (47). Adaptive functional avoidance RT (48) that accounts for such changes may provide added benefit. Lastly, there are technical limitations to 4D-CT ventilation imaging, including 4D-CT image artifacts that deteriorate the accuracy and precision of ventilation quantification (49) and wide variations with algorithms (50). Further development of strategies to improve 4D-CT and validation of ventilation quantification are warranted.

Conclusion

This study represents one of the first prospective investigations on lung functional avoidance RT. Functional avoidance RT with 4D-CT ventilation imaging, which only requires a standard-of-care 4D-CT scan and image processing/analysis, significantly reduced dose to ventilated lung regions and could be safely administered. Although larger studies are required to estimate the AE rates with greater precision and to make statistically valid inferences, this study adds to the growing body of evidence for the clinical utility of functional avoidance RT.

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Figure captions

Figure 1. Comparison of isodose distributions between the standard and functional avoidance RT plans of a representative case who received CFRT. 4D-CT ventilation image is overlaid on the planning CT image. The 10- and 20-Gy isodose curves are pushed away from well-ventilated regions (denoted by red arrows) in the functional avoidance RT plan compared to the standard plan.

Table 1. Patient and treatment characteristics

Characteristic	Median (range) or n (%) CFRT (n=24)	SBRT (n=9)
Age	74 (57-84)	76 (65-92)
Gender		
Male	10 (42%)	4 (44%)
Female	14 (58%)	5 (56%)
Karnofsky performance status (KPS)	80 (60-100)	70 (50-90)
Smoking history		
Never	3 (12%)	1 (11%)
Former	17 (71%)	7 (78%)
Current	4 (17%)	1 (11%)
Histology		
Adenocarcinoma	13 (54%)	6 (67%)
Squamous cell carcinoma	11 (46%)	2 (22%)

Unknown	0 (0%)	1 (11%)
Disease stage		
IA	0 (0%)	6 (67%)
IB	0 (0%)	2 (22%)
IIB	1 (4%)	1 (11%)
IIIA	14 (58%)	0 (0%)
IIIB	9 (38%)	0 (0%)
Prescribed radiation dose		
60 Gy in 2 Gy fractions	24 (100%)	0 (0%)
54 Gy in 18 Gy fractions	0 (0%)	4 (44%)
55 Gy in 11 Gy fractions	0 (0%)	5 (56%)
PTV volume (cm^3)	401 (255-750)	26 (12-157)
Concurrent chemotherapy		
Yes	24 (100%)	0 (0%)
Chemotherapy agent		
Carboplatin/paclitaxel	21 (88%)	
Cisplatin/etoposide	2 (8%)	
Cisplatin/pemetrexed	1 (4%)	
No	0 (0%)	9 (100%)
Consolidation immunotherapy (durvalumab)		
Yes	4 (17%)	0 (0%)
Timing (days after RT completion)	38 (21-100)	
No	20 (83%)	9 (100%)

Abbreviations: CFRT = conventionally fractionated radiotherapy; PTV = planning target volume; SBRT = stereotactic body radiotherapy; RT = radiotherapy.

Table 2. Adverse events frequency by grades, definitely, probably, or possibly related to protocol treatment.

	CFRT (n=24)			SBRT (n=9)		
Adverse event	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Pneumonitis	3 (13%)	1 (4%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)
Esophagitis	10 (42%)	1 (4%)	2 (8%)	0 (0%)	0 (0%)	0 (0%)
Dyspnea	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dysphagia	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Altered mental status	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cough	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dehydration	3 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dermatitis	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	5 (21%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nausea	2 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pharyngitis	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 3. Dose-volume/function metrics of the standard and functional avoidance RT plans for the CFRT group (n=24)

Dose-volume/function metric	Standard RT median (range)	Functional avoidance RT median (range)	Median absolute difference* (range)	*P*
Lung dose-function				
Mean dose (Gy)	16.8 (5.3 – 21.7)	16.3 (5.4 – 21.2)	-0.8 (-2.1 – 0.3)	<0.01
fV_5 (%)	69.4 (37.1 – 89.8)	70.3 (38.5 – 86.3)	-0.9 (-9.1 – 4.8)	0.16
fV_{10} (%)	51.0 (11.0 – 66.4)	48.2 (10.4 – 65.2)	-1.6 (-11.5 – 2.7)	<0.01
fV_{20} (%)	32.2 (5.8 – 44.4)	28.4 (5.6 – 34.1)	-3.4 (-14.3 – -0.2)	<0.01
fV_{30} (%)	17.5 (0.2 – 28.2)	16.6 (0.3 – 25.8)	-1.4 (-5.7 – 0.0)	<0.01
Lung dose-volume				
Mean dose (Gy)	15.4 (11.0 – 21.1)	15.2 (9.8 – 20.6)	-0.4 (-1.7 – 1.0)	<0.01
V_{20} (%)	29.5 (14.7 – 39.4)	26.6 (11.8 – 36.2)	-2.6 (-10.2 – 2.0)	<0.01
Spinal cord				
Maximum dose (Gy)	43.2 (11.6 – 46.4)	44.1 (8.0 – 46.3)	0.7 (-4.8 – 8.5)	0.02
Esophagus				
Mean dose (Gy)	24.8 (5.6 – 41.4)	24.9 (6.0 – 42.9)	0.1 (-1.1 – 4.4)	0.68
Heart				
Mean dose (Gy)	14.0 (3.5 – 24.9)	13.4 (3.1 – 23.8)	-0.5 (-5.7 – 1.3)	0.16
PTV				
Maximum dose (Gy)	66.4 (63.9 – 72.5)	66.7 (64.1 – 72.8)	0.3 (-2.1 – 3.2)	0.13

Abbreviation: fV_x = percentage lung function receiving ≥x Gy; PTV = planning target volume; RT = radiotherapy; SD = standard deviation; V_x = percentage volume receiving ≥x Gy.
* Absolute difference = functional avoidance RT metric – standard RT metric.

Table 4. Dose-volume/function metrics of the standard and functional avoidance RT plans for the SBRT group (n=9)

Structure and metric	Standard RT median (range)	Functional avoidance RT median (range)	Median absolute difference* (range)	*P*
Lung dose-function				
Mean dose (Gy)	4.5 (2.7 – 7.0)	3.3 (2.1 – 5.8)	-1.1 (-1.4 – -0.2)	<0.01
fV_5 (%)	22.1 (13.8 – 36.9)	13.9 (10.7 – 28.6)	-8.3 (-11.2 – -1.5)	<0.01
fV_{10} (%)	11.6 (5.6 – 21.8)	7.2 (5.2 – 16.4)	-4.3 (-9.4 – -0.4)	<0.01
fV_{20} (%)	4.0 (2.2 – 9.1)	3.4 (2.2 – 7.4)	-1.3 (-1.9 – -0.1)	<0.01
Lung dose-volume				
Mean dose (Gy)	4.7 (2.4 – 7.0)	3.6 (2.2 – 5.9)	-1.0 (-1.3 – -0.1)	<0.01
V_{20} (%)	5.6 (1.8 – 9.4)	4.1 (1.7 – 7.8)	-1.0 (-1.6 – 0.2)	0.01
Spinal cord				
Maximum dose (Gy)	15.4 (0.2 – 21.0)	11.1 (0.2 – 23.4)	0.0 (-10.4 – 3.7)	0.46
Esophagus				
Maximum dose (Gy)	10.1 (5.0 – 27.2)	9.4 (5.9 – 29.7)	-0.2 (-4.9 – 2.4)	0.73
Heart				
Maximum dose (Gy)	20.5 (0.7 – 29.4)	25.4 (0.6 – 35.2)	-0.1 (-4.3 – 5.8)	0.65
Great vessels				
Maximum dose (Gy)	15.5 (5.5 – 23.3)	18.1 (5.2 – 24.5)	-0.3 (-5.9 – 8.4)	0.91
Proximal bronchial tree				
Maximum dose (Gy)	13.8 (6.6 – 26.2)	9.9 (6.2 – 22.3)	-3.1 (-6.0 – 1.4)	0.02
PTV†				
Maximum dose (Gy)	69.8 (64.3 – 76.1)	72.0 (66.9 – 76.2)	1.9 (-6.9 – 7.6)	0.19

Abbreviation: fV_x = percentage lung function receiving ≥x Gy; PTV = planning target volume; RT = radiotherapy; SD = standard deviation; V_x = percentage volume receiving ≥x Gy.
* Absolute difference = functional avoidance RT metric – standard RT metric.
† One patient had two PTVs.

Table 5. Changes from baseline in the physiological measurements at 6 months after treatment.

Parameter	CFRT	SBRT
FEV_1 (% predicted)		
n with data available	11	8
Median absolute change (range)	-1 (-16 – 10)	6 (-2 – 23)
FVC (% predicted)		
n with data available	11	7
Median absolute change (range)	1 (-30 – 19)	9 (-4 – 17)
TLC (% predicted)		
n with data available	11	8
Median absolute change (range)	-5 (-27 – 25)	1.5 (-7 – 11)
VC (% predicted)		
n with data available	9	7
Median absolute change (range)	-3.0 (-9 – 20)	9 (-8 – 12)
RV (% predicted)		
n with data available	11	7
Median absolute change (range)	-13 (-40 – 42)	-1 (-25 – 13)
D_{LCO} (% predicted)		
n with data available	4	4
Median absolute change (range)	-10 (-27 – 6)	-0.5 (-4 – 9)
6-min walk distance (m)		
n with data available	10	6
Median absolute change (range)	9.3 (-69.5 – 105.1)	-5.3 (-93.9 – 204.2)
BODE-index (point)		
n with data available	8	6
Median absolute change (range)	-1 (-2 – 1)	-1 (-3 – 0)

Abbreviation: FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; TLC = total lung capacity; VC = vital capacity; RV = residual volume; D_{LCO} = diffusing capacity of the lung for carbon monoxide.