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Richard Castillo, Emory University
F Forghani, Univ Colorado
T Patton, Univ Colorado
J Kwak, Univ Colorado
D Thomas, Univ Colorado
Q Diot, Univ Colorado
C Rusthoven, Univ Colorado
I Grills, Beaumont Hlth Syst
T Guerrero, Beaumont Hlth Syst
M Miften, Univ Colorado

Only first 10 authors above; see publication for full author list.

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Farnoush Forghani, PhD, Taylor Patton, PhD, Jennifer Kwak, MD, David Thomas, PhD, Quentin Diot, PhD, Chad Rusthoven, MD, Richard Castillo, PhD, Edward Castillo, PhD, Inga Grills, MD, Thomas Guerrero, MD, PhD, Moyed Miften, PhD, Yevgeniy Vinogradskiy, PhD

1Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO
2Formerly at the Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO; Currently at the Department of Radiation Oncology, Mayo Clinic, Rochester, MN
3Department of Radiology, University of Colorado School of Medicine, Aurora, CO
4Department of Radiation Oncology, Emory University, Atlanta, GA
5Department of Radiation Oncology, Beaumont Health System, Royal Oak, MI

Summary:
This study investigates agreement between ventilation and perfusion for lung cancer patients undergoing radiotherapy. Ventilation-perfusion scans of nineteen patients with stage III lung cancer from a prospective protocol were compared using voxel-wise Spearman correlation-coefficients. The presented results show in about 25% of patients, ventilation and perfusion exhibit lower agreement.

Keywords
SPECT; Ventilation; Perfusion; functional avoidance; lung cancer; Spearman correlation; Dice Similarity; 4D-CT

Introduction:
Functional avoidance thoracic radiotherapy is a paradigm that proposes to use functional imaging to generate radiation treatment plans that preferentially avoid the functional portions of the lung. The hypothesis of functional avoidance radiotherapy is that reduced dose to functional portions of the lung can lead to reduced probability that patient develop pulmonary side-effects. One form of functional imaging that has been proposed for functional avoidance is 4-dimensional computed tomography (4DCT)-derived ventilation.
4DCT images contain the local density changes in the pulmonary parenchyma due to respiration. These changes can be extracted mathematically by correspondence of image intensity values between spatially registered 4DCT phase images to obtain a surrogate for pulmonary ventilation. This technique is well suited for integration into the radiotherapy workflow because 4DCT scans are routinely acquired for treatment planning for most lung cancer patients. Therefore, obtaining 4DCT-ventilation images can provide functional information while eliminating the extra cost and reducing imaging-based radiation exposure.

Early research efforts focused on validation of 4DCT-ventilation followed by modeling studies that demonstrated the potential clinical utility of 4DCT-ventilation-based functional avoidance for reducing treatment-related toxicity outcomes. Based on the retrospective data, several clinical trials investigating the use of 4DCT-ventilation in the context of functional avoidance radiotherapy are underway. One potential limitation of current formulations of 4DCT-ventilation imaging is that only ventilation information is generated. An implicit assumption in most 4DCT-ventilation studies has been that for most lung cancer patients, the spatial profiles of ventilation and perfusion are similar. The similarity between ventilation and perfusion for lung cancer patients has been noted in other clinical scenarios. While ventilation and perfusion have been shown to be spatially similar for most patients, there are clinical scenarios where spatial differences exist. The underlying cause of dissimilarity between ventilation and perfusion can be due to perfusion defects for patients with a pulmonary embolism (blood clot in one of the pulmonary vessels) or due to ventilation defects for patients with pulmonary edema (alveoli filling with fluid), atelectasis (deflation of the alveoli), pleural effusion (a build-up of fluid around the lung), or obstruction of the airways. While there have been studies comparing 4DCT-ventilation to other lung function imaging modalities (both ventilation and perfusion), there has been no work to quantitatively test the assumption that ventilation profiles are spatially equivalent to perfusion profiles for lung cancer patients undergoing radiotherapy. In order to accurately characterize the physiological spatial differences between ventilation and perfusion, a study is needed that can evaluate spatial differences between ventilation and perfusion using the same imaging modality. The purpose of this study was therefore to use single-photon emission computerized tomography (SPECT) imaging to quantitatively characterize the agreement between ventilation and perfusion for lung cancer patients undergoing radiotherapy.

**Methods and Materials:**

**Patient cohort**

Patients for the current study were selected from those enrolled on a 2-institution, prospective clinical trial for functional avoidance thoracic radiation therapy. 67 patients with biopsy proven lung cancer included in the trail. Informed consent was obtained for all subjects for this study. The trial aim was to use 4DCT-based ventilation imaging to reduce dose to functional portions of the lung with the idea that reduced doses to functional lung may lead to reduced rates of radiation-related thoracic toxicity. The primary objective of the trial was to determine whether 4DCT-ventilation-based functional
avoidance results in reduced radiation pneumonitis when compared to current standard of
care techniques. The primary end-point of the trial was to evaluate the rate of radiation
pneumonitis. The trial was approved to enroll patients by the institutional review boards
(IRB) at the University of Colorado (Aurora, CO) (IRB #14–1586) and Beaumont Health
System (Royal Oak, MI) (IRB #2016–037). Of the patients enrolled on the functional
avoidance clinical trial, nineteen patients with stage III lung cancer who underwent pre­
treatment SPECT-CT imaging were eligible for the current analysis.

**Pulmonary SPECT imaging**

SPECT imaging started with ventilation imaging using Technetium-labeled (Tc-99m)
diethylenetriaminepentaacetic (DTPA) acid aerosol inhalation with the approximate activity
of 30 MBq. Immediately after ventilation, perfusion images were acquired using
Technetium-labeled particles of macroaggregates of albumin (Tc-99m, MAA) with the
approximate activity of 100 MBq that were given intravenously. The number of expected
ventilation and perfusion counts is on the order of few $10^6$ per 10 min. Perfusion
counting rate is about 4 times of ventilation counting rate. A Siemens Simbia T6 SPECT
—CT scanner (Siemens, Hoffman Estates, IL) was used to acquire the SPECT images.
Patients were in the supine position with normal resting breathing. Two detectors with low­
energy and high-resolution collimation were used to obtain the raw emission data. Image
reconstruction was performed using the 3D ordered-subset expectation—maximization (3D
OSEM) iterative reconstruction method. Co-registered CT images were acquired to perform
attenuation correction of the SPECT images. The voxel size in the SPECT data was 7.75 mm
× 7.75 mm × 3 mm.

**Quantitative functional comparison**

The ventilation and perfusion components of the SPECT-CT were registered using MIM
Software (Cleveland, OH). Each ventilation-perfusion registration was manually reviewed
and adjusted if necessary. The next step was to appropriately segment the lung volume
of interest on both the ventilation and perfusion scans. Lung segmentation for the current
analysis included the lung parenchyma and excluded the gross tumor volume as well as any
aerosol deposition artifacts. Both SPECT-ventilation and SPECT-perfusion are susceptible
to aerosol clumping artifacts. The clumping of radioactive aerosol results in locally
enhanced counts that manifest as bright image hotspots. We carefully excluded radioaerosol
deposition artifacts from the SPECT images based on the location of these hotspots in the
central airways (trachea, bronchi). Central airways are the sites for radioaerosol deposition
due to turbulent air flow in the airways caused by obstructive airways processes such
as COPD (chronic obstructive pulmonary disease) and chronic bronchitis. In addition,
hotspots located in the posterior aspects of the lower lobes of the lung caused by dependent
atelectasis from supine positioning during imaging were excluded. A board-certified nuclear
medicine radiologist oversaw the identification of artifacts and the review of the SPECT-CT
images.

In order to improve the quantitative accuracy of the analysis, each ventilation and
perfusion artifact was manually removed from the lung segmentation. The final step in the
segmentation was to crop the contour 5 mm away from the lung boundary in order to reduce
the partial volume artifact\textsuperscript{24}. Once the lungs were appropriately segmented, normalization of ventilation and perfusion raw data was done by converting both images to percentile images to facilitate direct comparison between the modalities\textsuperscript{25,26}. Two metrics previously used for image comparison studies\textsuperscript{5–9,25} were employed to compare the ventilation and perfusion distributions: Spearman correlation coefficients and Dice Similarity Coefficients (DSC). DSCs were calculated for different functional zones defined as 0–25th percentile, 25–50th percentile, 50–75th percentile, and >75th percentile\textsuperscript{25}. Previous studies show the most reproducible functional profiles are in the highest and lowest functional zones \textsuperscript{5,6,27}. Therefore, this study focuses on 0–25th percentile and >75th percentile functional zones.

In addition to analyzing the whole lung, ipsilateral and contralateral lungs were analyzed separately. The correlation data are presented in the form of histogram distributions with the results summarized as mean ± standard deviation (range). All computational analysis was done using MIM Extensions.

Spearman correlation and Dice similarity metrics may not elucidate spatial differences between SPECT ventilation and perfusion images and could be influenced by non-relevant outlier such as the residual of hotspot artifacts. Therefore, voxel-wise scatter plots of percentile perfusion versus ventilation values were also generated for each patient and included in the supplementary materials.

**Results and Discussion**

The median age of the cohort was 70 (range 54–84) years, all patients had stage III lung cancer, and 63% of patients had chronic obstructive pulmonary disease.

The SPECT-CT scans in Figure 1 represent an example of high spatial correlation (Figures 1A and 1B) and an example of low spatial correlation (Figures 1C and 1D) between ventilation and perfusion. In the top row of Figure 1 the Spearman correlation coefficients for the presented patients are 0.84 and 0.82 for the right and left lungs, respectively. The Spearman correlation coefficient for the presented patient in the bottom row is 0.19 for both the right and left lung. The high (>75\%) and low functional zones (<0.25\%) (the 25\%-50\% and 50\%-75\% functional zones contours are omitted for clarity) for the patients are overlaid on the scans. Similar to the visual percentile correlations, the high and low functional zones show good agreement for the patient presented in the top row and poor agreement between the patient presented in the bottom row.

The mean ± standard deviation (range) of Spearman coefficients was 0.64±0.19 (0.19, 0.91) for the whole lung, 0.66±0.23 (0.19, 0.91) for the ipsilateral, and 0.62±0.16 (0.19, 0.82) for the contralateral lungs. For the low functional zones (0–25 percentile), the mean ± standard deviation (range) of DSC was 0.65±0.13 (0.38, 0.92) for the whole lung, 0.67± 0.16 (0.38, 0.92) for the ipsilateral, and 0.63±0.09 (0.47,0.83) for the contralateral lungs. The mean and range of DSC for the high functional zones (75–100 percentile) was 0.54±0.14 (0.19, 0.80) for the whole lung, 0.55±0.15 (0.24, 0.80) for the ipsilateral, and 0.53± 0.13(0.19,0.75) for the contralateral lungs.
Histogram distributions of Spearman correlation coefficients between ventilation and perfusion for the ipsilateral, contralateral, and the whole lung for the entire patient cohort are shown in Figure 2. For the ipsilateral lungs, 73.7% of the scans exhibit a higher correlation (≥0.5) between ventilation and perfusion and 26.3% of the scans exhibit lower correlation (<0.5). For the contralateral lungs, 79.0% of the scans exhibit a higher correlation and 21.0% of the scans exhibit lower correlation. For the whole lung, 76.3% of the scans exhibit a higher correlation and 23.7% of the scans exhibit lower correlation.

Examples of the scatter plots for two patients with lower and two patients with higher similarity coefficients between ventilation and perfusion are provided in Figure 2 of the supplementary materials. These examples showed agreement between the scatter plot and quantitative analysis by Spearman and Dice coefficients in determining the similarity between the perfusion and ventilation scans.

The presented work quantitatively evaluated the spatial agreement between SPECT ventilation and perfusion using 19 SPECT scans for stage III lung cancer patients. The data can be interpreted from the perspective of 4DCT-based functional avoidance, that uses functional imaging to generate radiation treatment plans that preferentially avoid the functional portions of the lung. The motivation for this work stems from 4DCT-ventilation because with current formulations of 4DCT-based functional imaging, only the ventilation component can be computed. One argument that 4DCT-ventilation studies have made is acceptable to use ventilation as a surrogate for both ventilation and perfusion because ventilation and perfusion are spatially similar for most lung cancer patients. However, this assumption (of ventilation/perfusion being spatially similar) has not been validated/quantified. Our results were consistent between the ipsilateral, contralateral, and the whole lungs among the patient cohort (histograms in Figure 2) and quantitatively revealed that about 74% of patients had ≥0.5 correlations for the ipsilateral lung, 79% of patients had ≥0.5 correlations for the contralateral lung, and about 76% had ≥0.5 correlations for the whole lung. The 74%-79% rate of patients with correlations ≥0.5 between ventilation and perfusion can be used as a baseline figure to evaluate in what percentage of cases does perfusion provide unique information when compared to ventilation alone. In other words, in about 21%-26% of patients both ventilation and perfusion would be needed to provide complete (ventilation and perfusion) lung function information. The subsequent extension of the current work is to propagate the ventilation-perfusion spatial differences into differences in the treatment planning domain. Previous studies \cite{28,29} have evaluated differences between 4DCT-ventilation-based and SPECT-perfusion-based dose-function metrics. Nakajima et al \cite{28} found strong correlations (range, r=0.94–0.97) between ventilation-based and perfusion-based dose-function metrics but noted wide variability possible among individual patients with differences as large as 6.6 Gy possible between ventilation and perfusion in functional dose-metrics. Using the data from the dose-function comparison studies \cite{28,29}, it is difficult to isolate whether the potential individual differences in dose-function metrics are due to differences between the two modalities (4DCT versus SPECT), true clinical differences between the patient’s ventilation and perfusion profiles, differences caused by the treatment plan itself, or whether the studies potentially did not have a large enough sample size (as may be the case for 8-patient study by Kida et al \cite{29}) to capture potential ventilation-perfusion differences. The importance of our study is that it used the same modality to
isolate physiological differences between ventilation and perfusion for lung cancer patients. The data from the current work will allow for future studies to de-couple and isolate dose-function differences due to physiological differences, differences due to using various imaging modalities, or differences due to treatment plan generation techniques.

The correlation of SPECT ventilation and perfusion was a research question specific to this study and was not defined as part of the protocol for the prospective clinical trial. Therefore, this study was limited only to nineteen patients who underwent pre-treatment SPECT-CT imaging. This sample size may not be optimal for comparison of a wide range of perfusion-ventilation SPECT scenarios. The current analysis is prone to uncertainties due to artifacts generated by deposition of the Technetium isotope in airways (ventilation) and blood vessels (perfusion). The strategy for the current study was to mitigate the impact of the artifacts by manually removing them during segmentation and employing normalization strategies. Future studies employing either numerical or imaging-based methods to reduce the deposition artifacts could further improve the physiological comparison between ventilation and perfusion differences. As was done in previous functional imaging comparison studies, the comparison metrics in our work included Spearman correlation coefficients, DSC.

Conclusions:

The current work performed a spatial comparison of SPECT-based ventilation and perfusion for 19 scans (38 individual lungs) acquired for nineteen patients with stage III lung cancer. The quantitative results demonstrated that about 74%-79% of scans had ventilation-perfusion correlations ≥0.5. In other words, in about 21%-26% of patients both ventilation and perfusion would be needed to provide complete (ventilation and perfusion) lung function information. Within the context of 4DCT ventilation functional avoidance, the results of the current investigation suggest that both ventilation and perfusion may be necessary to achieve complete lung function information. However, future studies may be beneficial to investigate the methodologies that identify patients for whom ventilation provides similar functional information to perfusion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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References:


Figure 1: Percentile SPECT-CT image sets: A) and B) show the images for a patient with high spatial agreement between ventilation and perfusion (Spearman correlation coefficient of 0.84 for the right lung and 0.82 for the left lung). The tumor was located in the right lung. The Dice similarity coefficients for the low and high functional regions of the whole lung are 0.83 and 0.57, respectively. C) and D) show the images for a patient with low spatial agreement between ventilation and perfusion (Spearman correlation coefficient of 0.19 for the right and left lungs). The tumor was located in the right lung. The Dice similarity coefficients for the low and high functional regions of the whole lung are 0.40 and 0.24, respectively. The segmented low and high functional lung regions are shown in blue and light green, respectively.
Figure 2: Histogram of Spearman correlation coefficients, illustrating the similarity distribution of ventilation and perfusion scans among all patients for the A) ipsilateral, B) contralateral, and C) whole lung.