REVIEW ARTICLE

CT-based ventilation imaging in radiation oncology

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ABSTRACT

A form of lung function imaging is emerging that uses phase-resolved four-dimensional CT (4DCT or breath-hold CT) images along with image processing techniques to generate lung function maps that provide a surrogate of lung ventilation. CT-based ventilation (referred to as CT-ventilation) research has gained momentum in Radiation Oncology because many lung cancer patients undergo four-dimensional CT simulation as part of the standard treatment planning process. Therefore, generating CT-ventilation images provides functional information without burdening the patient with an extra imaging procedure.

CT-ventilation has progressed from an image processing calculation methodology, to validation efforts, to retrospective demonstration of clinical utility in Radiation Oncology. In particular, CT-ventilation has been proposed for two main clinical applications: functional avoidance radiation therapy and thoracic dose–response assessment. The idea of functional avoidance radiation therapy is to preferentially spare functional portions of the lung (as measured by CT-ventilation) during radiation therapy with the hypothesis that reducing dose to functional portions of the lung will lead to reduced rates of radiation-related thoracic toxicity. The idea of imaging-based dose–response assessment is to evaluate pre- to post-treatment CT-ventilation-based imaging changes. The hypothesis is that early, imaging-change-based response can be an early predictor of subsequent thoracic toxicity. Based on the retrospective evidence, the clinical applications of CT-ventilation have progressed from the retrospective setting to on-going prospective clinical trials. This review will cover basic CT-ventilation calculation methodologies, validation efforts, presentation of clinical applications, summarize on-going clinical trials, review potential uncertainties and shortcomings of CT-ventilation, and discuss future directions of CT-ventilation research.

## INTRODUCTION TO CT-BASED VENTILATION IMAGING IN RADIATION ONCOLOGY

A form of lung function has been developed that uses phase-resolved CT images to generate lung ventilation maps. The idea is to use four-dimensional CT (4DCT) or breath-hold CT images along with image processing techniques to generate lung function maps that provide a surrogate of lung ventilation. CT-based ventilation (referred to as CT-ventilation) has gained momentum in Radiation Oncology because many lung cancer patients undergo 4DCT simulation as part of the standard treatment planning process.[1] Therefore, CT-ventilation can provide lung function information without burdening the patient with an extra imaging procedure. CT-ventilation has progressed from an image processing research idea,[2–6] to validation efforts,[7–11] to retrospective presentation of clinical applications of CT-ventilation in Radiation Oncology,[12–16] and most recently, to prospective clinical trials using CT-ventilation (NCT02528942, NCT02308709, NCT02843568). This review will cover the calculation methodologies of CT-ventilation, review image validation efforts, present

clinical applications of CT-ventilation in Radiation Oncology, summarize ongoing clinical trials, review potential uncertainties and shortcomings of CT ventilation, and discuss future directions of CT-ventilation research. The literature presented in the current review was identified using the author's knowledge of the topic as well as using search terms of "CT ventilation," "4D CT ventilation," and "ventilation radiation," on PubMed.

CALCULATION METHODOLOGIES OF CT-BASED VENTILATION IMAGING

There have been two main methods proposed for calculating CT-ventilation: the Jacobian-based method[4] and the Hounsfield unit (HU)-based method.[3,17,18] Both methods involve using deformable image registration (DIR) to register lung voxels from the inhale to the exhale phases of the breathing cycle. The Jacobian-based method generates CT-ventilation images by calculating the Jacobian of the generated DIR and is based on the theory that local partial derivatives are related to the volume of change of a given lung voxel.[4] The HU-based method is formed on the

Figure 1.A CT-ventilation image overlaid with a standard CT. Bright colors represent higher functioning regions of the lung while blue and darker tones represent areas of ventilation defect. The patient shown in Figure 1 presents with a ventilation defect in the left lung due to a central mass occluding an airway (outlined in red).
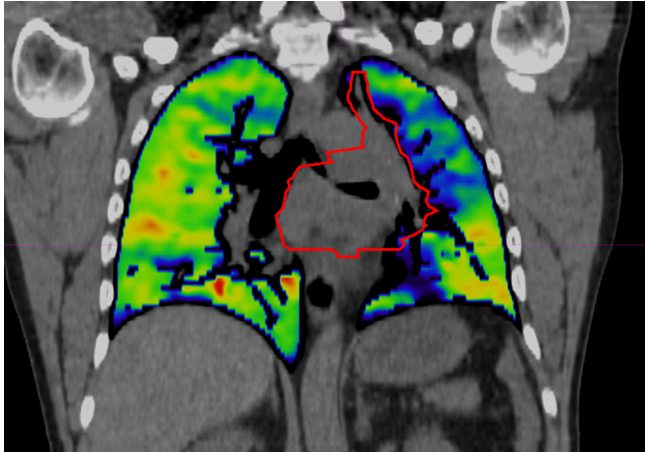
idea that the HU in a given lung voxel is composed of a linear combination of a water-like material and air-like material.[17] The HU-based method first applies a DIR to map how the lung voxels in the inhale and exhale CT images are linked. Once the inhale and exhale voxels are linked, a density-change based equation is applied to calculate ventilation[3,17]:

$$\frac{V_{in}-V_{ex}}{V_{ex}} = 1000\frac{HU_{in}-HU_{ex}}{HU_{ex}\left(1000HU_{in}\right)}, \qquad 1$$

where V_{in} and V_{ex} are the inhale and exhale volumes and HU_{in} and HU_{ex} are the inhale and exhale HUs of the individual lung voxels. Equation 1 calculates the local change in air content for each voxel and produces a three-dimensional map of a surrogate of ventilation. An example of a CT-ventilation image derived using the HU method is shown in Figure 1; with the bright colors representing functional lung and areas of blue representing ventilation defect regions. The patient shown in Figure 1 presents with a ventilation defect in the left lung due to a central mass occluding an airway.

For both the Jacobian- and HU-based methods of calculating ventilation, there are pre- and post-calculation image processing parameters that are typically applied. Two common examples of pre- and post-processing steps of CT-ventilation images are advanced lung segmentation and smoothing operations. Advanced lung segmentation is applied to determine the spatial domain where the CT-ventilation calculation occurs. For example, Castillo et al[2] segment the lungs using a semi-automated approach to delineate out the bronchi, trachea, and pulmonary vasculature. The idea is that the calculation methodologies are determining ventilation and it is not physiologically accurate to calculate ventilation in the bronchi, trachea, or pulmonary vasculature; therefore these structures are omitted using segmentation. Segmentation can also be used to remove potential artifacts due to poor quality 4DCTs (discussed in Section 6) by delineating

out the partial volume image artifacts. The other operation that is typically applied is some level of smoothing of the CT ventilation images.[3] The smoothing is intended to help mitigate some of the uncertainties of inaccurate DIRs. The level of smoothing that is applied to the ventilation images varies by research group and implementation.[19]

While the Jacobian and HU-based methods are the two main methods that are used for calculating CT-ventilation, there have been other methods proposed in the literature.[11,20–22] Kipritidis et al proposed a modified HU-based approach where the values calculated from Equation 1 are scaled by the local density of a given voxel.[11] Kipritidis et al note that a first order definition of physiological ventilation involves the product of local air-flow and local alveolar density. They hypothesize that the local alveolar density can be approximated by local tissue density while the local air-flow is modeled by Equation 1. In another work, Kipritidis et al[20] propose to calculate ventilation by a direct scaling of the HU values, bypassing the need for a DIR solution. Castillo et al[22] have proposed an alternative to the Jacobian-based approach using a mass conserving point cloud density function. Neural networks have also been proposed as a means of generating ventilation images.[21] The majority of described CT ventilation methods have been applied to 4DCT data; however, Eslick et al[23] recently demonstrated improved accuracy of CT ventilation images using breath-hold CTs for ventilation image calculation. Although these more recently proposed methods of calculating CT ventilation are in their nascent state, early results suggest promise in overcoming some of the challenges associated with conventional CT-ventilation calculation methodologies.[20,22]

CORRELATING CT-VENTILATION TO EXISTING LUNG FUNCTION IMAGING MODALITIES

Once the calculation methodology has been developed for a novel imaging modality it is desirable to validate the new imaging method against other forms of lung function imaging. Studies aiming to validate CT-ventilation, have compared it against nuclear medicine planar ventilation-perfusion (VQ) images,[8,24] Single photon emission CT (SPECT) perfusion and ventilation imaging,[2,7,9] positron emission tomography (PET) imaging with a Galligas tracer,[11] MRI using hyperpolarized helium,[10,25] xenon-based CT,[15,26,27] and clinical correlations with pulmonary function testing (PFTs).[9,28] An example of CT ventilation images compared with PET Galligas images from Kipritidis et al[11] is presented in Figure 2. Correlations between CT-ventilation and other lung function imaging modalities have been assessed using Spearman correlations and dice similarity coefficients (DSC) evaluating contours of overlapping high and low functioning regions. Spearman correlations comparing CT-ventilation to other lung function imaging modalities have been reported to be in the range of 0.20–0.85 and DSCs evaluating functional and non-functional regions have been reported to range from 0.3 to 0.9.[11] For example Rankine et al[25] reported correlations between CT-ventilation and Hyperpolarized [129]Xe MRI of 0.39 ± 0.15 in healthy volunteers and 0.53 ± 0.02 for radiation therapy patients prior to therapy. Castillo et al[7] noted DSC of 0.78 for their study cohort comparing CT-ventilation to SPECT perfusion images and Kipritidis et al reported correlations of 0.42

Figure 2.A comparison of CT ventilation images and PET Galligas images for three patients is presented from the work by Kipritidis et al[11] (Printed with permission). The lower row of images shows scatter plots of the voxel correlations between the two imaging modalities for each patient. PET,positron emission tomography.
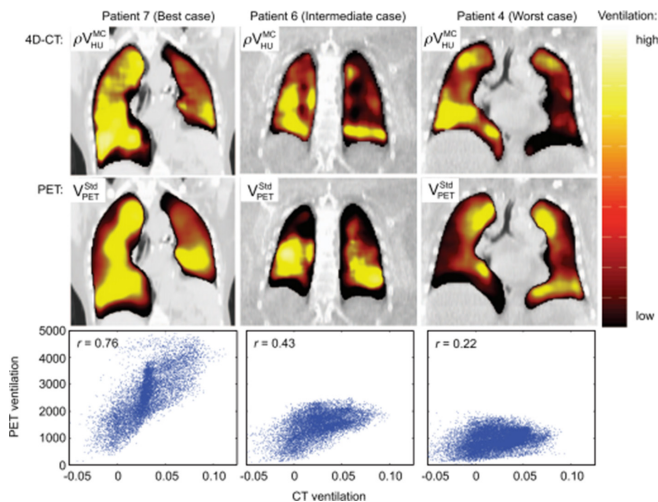
± 0.16 comparing CT-ventilation to PET Galligas imaging. In general, the correlations appear to be strongest on a global and lobar scale and get worse as the comparisons are made on a voxel to voxel level. Studies comparing CT-ventilation to PFTs show similar correlations in the range of 0.6–0.7.[9,28]

It is important to note the unique challenges that the field of CT-ventilation faces in the goal of physiological validations. In addition to the uncertainties of CT-ventilation, there are two aspects that complicate validation efforts: (1) different lung function imaging modalities are principally measuring different physiological quantities and (2) there is a lack of a true gold-standard. While all of the discussed imaging modalities are measuring some form of lung function, CT-ventilation measures voxel volume change and the amount of air change in a given voxel, while SPECT imaging, e.g. measures the percentage of counts that correlate with perfusion or ventilation. While these different thoracic physiological processes should theoretically correlate, there are physiological differences in certain patients that may make these quantities different. The other major challenge for physiological validation of CT-ventilation is that there are uncertainties in the existing lung function imaging modalities that amount to a lack of a true gold standard. For example, while planar VQ imaging has been established as a clinical standard,[29] it can suffer from aerosol deposition artifacts[7] and poor spatial resolution. The shortcomings of VQ scans increase the complexity of the correlation studies and potentially decrease the noted correlations. Other imaging modalities (PET imaging with Galligas, hyperpolarized Helium-based MRI) are still considered experimental, may not be available to all clinics, and suffer from their own artifacts.[11] The variation in the physiological lung quantity being measured and a lack of a ground truth have increased the complexity of the physiological validation efforts of CT-ventilation.

APPLICATIONS OF CT-VENTILATION IN RADIATION ONCOLOGY

There have been two main applications proposed for CT-ventilation in Radiation Oncology: functional avoidance radiation therapy and thoracic dose–response assessment. Functional avoidance implies designing radiation treatment plans that avoid functional portions of the lung (as measured by CT-ventilation) in favor of irradiating through less functioning tissue. The hypothesis is that reducing dose to functional portions of the lung can reduce the probability that patients develop thoracic toxicity (radiation pneumonitis and pulmonary fibrosis).[12,30] Early studies demonstrated the feasibility of reducing dose to functional portions of the lung while still meeting target coverage and respecting standard thoracic target and organ at risk (OAR) constraints.[13] Modeling studies have demonstrated that metrics combining dose and function (based on CT-ventilation) were a better predictor of thoracic toxicity than dose metrics alone.[12,31,32] For example, Faught et al[31] demonstrated that the volume of lung receiving ≥20 Gy (V20) predicted for ≥Grade 3 radiation pneumonitis with an area under the curve (AUC) value of 0.52, while a functional-based V20 metric predicted for ≥Grade 3 radiation pneumonitis with an AUC of 0.70. Lan et al[32] demonstrated that dose–function metrics were a predictor for lung consolidation, volume loss, and airway dilation with AUC values ranging from 0.63 to 0.80. Faught et al[33] quantified the magnitude of the potential toxicity reduction with functional avoidance. They showed that by using functional avoidance, the probability of developing ≥Grade 3 radiation pneumonitis can be reduced by 3.6% absolute (18% relative) with reductions as high as 20% possible for individual patients. The retrospective work demonstrating that incorporating dose–function information can improve prediction of thoracic toxicity suggests that prospectively incorporating functional information can reduce the rates of thoracic side-effect after radiotherapy.

Functional avoidance radiotherapy requires a modified approached to the treatment planning process in that functional information has to be incorporating into the design of the treatment plan. There have been two methods proposed to incorporate functional information into treatment planning: the structure-based approach[13,14,34–38] and the image-based approach.[39,40] The structure-based approach involves generating a "functional" structure or structures by applying thresholds to the CT-ventilation image. The functional structures represent the functional or non-functional portions of the lung and are directly used for optimization. The image-based approach involves directly incorporating the CT-ventilation imaging information into the planning process. For both the structure and image-based approaches, functional avoidance is achieved by directing the optimizer to reduce dose to the functional lung and when appropriate, by changing the gantry, collimator, and couch angle to create favorable beam geometry to reduce dose to functional lung. There are advantages and disadvantages to the structure and image-based functional avoidance planning approaches. The structure-based approach is attractive to use because manipulating dose to structures is a standard workflow in treatment planning systems while altering dose to functional images is an advanced technique that typically requires

customized scripting.[14,41] On the other hand, converting functional images to functional contours using thresholding by definitions reduces the functional resolution information of the original functional image.

When comparing functional avoidance radiotherapy to standard thoracic treatment plans, treatment planning studies have reported reductions in dose to functional lung metrics on the order of 3–9% in functional V20[6,35,38,42–44] and reductions in mean dose to functional lung from 0 Gy up to 8.2 Gy.[13,14,34,35,37,40,42,45] The magnitude of reduction in dose to functional lung that can be achieved with functional planning has been shown to be dependent on the spatial relationship between the tumor and ventilation distribution,[46] dose–function metric being evaluated, thresholds used to generate functional contours, and treatment planning system and technique [e.g. differences between three-dimensional planning, intensity modulated radiation therapy (IMRT), and rotational IMRT]. As a byproduct of reducing dose to functional lung, other dose metrics can suffer. Studies have shown that as the dose to functional lung is reduced the hot spot within the target can increase, the conformity of a plan can get worse, and doses to OARs (e.g. maximum dose to the spinal cord) can increase.[14,34,40,42,43] However, it should be noted that most studies report that while certain dose metrics can degrade as dose to functional lung is reduced, the changes still result in clinically acceptable plans.[13,41,42]

With functional avoidance radiotherapy, it will no longer be sufficient to evaluate dose metrics alone, rather metrics will be needed that combine dose and function. There has not been consensus as to which dose–function metrics are most important to evaluate. Faught et al investigated an array of dose–function metrics (including structured-based, image-based, and non-linear dose–function metrics) and how well each metric predicted for toxicity.[31] The group showed that structure-based approaches of functional V20 produced the most accurate prediction of radiation pneumonitis; however, the author's also noted that modeling results were relatively insensitive to the choice of dose–function metric selection.[31] On the other hand, Patton et al[47] showed that the highest functioning regions of the lung showed the most dramatic functional decline. Analysis of ongoing clinical trials will be needed to definitively determine which dose–function metrics are most critical when assessing for toxicity.

The other proposed use of CT-ventilation in Radiation Oncology is to evaluate imaging-based thoracic dose–response throughout and after radiation treatment.[15,47–52] The idea is that early, imaging-change-based response can be an early predictor of subsequent thoracic toxicity. Patton et al[47] demonstrated CT-ventilation-based image reductions of 3.3% for regions receiving ≥20 Gy while King et al[50] showed reduction on the order of 5% in lung regions receiving 20–40 Gy. Interestingly, Patton et al[47] demonstrated that image-based reduction was greatest for lung regions with the greatest pre-treatment CT-ventilation values; supporting the idea of avoiding these regions in the functional avoidance planning process. Latifi et al[53] showed that CT ventilation was significantly reduced for lung regions receiving ≥20 Gy for patients treated with SBRT. Although CT-ventilation studies have shown that imaging

changes occur post radiation therapy; there have been no CT-ventilation-specific studies linking the imaging changes to subsequent thoracic toxicity (there have been SPECT-based imaging studies which have shown that imaging-based changes can predict for subsequent thoracic toxicity[54,55]).

Multiple studies have shown that the CT-ventilation distribution can change throughout treatment both as a function of lung damage due to the delivered dose and re-ventilation due to reduction in tumor size and subsequent airway opening.[48,51,52] The changing in spatial lung function throughout treatment makes an adaptive approach important for functional avoidance as the changing ventilation distribution can potentially negate the initial functional dose reductions. Yamamoto et al[51] reported on a study that used the change in CT-ventilation distribution to design an adaptive planning approach that demonstrated reductions in functional mean dose of 5% when compared to 3.6% using a non-adaptive strategy.

ONGOING PROSPECTIVE CLINICAL TRIALS USING CT-VENTILATION IN RADIATION ONCOLOGY

Based on the retrospective data on functional avoidance and dose–response modeling, there have been multiple prospective clinical trials initiated. The current review will cover three ongoing prospective clinical trials on functional avoidance: trials with ClinicalTrial.gov numbers of NCT02528942, NCT02308709, NCT02843568. The NCT02308709 study is enrolling at the University of California Davis and is titled Novel Lung Functional Imaging for Personalized Radiotherapy. The study is a single arm functional avoidance study looking to accrue 33 lung cancer patients [both advanced stage and early stage patients being treated with Stereotactic Body Radiation Therapy (SBRT) are eligible]. The end point for the study is any grade ≥3 adverse events. The group have reported on the first patient treated with functional avoidance[41] as well as preliminary results for the first 19 patients treated on the study.[56] The NCT02528942 study is a two-institution functional avoidance study titled Feasibility Study Incorporating Lung Function Imaging into Radiation Therapy for Lung Cancer Patients. The study goal is to accrue 67 patient at the University of Colorado and at the Beaumont Health System. The study is open to lung cancer patients receiving definitive radiotherapy (defined as prescription doses of 45–75 Gy) and excludes patients getting treated with SBRT. The group has included an image heterogeneity assessment as an additional trial inclusion criteria[42] which attempts to include patients with significant ventilation defects while excluding patients that have spatially homogenous lung function. The rationale for the imaging-based inclusion criteria is that if a patient has homogenous lung function, there are no regions to preferentially spare. On the other hand, if a patient displays a major ventilation defect; functional avoidance can be used to spare functional portions of the lung. The end point for the study is grade ≥2 radiation pneumonitis. An example of a functional avoidance plan generated for a patient on the study is shown in Figure 3. The group has reported on a planned interim analysis[42] noting a 17.6% rate of grade ≥2 radiation pneumonitis which met the futility criteria for the study. The NCT02843568 study is enrolling at the University of Wisconsin and is titled Improving Pulmonary Function Following Radiation

Figure 3.A comparison of a functional avoidance plan and a standard, non-functional plan. The CT, CT-ventilation images, isodose lines, and PTV (shown in red) are presented for both plans. The arrows highlight the regions with the most prevalent functional lung sparing. Printed with permission from Vinogradskiy et al.[42] PTV, planning target volume.
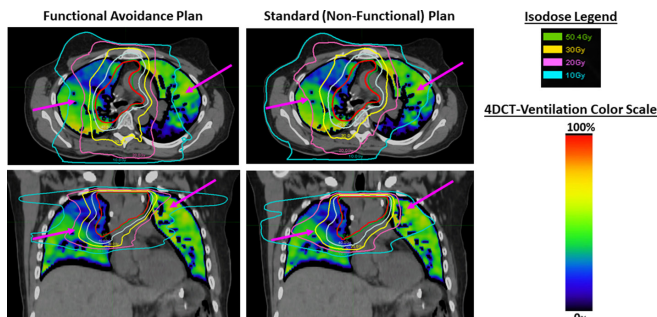
Therapy. The study is accruing 120 lung cancer patients. Patients being treated with both conventional fractionation and SBRT are being recruited. The study is designed as a two-arm, randomized study with separate cohorts for patients treated with conventional fractionation and SBRT. In total, there are four cohorts (with an accrual goal of 30 patients per cohort): functional avoidance SBRT cohort, non-functional avoidance SBRT cohort, functional avoidance standard fractionation cohort, and non-functional avoidance standard fractionation cohort. The end point of the study is imaging changes in CT-ventilation 3 months following radiation therapy. In addition to the noted primary study end points, all three studies are acquiring additional outcome metrics including PFTs, patient-reported outcomes, and other imaging assessments (VQ scans, follow up CT-ventilation, and PET imaging). The additional end points will aide in performing a complete analysis of post-treatment toxicity.

UNCERTAINTIES IN CT-VENTILATION

As with any imaging modality, there are uncertainties and shortcomings associated with CT-ventilation. The quality of the generated CT-ventilation images has been noted to vary with the quality of the acquired 4DCT data and the accuracy of the DIR.[57–59] Inaccurate registrations can result in lung tissue being mapped to blood vessel voxels which will cause artifacts in the CT-ventilation image in both the Jacobian and HU formulations. One method that has been proposed for mitigating the uncertainties caused by inaccurate registrations is to segment out the airway and blood vessels as described by Castillo et al.[2] Repeat imaging studies have noted good reproducibility of CT-ventilation imaging in mechanically ventilated animals but reduced reproducibility in spontaneously breathing humans.[60,61] Du et al noted mean Jacobian ratios (baseline Jacobian divided by follow-up Jacobian values) of 1.022 ± 0.058 for their human data.[60] The decrease in reproducibility in humans

has been noted to be caused by variations in breathing effort and inconsistent breathing patterns.[60,62,63] Another limitations of CT-ventilation is that with current image processing techniques no perfusion data are provided. In the case of lung cancer, the data assessing whether there are clinically significant differences between the ventilation and perfusion components are limited and generally inconclusive.[55,64,65] In a functional avoidance review, Ireland et al[44] cited that perfusion may be more clinically relevant when performing functional avoidance than ventilation. More data are needed from the ongoing clinical trials (which capture nuclear medicine SPECT scans in addition to CT-ventilation) to definitively determine whether ventilation or perfusion is more salient for functional avoidance.

FUTURE WORK AND SUMMARY

Efforts are ongoing to improve the accuracy and robustness of the CT-ventilation calculation methodologies[20,22] including studies to develop a phantom for CT-ventilation validation.[66] Techniques are emerging to perform 4D cone beam CT (4D CBCT) as part of daily patient set-up for treatment. The 4D CBCTs can potentially be used to calculate ventilation and provide functional data throughout treatment. Calculating ventilation with 4D CBCTs poses an even greater image processing challenge as 4D CBCTs are lower quality than 4DCT images. Studies are underway to address the challenges of calculating ventilation information from 4D CBCT images.[22,52] In terms of treatment planning, researchers are employing knowledge-based treatment planning approaches to potentially improve the quality of functional avoidance radiotherapy plans.[67] CT-ventilation based functional avoidance is also being explored retrospectively for use in thoracic proton radiotherapy.[68] Finally, CT-ventilation is being evaluated for applications outside of thoracic Radiation Oncology, including assessment for esophageal cancer patients,[69] thoracic surgery evaluation[70,71] as well as pulmonary function assessment in non-Radiation Oncology settings.[9,72]

CT-ventilation is a developing imaging modality in Radiation Oncology that uses phase-resolved CT data (4DCT or breath-hold CT) and image processing to calculate a surrogate for lung ventilation. CT-ventilation is attractive to use in Radiation Oncology because most patients undergo 4DCTs as standard of care which enables the generation of CT-ventilation images at no extra burden to the patient. Retrospective studies have presented evidence for using CT-ventilation for functional avoidance radiation therapy and for thoracic dose–response assessment. Based on the retrospective data, multiple early-phase clinical trials are underway to evaluate CT-ventilation in lung cancer patients in the prospective setting. Results from the ongoing clinical trials and work further developing CT-ventilation will guide future implementation of the novel imaging modality into large-scale trials and expanded clinical utility.

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