Functional-guided thoracic radiotherapy

Vika Gorobets
Layman Summary

This literature project focused on evaluating various methods for functional-guided thoracic radiotherapy, targeting the reduction of radiation-induced lung injury (RILI) in lung cancer patients. Functional information illustrates how multiple regions of the lungs perform their physiological roles. Several studies have highlighted the potential of reducing radiation doses in these critical areas, which can significantly influence the quality of patients' lives.

The primary aim of the research was to explore various ways of implementing high-functional information for patients with lung cancer. The study examined different advanced imaging techniques that could provide more detailed assessments of lung functionality, such as 4DCT, DECT, MRI, and SPECT, and the ways in which the ventilation information was used for patients' treatment plans.

The research concluded that functional imaging-guided radiotherapy holds significant potential to improve patient outcomes by reducing RILI. However, it also identified challenges, such as the need for standardized definitions of functional lung volumes, the integration of various imaging modalities into clinical practice, and a thorough understanding of how lung functionality can be effectively introduced into clinical settings. Ongoing clinical trials and further research are essential to validate these methods and optimize their application in radiotherapy.

In conclusion, the research highlighted that by incorporating detailed functional information into treatment planning, it is possible to enhance the precision of radiotherapy, protect healthy lung tissue, and improve the overall quality of life for lung cancer patients.

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Vika Gorobets
Department of Radiotherapy
UMC Utrecht, the Netherlands

I. Introduction

Lung cancer is the most widespread cancer diagnosis, with 12.4% of all cases. It is the leading cause of cancer-related death in men and women, resulting in 1.8 million deaths in 2022 (18.7% of all cancer deaths) [1]. Over half of lung cancer patients are advised to undergo radiotherapy [2]. However, the potential for radiation-induced lung injury (RILI) remains a considerable constraint, as over a third of those treated with radiotherapy experience RILI [3]. Often irreversible, RILI significantly diminishes the quality of life for patients and can even be fatal. Hence, one recommended way to reduce the risk of RILI while potentially improving overall survival is to evaluate the level of pre-existing lung dysfunction during treatment planning. This would include deliberately reducing the dose to areas of the lung that function well while giving a larger dose to areas with lower ventilation and blood flow [4].

One of the most important aspects of evaluating lung functionality is measuring the amount of air that the lungs inhale or exhale over time. This process is known as pulmonary ventilation function measurement. Pulmonary Function Tests (PFTs) are routinely used in clinical processes to assess a patient's ventilatory function [5]. However, these tests primarily provide an overview of lung function and are limited in their ability to pinpoint variations in function across different regions of the lung or to detect early functional changes associated with diseases [6]. Many invasive approaches (bronchoscopy, lung biopsy, pulmonary artery catheterization etc.) and radioactive imaging modalities (pneumonectomy using Xenon-133 or Nitrogen-13) have been investigated for the purpose of directly or indirectly measuring regional lung ventilation. However, because of their invasiveness and poor temporal and spatial resolution, these methods have limited practical use [7]. Beyond air exchange, the health of the lungs is also influenced by the circulation of blood. The measurement of pulmonary perfusion function evaluates the rate of blood flow through lung tissues. The interplay between perfusion and ventilation is complex, with each impacting the other through various mechanisms. Therefore, a combination of ventilation and perfusion information may offer more accurate knowledge about lung function since it shows both fluctuations in lung volume throughout the respiratory cycle and the distribution of blood flow [6].

Single Photon Emission Computed Tomography (SPECT) has improved the evaluation of respiratory diseases by enabling three-dimensional (3D) functional imaging and differentiating between healthy and dysfunctional lung tissues. This development allows for the preservation of highly functional lung areas by the modification of beam directions, which allows for lung dose optimization. While SPECT remains a widely used technique, there are now multiple clinical alternatives for ventilation and perfusion imaging. These include Four-Dimensional Computed Tomography (4DCT), Dual-Energy Computed Tomography (DECT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET) [4].

Several studies indicated that incorporating functional imaging into the treatment planning can decrease the occurrence of RILI by minimizing the radiation dose to functional lung tissue [4]. This manuscript examines the current methods of practical application of functional information.

II. Nuclear medicine imaging

A. Single-photon emission computed tomography (SPECT)

The development of SPECT/CT scanners during the past 10 years has allowed for the acquisition of CT imaging data at low radiation dose levels for attenuation correction in addition to obtaining SPECT breathing and perfusion imaging data. The application of SPECT in guiding radiation therapy to reduce RILT has been shown in numerous investigations [8].

Christian et al. (2005) [9] investigated the potential of integrating functional lung data into radiotherapy planning through an inverse planning system. This approach aimed to develop three-dimensional conformal radiation therapy (3D-CRT) plans that could minimize radiation dose to "healthy" functioning lung tissue. The process involved an iterative exploration of numerous beam angles. The primary objective of each plan was to minimize the volume of either functional lung (FL) or whole lung (WL) receiving a dose of 20 Gy, while adhering to specified constraints. The findings indicated that one patient experienced a 16% decrease in FL volume receiving a dose of 20 Gy (FLV20), while the rest exhibited non-uniform perfusion deficits, making it challenging for inverse planning to effectively optimize beam angles. The study results showed that SPECT perfusion images may be helpful for creating treatment plans for patients with significant perfusion disabilities.

Following this research, Lavrenkov et al. (2009) [10] used SPECT images to create a contour of FL using a threshold of 60% of the maximum uptake for each patient. Despite the fact that patients received conventional treatment without the use of functional information, a lung avoidance plan was developed. The main goal was to minimize the dose to functional volume receiving at least 20 Gy (fV20), while maintaining a constant

64 Gy dose inside the PTV and limiting the maximum doses to 46 Gy and 60 Gy for the spinal cord and normal volume, respectively. The results showed that when IMRT was used, stage III patients' mean lung dose (MLD) and functional V20 significantly decreased.

The Farr et al. (2019) [11] study aimed to assess the clinical viability of SPECT-guided functional avoidance planning. In order to do this, several non-overlapping functional lung zones (FL20%–FL80%) were created, with a focus on those showing better functionality. Priority was given to each FL20%–FL80% zone in ascending order. To create functional avoidance plan further optimization was performed for FL40%: mean dose to FL40% $\leq$ 16 Gy, V20 $\leq$ 30%, and V30 $\leq$ 23%. PTV coverage and dose to other organs at risk were maintained. The results showed that planning guided by SPECT/CT produced better dose-volumetric results for functional lung.

Khalil et al. (2021) [12] recently started a clinical trial (NCT04676828). They employed SPECT images to identify functional lung contours, which were determined as 20–80% subvolumes of the maximal perfusion count (FL20%–FL80%). This was done for secondary optimization. To obtain functional avoidance plan the doses to highly perfused lung subvolumes were set as low as possible, while maintaining CTV/PTV coverage and keeping the dose to OAR within specified constrains. The standard plan was used as a reference for optimizing the functional avoidance plan. Additional mean constraints were incorporated to ensure comparable doses to anatomical lung and heart between the two plans: total lung mean Dose $\leq$ 1.5 Gy and heart mean Dose $\leq$ 1.5 Gy. This clinical trial is currently in progress, and the results have not yet been released.

B. Positron emission tomography (PET)

A significant development in improving the quality of functional lung imaging is positron emission tomography (PET), which enhanced spatial and temporal resolution, and exhibited noteworthy sensitivity in the detection of radioactive substances.

The first study using ^{68}Ga-4D-V/Q PET/CT ('HI-FIVE') to derive functional lung volumes and treat patients with functional lung avoidance plans with VMAT was performed by Bucknell et al. (2021-2023) [13; 14]. The functional plans were created based on the ventilation and perfusion information. The lungs were divided into the following parts: high functioning, functioning, perfused and ventilated [13]. The goal of the avoidance plan was to achieve at least a 2% reduction in the MLD and a 4% reduction in the fV20Gy. The mean dose to heart was limited by 30 Gy and no more than 50% of heart received 25% of dose. The research showed a significant reduction in functional mean lung dose of 12.4% ± 12.8% and mean relative reduction of the fV20Gy of 22.9% ± 11.9%.

The PEGASUS trial (2021), a study on SBRT for lung lesions, has been recently launched [15]. During the first phase patients will receive standard, anatomical planning, blinded to the results of the ^{68}Ga Q PET/CT. The following step involves functional planning based on PET data to maintain functional lung volume. The particular difference between anatomical and avoidance plans has yet to be established. The goal of the trial is to measure dose reduction in functional lung areas, with at least 5% drop in either volume within the V20Gy range or overall relative lung function within the same range (fV20).

The "FLARE RT" study investigated the use of PET/CT and SPECT/CT imaging during stage IIB-IIIB non-small cell lung cancer therapy to predict outcomes and identify healthier lung tissues for individualized treatment plans [16–18]. This technique aimed to increase survival rates while minimizing side effects. The protocol included the early weeks of functional avoidance irradiation, with important evaluation points using FDG PET/CT and SPECT/CT to modify treatments for non-responders by increasing radiation doses. The regions were defined by applying various thresholds to the continuous SPECT uptake distribution. This technique produced functional lung volumes ($PERFL_i$) with seven levels that were uniformly distributed throughout intervals between the lowest and highest normalized MAA SPECT uptake values [19]. The amount of levels required for avoidance planning is directly related to the spatial resolution of the functional imaging technique, differences in uptake patterns, and the dose-response ratio. 20 Gy of MLD were redistributed based on the inverted relative mean uptake at each perfusion level. The equations are shown in Table 1 from [16]. A similar technique was used to determine biological target volume (BTV). Substructures were determined using automated subthresholding and divided into seven uptake bins/levels that were distributed equally between the lowest and highest FDG standardize uptake value (SUV) [19]. The 14 Gy mean BTV concurrent boost dose was modified based on the relative mean intake within each FDG level (Table 1 from [16]).

III. Computed Tomography

A. Four-dimensional computed tomography (4DCT)

CT remains the primary modality in radiotherapy planning because of its high geometric accuracy and capability to provide the electron density needed for accurate dose calculations. This technique also improves the clarity of details, decreases imaging time and removes the need for radioactive contrast materials [20]. A wide range of pulmonary non-contrast CT image processing methods have been investigated as potential sources of useful information for lung avoidance therapy planning. One technique for estimating regional ventilation is to use CT images to measure specific volume changes [4].

Further advancements resulted in the development of four-dimensional computed tomography (4D-CT) that generates moving structure over time [20–23]. These scans are essentially 'free' sources of data because they are also routinely obtained during the treatment planning process in the majority of hospitals [24]. Additionally, because 4D-CT-based images are more accessible than high-quality lung MR or PET/CT, they are beneficial for determining functional metrics [20]. Several clinical studies (NCT02528942, NCT02308709, NCT02843568) that used 4D-CT ventilation information were started to investigate if the dosimetric significance observed in lung function image-guided radiotherapy planning led into meaningful clinical results.

Yamamoto et al. (2011) [24] segmented the lungs into three equal functional regions — high, moderate, and low-functional lung. In order to divide, the zone free of lungs was reset to zero and the probability density function was calculated. Two thresholds were selected, and the result was a functional division of the lungs. To integrate this information into the patient's treatment plan, they minimized the mean dose to the highly functional lung areas by applying an equivalent uniform dose (EUD) constraint, alongside traditional dose-volume constraints. The findings revealed the potential of using functional planning for IMRT and VMAT.

Vinogradskiy et al. (2013) [25] determined the lung dose–function constraints to evaluate ventilation images. Following deformable image registration (DIR), the corresponding Hounsfield units (HU) should be fed into a model based on changes in density (equation 1) to generate ventilation maps [20].

$$\frac{V_{\text{in}} - V_{\text{ex}}}{V_{\text{ex}}} \times 1000 = \frac{HU_{\text{in}} - HU_{\text{ex}}}{HU_{\text{ex}} \times (1000 + HU_{\text{in}})}, \qquad (1)$$

where V_{in} and V_{ex} are the volumes of the lungs during inhale and exhale, respectively, and HU_{in} and HU_{ex} are the HU for the inhale and exhale phases of the individual lung voxels.

These maps provide a quantitative and visual representation of lung functionality, where darker colors show lower ventilation and brighter colors show higher ventilation. In addition to conventional metrics used in planning RT, the study used fMLD, which represents the average dose weighted by lung function; fV20, which represents the volume of functional lung receiving 20 Gy; and fDeff (functional effective dose), which integrates the functional aspect into the dose calculation for the lung regions.

The study by Vinogradskiy et al. [25] represents a significant initial step in validating the application of 4D-CT-based ventilation imaging for thoracic treatment planning. This method was further applied by Yamamoto et al. (2016) [26] for the first clinical application and treatment of patients with lung cancer with CT ventilation functional image-guided RT. Using the method similar to Vinogradskiy et al. [25] the authors converted CT ventilation images into percentile distribution images and created a non-uniform lung weight factor map, which is incorporated into an optimization's cost function. Two types of lung dose–function objectives were developed: (1) fMLD and (2) maximum functional Vx (% of ventilation receiving $\geq x$ Gy). The beam angles for IMRT were optimized manually to prevent from going through highly-functional lung regions. The investigation revealed that fV20 and V20 were reduced by around 5%. However, it was achieved at the expense of increased doses to other critical organs and/or degraded target dose homogeneity and conformity. Furthermore, it was observed that the volume of the lung receiving lower doses was higher in the plan guided by functional imaging (90.3%) compared to the plan based on anatomical imaging (79.7%).

Waxweiler et al. (2017) [27] conducted research to perform a complete virtual trial using retrospective data to develop the practical components of a 4D-CT-ventilation functional avoidance clinical trial. Three key topics were covered in their development process: (a) defining the criteria for clinical trial participation, (b) formulating strategies for functional avoidance in treatment planning, and (c) specifying the maximum amount of dose reduction that could be achieved in functional lung regions. DIR and a HU density-change algorithm were used to generate the ventilation images. Building on their earlier work that investigated qualitative and quantitative metrics to assess spatial lung function [25; 28], they applied these metrics in the virtual trial to determine the eligibility of patients for functional planning. These assessments included a binary metric indicating the presence of ventilation defects, the percentage of ventilation in the lung third that contained the tumor (%VTT), and the minimum percentage of ventilation in the tumor-containing third or any adjacent third (%VTA). A functional-avoid region was created by automatically segmenting the functional areas of the lung tissue, using a 15% threshold. This threshold was determined based on Area Under the Curve (AUC) analysis, which identified the %VTA giving the most favorable operational point. Following the auto-segmentation, the defined GTV or ITV were then excluded from the functional-avoid region. Reducing the dose to the functional-avoid area was achieved by integrating specific parameters into the treatment planning optimization. This involved adjusting the directions of the treatment beams by modifying couch angles and the gantry's start and stop angles. The results indicated that 60-70% of patients exhibited regional variations in lung function that were suitable for functional treatment planning. Moreover, functional planning revealed an average decrease of 2.8 Gy could be achieved in the mean dose to the functional lung areas.

Following this virtual trial, Vinogradskiy et al. (2018) [29] started a 2-institution, phase 2 prospective trial evaluating the feasibility, safety, and preliminary efficacy of 4DCT-ventilation functional avoidance. The same algorithms were used to generate and assess the ventilation images as in Waxweiler et al. (2017) [27]. Using a lower threshold of 15%, areas of the 4DCT-ventilation image were autosegmented to create the functional avoid contour. The nonfunctional plan was created by the treatment planner first, and the functional avoidance plan was created using the nonfunctional plan as a baseline. The planners were directed to give priority to the following tasks: (1) giving the recommended dose to the PTV; (2) meeting the standard limitations for thoracic organ at risk (OAR); and (3) lowering the dose to the functional avoid contour. To evaluate the dose function, they documented dose metrics related to the functional contour, which encompassed the mean dose delivered to the functional contour, fV5, fV10, fV20, and fV30. The study revealed that functional avoidance satisfied target and OAR constraints while achieving a dosimetric decrease in doses to functional lung. Vinogradskiy et al. (2022) [30] completed a multi-institutional phase 2 clinical trial, building on the foundational work [29]. The results showed that treatment using 4DCT-ventilation led to lower incidences of radiation pneumonitis when contrasted with traditional thoracic radiotherapy approaches.

CT ventilation images can also be derived from the local expansion ratio (LER) of the lung, which calculates the ratio between the maximum and minimum lung volumes during a breathing cycle [22]. Commonly, CT ventilation imaging methods employ pairwise image registration to map each point from the end of the exhale phase (0EX) CT image to the corresponding point in the end of the inhale phase (100IN) CT image. The ventilation at each point in the lung is then determined by the Jacobian determinant at that point within the mapping (LER3D). However, this approach may not accurately show situations where the lung's volume changes are not synchronized with the overall lung expansion and contraction, known as out-of-phase ventilation. This discrepancy could lead to an underestimation of LER when only using the 0EX and 100IN phases. Reinhardt et al. (2018) [31] study introduced an enhanced LER measure that used all phases of 4D-CT (LER4D) by applying a noise threshold. The lung is segmented into four regions, with low-functioning regions defined as those with less than 10% change, and high-functioning regions with greater than 10% change. The research revealed that over 10% of the lung volume had out-of-phase ventilation.

B. *Dual-energy computed tomography (DECT)*

Dual-energy computed tomography (DECT) is a modern imaging technique that has recently been used in radiation oncology. It works on the basis that using two different X-ray energies causes attenuation that is specific to the material. The ability to differentiate tissues is enhanced by this characteristic. Regional blood volume maps are made by DECT's voxel-level partial electronic density of iodine measurement capability. The study by Bahig et al. (2017) [32] aimed to evaluate lung function using DECT-derived iodine maps on a relative basis and to compare the results with the current standard (SPECT/CT). Although the study does not include reoptimization of treatment plans based on lung function data, it represents a first step towards the practical implementation of these strategies in clinical settings. The proper application of function-sparing optimization needs the development of techniques that allow the use of weighted volumes in clinically approved TPSs. In this research, a radiation oncologist manually segmented lung lobes on both DECT and SPECT/CT images for every patient. An in-house script was used to derive the iodine concentration by calculating the partial electron density of iodine within each lung voxel. This was achieved through a dual-material decomposition technique that distinguishes between the contrast agent and lung tissue [33]. Each lung lobe's functional evaluation was measured by summing together all of the iodine concentrations from each voxel, dividing the result by the total iodine concentration in the lung parenchyma, and then determining the total iodine concentration inside that lobe. For integration into the TPS, functional lung volume was imported under 6 functional subvolumes and the iodine concentration range for each patient was divided into six equal segments on the map from the minimum to the maximum value. Radiation plans were retrospectively applied to these functional subvolumes. The research revealed significant statistical differences in fV5 and f-MLD between clinical plan and avoidance plan (Pearson correlation coefficient is 0.89). The results of another study by Si-Mohamed et al. (2020) [34] also showed strong correlations between DECT and SPECT-CT in measuring relative lobar perfusion, with a Pearson correlation coefficient of 0.93.

Traditionally, DECT has been primarily used for diagnosis and differential diagnosis, staging, prognostication, and the characterization of tumor differentiation and gene expression [35]. Its application in lung avoidance treatment hasn't been thoroughly investigated, though. Filion et al.'s recent clinical study (NCT04863027) included using DECT information for treatment planning to favorably manage functional lung tissue. However, specific implementation procedures for these lung avoidance plan have not been made public.

IV. Magnetic Resonance Imaging

MRI has many benefits over CT scans, including enhanced soft tissue resolution, the absence of ionizing radiation, the ability to collect a wide range of nuclear information, and higher spatial resolution compared to nuclear medicine imaging methods [36]. However, MRI imaging of the lungs has traditionally been challenging due to the low proton concentration in the lung parenchyma and millions of air-tissue boundaries that cause magnetic susceptibility artifacts result in almost no signal from the airspaces, which complicates the generation of MR signals [4; 37]. These challenges can be addressed by the use of high polarization (HP) noble gases such as helium-3 (^{3}He) and xenon-129 (^{129}Xe), which allows for the acquisition of high-resolution, high-contrast images of the air spaces in the lungs, providing comprehensive information about regional lung function [38; 39].

While early imaging experiments used ^{129}Xe, focus swiftly moved to Helium-3 because to its superior gyromagnetic ratio and ability to obtain greater polarizations, which exceeded 50% compared to ^{129}Xe sub-10% level [40]. Consequently, the majority of human imaging investigations have used ^{3}He. It has been used to assess lung ventilation in a number of pulmonary diseases, including emphysema, asthma, cystic fibrosis, and lung cancer. This imaging technology has also been used in treatment planning studies that focus on lung function, with radiation beam angles carefully optimized to protect healthy lung tissue. A small but statistically significant improvement in results was observed [41; 42]. However, ^{3}He practically insufficient natural abundance, which is mostly produced from the decay of tritium in nuclear explosives, presents a significant obstacle and resultant high cost. Given a lack of ^{3}He, several HP gas study groups have returned to ^{129}Xe, relying on its natural abundance as an alternative [43–47]. Due to developments in HP technologies, ^{129}Xe can now obtain polarizations high enough to provide images with signal-to-noise ratios comparable to ^{3}He. Besides, Xenon-129 has a low solubility in biological tissues and can diffuse through cell membranes from the alveoli, allowing detection of gas absorption and exchange in the dissolved phase [48].

HP gas imaging is on its way toward clinical use. It provides a personalized way to monitor lung function through particular biomarkers and holds promise for tracking the success of treatments for lung diseases, all without the use of harmful ionizing radiation. However further research is needed to determine how integrating ventilation, gas exchange, and perfusion data into patient treatment plans affects radiation therapy results.

Bates et al. (2009) [41] made a simulation to investigate which patient groups may benefit most from functional image-based planning when using it for NSCLC IMRT treatment. Simulated functional images data were generated using a breath-hold CT image volume obtained from a patient involved in a related HP 3He-MRI lung planning study. An avoidance structure was then delineated by subtracting the PTV from the external contour of the patient. Anatomical plans aimed at minimizing the entire lung's exposure to radiation doses of 20 Gy or higher (V20) through beam angle and beamlet fluence adaptation, while functional plans focused on reducing the radiation dose to functioning lung areas (FV20) exceeding 20 Gy. Additional constraints detailed in [41] were introduced during the inverse planning process. The findings revealed that functional planning, when contrasted with anatomical plans, led to a reduction in the FV20 (median of 2.7%), in the total lung V20 (median of 1.5%) and in MFLD.

Ireland et al. recently enhanced radiotherapy planning and successfully identified RILI in patients undergoing radiotherapy, using HP 3He MRI [42; 49–52]. The double-masked, randomized controlled trial, that was started to assess the effect of Functional Lung Avoidance for Individualized Radiation Therapy (FLAIR), have been recently completed [51]. Pulmonary segmentation was performed using semiautomated algorithms to assess gas distribution [53]. The approach used an updated k-means clustering algorithm to classify pixels based on the presence or absence of ^{3}He MRI signal intensity. The lungs' total ventilated volume (VV) was calculated by combining the clustered regions. To create a functional avoidance plan two types of lung functioning were identified: the normally ventilated lung (NVL), which consists of medium and high ventilation regions, and the ventilated lung (VL), which contains all areas with any detectable ventilation. Planners were tasked to achieve a 3% decrease in V20 for the NVL or a 1.5% reduction for the VL, compared to conventional plans. Additionally, the plan aimed for a 2-Gy reduction in the average dose to the NVL or a 1-Gy reduction to the VL. Larger-than-normal 105% hotspots were permitted. This trial successfully created functional lung avoidance plans but was unable to achieve its accrual goals. Using 3He-MRI for functional lung avoidance in the FLAIR study did not improve pulmonary quality of life. However, all aspects of planning, delivering radiation with functional lung avoidance, and the study's double-masked design were achievable.

Recent developments in HP-^{129}Xe MRI technology have made it possible to assess regional lungs gas exchange. The presence of ^{129}Xe in the alveoli after inhalation is indicative of lung ventilation [44], while ^{129}Xe that moves from the airspaces, through the alveolar barrier tissues, and into the capillary red blood cells (RBCs) provides insights into the comprehensive lung function, also known as "gas exchange" [45]. When comparing the ventilation function represented by ^{129}Xe MRI to the functional planning that shows the actual regional lung function in gas exchange imaging, Rankine et al. (2018) [46] found differences in f-MLD and fV20. They also stated that the ventilation function shown by ^{129}Xe MRI does not effectively substitute an accurate assessment of regional lung function in every patient. In a recent study, Rankine et al. (2021) [47] employed pulmonary gas exchange map obtained using HP-^{129}Xe MRI to guide functional avoidance in treatment planning and evaluated its effectiveness against ventilation-guided treatment planning. The treatment plans were generated using a semi-automated approach, with constraints described in Table 1 from [47] and a focus on minimizing the mean dose and V20 to the highly functional lung areas. In this study, gas exchange-guided planning most effectively lowered the dose to high gas-exchanging areas. However, for several patients, ventilation-guided planning also produced similar outcomes.

V. Discussion

This research examines several options for implementing lung avoidance into patients clinical plans which are summarized in Table I. However, before functional lung avoidance planning can be effectively implemented, several issues must be addressed. First of all, there is no agreement on the best definition of a functional region, and there are discrepancies in the definition of functional lung volumes among publications. While many planning systems require a functional threshold definition, there is potential for continuum-based planning. An alternative approach is to define several non-overlapping levels of functional lung regions, with the most functional regions having priority [15].

Secondly, there are currently multiple modalities (SPECT, MR, ventilation CT, and PET/CT) for the implementation of image-guided functional planning. The clinical implementation of MR HP gas imaging has been hindered by the availability and cost of the gas, the expertise required for gas imaging (including access to specialized equipment), and the necessity for image registration to the planning CT. Meanwhile, 4D CT-based methods have emerged as promising alternatives for estimating regional ventilation lung function. However, the quality of CT imaging is crucial due to the susceptibility to potential artifacts. Although perfusion SPECT/CT has shown efficacy in enhancing functional lung avoidance during lung radiotherapy planning, it presents drawbacks such as ionizing radiation exposure, poorer spatial and temporal resolution compared to CT, MR, or PET imaging, and potential errors in attenuation and scatter correction during image registration. PET, on the other hand, has better quantification capabilities, shorter acquisition times, improved temporal and spatial resolution, and higher sensitivity for detecting radioactive decay.

However, PET also involves exposure to ionizing radiation due to the radioactive tracer used to obtain images [6].

Finally, the question remains whether to optimize functional planning based on ventilation, perfusion, or the ventilation-perfusion ratio. Most studies indicate that choosing between perfusion or ventilation data may be less crucial than minimizing the dose to highly functional regions. However, some studies have noted lower concordance between SPECT/CT ventilation and perfusion data [54; 55]. A novel approach was described in 'HI-FIVE' study [13; 14] that used both ventilation and perfusion data obtained from ^{68}Ga PET/CT to create functional lungs areas with ventilation areas having the priority. Maintaining a balanced ventilation-perfusion ratio is critical for optimal gas exchange, which reflects actual lung functionality. This leads to the important question of whether obtaining both ventilation and perfusion images is necessary for creating functional lung avoidance plan [6].

A key question about the implementation method is thrown up by the application of functional lung information: particularly, how do functional plan constraints vary from anatomical plan constraints? In at least two studies, the dose constraints for functional lung were identical to those used in anatomy-based planning. The most common approach, documented in at least ten publications, involved reducing the dose to functional mean lung dose (f-MLD), functional volume receiving 20 Gy (fV20), and/or total volume receiving 20 Gy (V20). Another approach involved lowering the radiation dose to highly functional lung areas. One research, for instance, focused on areas that, according to perfusion data, were at least 40% functioning. A unique method was proposed in the 'FLAIR RT' study, which recalculated the dose for each lung area based on the inverse of the relative mean uptake at each perfusion level.

Recent studies have also explored the use of biologically-guided RT, where PET images were used to measure metabolic activity to potentially escalate the dose. This strategy primarily focuses on maximizing the dose to the target area rather than avoiding highly functional regions. Currently, a phase III trial in Denmark is investigating this approach by increasing radiation doses as much as possible while protecting surrounding healthy tissue [56]. Additionally, the 'FLAIR RT' study proposed combining both avoidance and biologically-guided RT strategies. This raises the question of whether it is necessary to employ both approaches simultaneously.

Many prospective clinical trials are now being conducted to determine the best way to minimize radiation dose to highly functioning lung regions (NCT04702607, NCT03077854, NCT02843568, NCT05302817, NCT04676828, NCT05302817). These studies' initial results are beneficial since they show that the method is achievable and that dose reduction to functioning lung tissue may be performed. A clinical trial conducted by Rankine et al. [47] demonstrated that gas exchange-guided planning effectively lowered radiation dose to regions of the lung with high gas exchange, while still maintaining a clinically acceptable quality of the treatment plan. Yamamoto et al. (NCT02308709) [51] conducted one of the first prospective studies evaluating the safety and feasibility of lung functional avoidance in radiotherapy. One crucial question is whether incorporating functional information into treatment plans leads to reduced toxicity and improves quality of life. A clinical trial (NCT02002052) by Yaremenko et al. [51] completed, with findings indicating that the implementation of the functional avoidance plan in the 'FLAIR RT' study did not lead to any improvements in patient QOL. To our knowledge, no studies have yet demonstrated a clinical benefit of functional lung imaging over anatomical lung imaging for radiotherapy planning. Further research in this area is ongoing and additional studies are needed to reach conclusive results.

VI. Conclusion

This paper reviews existing methods of implementing lung function data into patient treatment plans. Clinical diagnosis has traditionally relied primarily on lung ventilation and perfusion imaging. Their integration into radiotherapy planning has grown significant interest, prompting ongoing research into new modalities and their clinical incorporation in functional lung imaging. A central question remains: can functional lung-related data from any imaging modality significantly affect healthy lung dose distributions, and what are the potential short- and long-term clinical benefits of such modifications? According to clinical and simulation studies, only a small number of patients with certain functional issues, tumor sites, and volumes may benefit from using functional data to lower normal lung dose. To further improve our understanding of the potential benefits and long-term effects of functional image-guided lung avoidance techniques in radiation planning, more validation tests, planning studies, and clinical trials are needed.

Author	ID	Modality	Lungs functional areas	Implementation	Institution
Cristian et al. (2005) [9]		SPECT/CT	A new contour of 'Functional lung' (FL) was created from the SPECT images.	The main objective for each plan was to minimise the volume of either FL or WL receiving R20 Gy.	
Lavrenkov et al. (2009) [10]		SPECT/CT	A contour of functioning lung (FL) was created from the SPECT images using a threshold of 60% of the maximum uptake for each patient.	The primary goal was to maintain a uniform dose of 64 Gy within the PTV, while minimizing to the fV20 and restricting maximum doses to the spinal cord and normal volume to 46 Gy and 60 Gy, respectively.	
Farr et al. (2015) [57]	NCT01745484	SPECT/CT	Contours of functional lung were created using a threshold of 20– 80% of maximum perfusion count (FLx, x = 20–80) for each patient individually. Dose to each FLx was assessed by functional DVH parameters (V5–V30f) and functional mean lung dose (MLDf).	SPECT-weighted parameters, normalised functional volumes receiving a minimum of 5–30 Gy (F-V5–V30) and normalised functional MLD (F-MLD) were calculated using the equation from [57].	Aarhus University Hospital
Farr et al. (2019) [11]		SPECT/CT	Several non-overlapping functional lung zones (FL20%–FL80%) were created	Optimization was performed for FL40%: mean dose to FL40% $\leq$ 16 Gy, V20 $\leq$ 30%, and V30 $\leq$ 23%.	Aarhus University Hospital
Khalil et al. (2020) 'ASPECT' [12]	NCT04676828	SPECT/CT	Functional lung contours, identified as 20–80% subvolumes of the maximum perfusion count (FL20–80)	The primary aim of functional avoidance is to decrease the radiation dose to highly perfused lung subvolumes by obtainig minimal dose to FL volumes while making sure that CTV and PTV are adequately covered. Dose to organs at risk must be kept within the specified dose constraints.	Aarhus University Hospital
Zeng et al. (2017-2023) 'FLARE RT' [16–18]	NCT02773238	99mTc-MAA SPECT/CT for FA, F-18 (FDG) PET/CT for BTV	Functional lung volumes ($PERFL_i$) with seven levels that were uniformly distributed throughout intervals between the lowest and highest normalized MAA SPECT uptake values [19]	20 Gy of mean lung dose were redistributed based on the inverted relative mean uptake at each perfusion level. The equations are shown in Table 1 from [16].	University of Washington
Bucknell et al. (2018-2021) 'HI-FIVE' [13; 14]	NCT03569072	^{68}Ga- PET/CT	The areas were divided based on the amount of radiation received (V20, fV20) using perfusion and ventilation images.	2% reduction in functional mean lung dose and 4% of fV20Gy; mean heart dose of less than 30 Gy and relative heart volume receiving 50 Gy of $<$ 25%	Peter MacCallum Cancer Centre
Lucia et al. (2021-2023) 'PEGASUS' [15]	NCT04942275	^{68}Ga-MAA-PET/CT		Functional lung volume constraint defined by pulmonary PET. A reduction in the dose to the functional lung will be defined by a decrease of at least 5% in functional lung volume included in V20Gy or a decrease of at least 5% in total relative lung function included in the V20G.	University Hospital, Brest
Yamamoto et al. (2011) [24]		4DCT	The lungs were equal ly divided into high-, moderate-, and low-functional lung volumes	In addition to the dose-volume limits, they used an equivalent uniform dose (EUD) constraint to lower the mean dosage to the high-functional lung.	University of California Davis Medical Center

Author	ID	Modality	Lungs functional areas	Implementation	Institution
Yamamoto et al. (2016) [26]	NCT02308709	4DCT	Functional image-guided radiotherapy is based on a non-uniform weight factor map of the lung.	(1) maximum fVx, and (2) maximum fMLD (MLD weighted by regional ventilation)	University of California Davis Medical Center
Yamamoto et al. (2022) [58]	NCT02308709	4DCT	Lung dose-function regions were established by incorporating percentile ventilation values on a voxel-by-voxel basis.	Functional avoidance plans were developed to minimize radiation dose to ventilated lung regions. For IMRT optimization, the f-MLD and fV20 were selected as dose-function constraints.	University of California Davis Medical Center
Vinogradskiy et al. (2015) [59]	NCT02843568	4DCT		An algorithm based on the percent ventilation in each lung third	University of Colorado Cancer Center
Vinogradskiy et al.(2016-2021) [27; 29; 30]	NCT02528942	4DCT	Using a lower threshold of 15%, areas of the 4DCT-ventilation image were autosegmented to create the functional avoid contour.	The functional avoidance plan was generated by altering arc geometry to avoid the functional contour whenever appropriate and by (1) giving the recommended dose to the PTV; (2) meeting the standard limitations for thoracic OAR; and (3) lowering the dose to the functional avoid contour.	University of Colorado Cancer Center
Hsu et al.	NCT03077854	4DCT		The avoidance plan is designed to optimize such that radiation dose to functional lung is as low as reasonably achievable.	National Taiwan University Hospital
Filion et al.	NCT04863027	DECT		DECT information was used at the time of treatment planning with preferential sparing of functional lung parenchymal.	Centre Hospitalier de l'Université de Montréal
Yegya-Raman et al. (Pilot study)	NCT04702607	DECT/4DCT	Not published	Not published	Hospital of the University of Pennsylvania
Yaremko et al. [50–52]	NCT02002052	MRI (^{3}He)	Normally ventilated lung (NVL) and ventilated lung (VL)	A 3% reduction in V20 to NVL or a 1.5% reduction in V20 to VL. A 2-Gy reduction in mean dose to NVL or a 1 Gy-reduction in mean dose to VL. Larger-than-normal 105% hotspots were permitted	London Health Science Centre
Rankine et al. (2018-2021) [47; 60]	NCT02478255	MRI (^{129}Xe)		Decreasing the mean dose and the volume of 20 Gy to highly functioning lung	Duke Institute Medical Center
Yegya-Raman et al. (Pilot study)	NCT05302817	MRI (^{129}Xe)		The 3D HXe images will be used to create a functional lung avoidance treatment map. The full implementation has not published yet	Hospital of the University of Pennsylvania

TABLE I: Various studies and ongoing clinical trials that involve the implementation of functional lung avoidance information.

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