STUDY ON VOXEL-GRADE PULMONARY FUNCTION IMAGING BASED ON VENTILATION-PERFUSION MAPPING AND ITS APPLICATION IN RADIOTHERAPY

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STUDY ON VOXEL-GRADE PULMONARY FUNCTION IMAGING BASED ON VENTILATION-PERFUSION MAPPING AND ITS APPLICATION IN RADIOTHERAPY

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ΔV	volume change
d_p^1	the displacement components of pixel points along the left and right, directions
d_p^2	the displacement components of pixel points along the abdomen and back directions
d_p^3	the displacement components of pixel points along the head and foot directions
G_{K1}	gaussian filters for image smoothing
G_{K2}	gaussian filters for image denoising
X	local volumes X
Y	local volumes Y
|X|	the number of elements in volume X
$\cap$	the intersection of two volumes
Vx	the volume of interesting region accepting xGy dose
Dmean	mean dose
Dx%	the dose at x% volume of interesting region
J	the Jacobian determinant
H	the number of voxels in the height
W	the number of voxels in the width
D	the number of voxels in the depth directions
D_y	partial derivative in the y direction
D_x	partial derivative in the x direction
D_z	partial derivative in the z direction
JAC	jacobian
I	ipsilateral

C	contralateral
TV_{PTV}	the PTV volume receiving 95% of the prescription dose
Dmax	the maximum dose
TV	the total volume of PTV
PIV	the total volume covered by the prescribed 95% isodose.
EXP	expiration
IN	inspiration
×	multiplication operation
A	number of PLS or PCA components in the model

LIST OF ABBREVIATIONS

4D-CT	Four-dimensional Computed Tomography
ANOVA	Analysis of Variance
CI	Conformity Index
CT	Computed Tomography
CTV	Clinical Target Volume
CTVI	CT-based Ventilation Imaging
DIR	Deformable Image Registration
DSC	Dice Similarity Coefficient
DVH	Dose-Volume Histogram
FDG	18F-fluorodeoxyglucose
HU	Hounsfield Unit
IMRT	Intensity-Modulated Radiation Therapy
IMPT	Intensity-Modulated Proton Therapy
Jacobian	Jacobian Determinant
MAE	Mean Absolute Error
MRI	Magnetic Resonance Imaging
NTCP	Normal Tissue Complication Probability
OARs	Organs at Risk
PET	Positron Emission Tomography
PETCT	PET/CT
PETPI	PET-based Perfusion Imaging
PFTs	Pulmonary Function Tests
PTV	Planning Target Volume
RIPI	Radiation-induced pulmonary injury

RIPF	Radiation-induced pulmonary fibrosis
RP	Radiation Pneumonitis
ROI	Region of Interest
RT	Radiotherapy
SBRT	Stereotactic Body Radiation Therapy
SPECT	Single Photon Emission Computed Tomography
SSIM	Structural Similarity Index
TPS	Treatment Planning System
VP-Imaging	Ventilation-Perfusion Imaging
V/Q	Ventilation-Perfusion Ratio
Vx	Volume receiving x Gy dose

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KAJIAN MENGENAI PENGIMEJAN FUNGSI PARU-PARU GRED VOKSEL BERDASARKAN PEMETAAN PENGUDARAAN-PERFUSI DAN APLIKASINYA DALAM RADIOTERAPI

ABSTRAK

Teknik pengimejan fungsi paru-paru unimodalisiti semasa untuk radioterapi (RT) kanser paru-paru gagal mencerminkan secara komprehensif ciri-ciri taburan spatial fungsi pengudaraan dan perfusi paru-paru, yang menghalang perancangan radioterapi (RT) tepat untuk kanser paru-paru. Kajian ini bertujuan untuk membangunkan dan menilai teknik pengimejan pengudaraan-perfusi (VP) pada tahap voxel yang baharu untuk pengoptimuman RT kanser paru-paru. Analisis retrospektif telah dijalankan ke atas 20 pesakit kanser paru-paru yang telah menjalani imbasan tomografi pengiraan empat dimensi (4D-CT) dan tomografi pelepasan positron/tomografi pengiraan (PET/CT). Data pengudaraan (V-Imaging) diperoleh daripada pendaftaran ubah bentuk 4D-CT, manakala data perfusi (P-Imaging) diperoleh daripada imbasan PET/CT pra-rawatan. Pengimejan VP bersepadu telah dijana melalui hasil Hadamard. Persetujuan antara modaliti dinilai menggunakan Pekali Keserupaan Dice (DSC) dan korelasi. Rancangan RT termodulasi keamatan (IMRT) telah dioptimumkan berdasarkan setiap imej fungsi, dengan membandingkan dos pada sasaran rawatan dan organ yang berisiko. Pengimejan VP menunjukkan persetujuan yang lebih baik dengan imej unimodalisiti (DSC sehingga 0.71, Pekali Korelasi Pearson sehingga 0.943) berbanding persetujuan yang lemah antara V-Imaging dan P-Imaging sahaja (DSC=0.11 di kawasan fungsi tinggi). Rancangan berpandu VP menghasilkan taburan dos yang berbeza secara signifikan ($p<0.05$) di paru-paru ipsilateral fungsi tinggi berbanding rancangan berasaskan V atau P, tanpa

menjejaskan dos organ yang berisiko yang lain. Kesimpulannya, Pengimejan VP berjaya menyepadukan data pengudaraan dan perfusi daripada imbasan klinikal rutin, memecahkan ketidaksesuaian V/Q dan menyediakan peta paru-paru fungsi yang lebih baik. Ia memudahkan perancangan RT personalisasi dengan membolehkan penjagaan selektif tisu fungsi tinggi, yang berpotensi mengurangkan ketoksikan paru-paru sambil mengekalkan keberkesanan rawatan.

STUDY ON VOXEL-GRADE PULMONARY FUNCTION IMAGING BASED ON VENTILATION-PERFUSION MAPPING AND ITS APPLICATION IN RADIOTHERAPY

ABSTRACT

Current single-modality lung functional imaging techniques for lung cancer radiotherapy (RT) fail to comprehensively reflect the spatial distribution characteristics of pulmonary ventilation and perfusion functions，hindering precise radiotherapy (RT) planning for lung cancer. This study aimed to develop and evaluate a novel voxel-level ventilation-perfusion (VP) imaging technique for lung cancer RT optimization. A retrospective analysis was performed on 20 lung cancer patients who underwent four-dimensional computed tomography (4D-CT) and positron emission tomography/computed tomography (PET/CT) scans. ventilation (V-Imaging) was derived from 4D-CT deformable registration, and perfusion (P-Imaging) from pre-treatment PET/CT. An integrated VP-Imaging was generated via Hadamard product. Agreement between modalities was assessed using Dice Similarity Coefficient (DSC) and correlation. Intensity-modulated RT (IMRT) plans were optimized based on each functional image, comparing doses to targets and organs at risk. VP-Imaging demonstrated superior concordance with single-modality images (DSC up to 0.71, Pearson CC up to 0.943) compared to the poor agreement between V- and P-Imaging alone (DSC=0.11 in high-function regions). VP-guided plans yielded significantly different dose distributions ($p<0.05$) in high-function ipsilateral lung compared to V- or P-based plans, without compromising other OAR doses. In conclusion, VP-Imaging successfully integrates ventilation and perfusion data from routine clinical scans, resolving V/Q mismatch and providing a superior map of functional lung. It facilitates

personalized RT planning by enabling selective sparing of high-function tissue, potentially reducing pulmonary toxicity while maintaining treatment efficacy.

CHAPTER 1

INTRODUCTION

Radiotherapy aims to deliver high doses of radiation to tumor volumes while minimizing exposure to surrounding healthy tissues. This is achieved through meticulous treatment planning that reduces radiation to critical and sensitive structures. However, when a tumor is embedded within a large, parallel-functioning organ such as the lung—where healthy tissue completely surrounds the target—sparing functional regions becomes particularly challenging. Lung function imaging studies have revealed that not all apparently healthy lung tissues function at the same capacity. The ability to map regional lung function through imaging offers the potential to differentiate functional subtypes, thereby enabling functionally adaptive radiotherapy planning that prioritizes the sparing of high-functioning lung regions.

1.1 Background to the Problem

Radiation-induced pulmonary injury (RIPI) constitutes a major dose-limiting toxicity in lung cancer radiotherapy, encompassing both early radiation pneumonitis (RIP) and late radiation-induced pulmonary fibrosis (RIPF), either of which can severely compromise quality of life and prove fatal (Hanania et al., 2019). While modern computed tomography (CT) provides exceptional anatomical visualization, functional assessment requires specialized techniques that characterize regional physiology rather than mere morphology.

Two primary imaging modalities currently dominate functional lung assessment. CT-based ventilation imaging (CTVI) employs deformable image registration (DIR) of four-dimensional CT (4D-CT) scans to compute voxel-level volume changes as a surrogate for regional ventilation (Vinogradskiy, 2019). This

approach offers the distinct advantage of deriving functional information from standard simulation imaging without additional patient burden. In contrast, PET-based perfusion imaging (PETPI) utilizes radiotracer distribution, typically from FDG-PET/CT, to map pulmonary blood flow, with regions of high perfusion demonstrating increased tracer uptake (Yamamoto et al., 2014).

Despite their individual clinical utility, these unimodal approaches present a fundamental limitation: each capture only one aspect of the dual-parameter system that defines lung function. CTVI meticulously maps air distribution but remains blind to perfusion, while PETPI accurately reflects blood flow but cannot identify ventilation defects. This inherent shortcoming manifests as significant spatial discordances between CTVI and PETPI functional maps, particularly in pathologically heterogeneous lungs affected by conditions such as emphysema or bronchiectasis (Pinot et al., 2023), as visually contrasted in Figure 1.1.

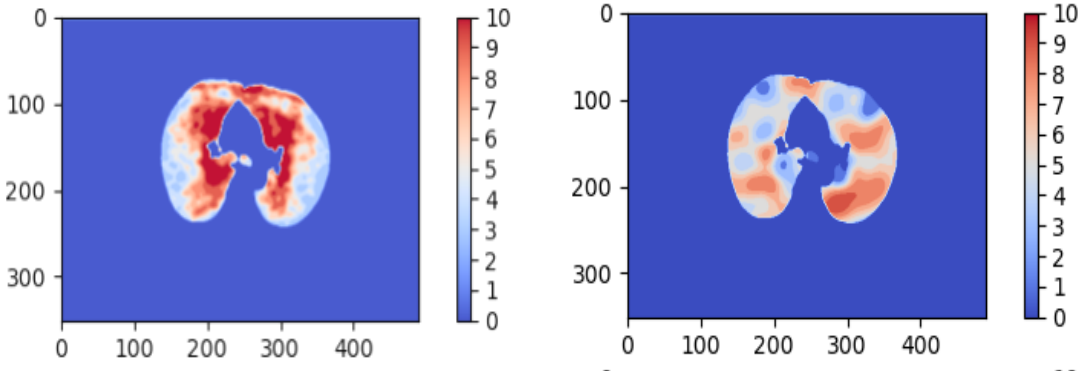

Figure 1.1 The difference of V-Image and P-Image

Such discrepancies underscore a crucial physiological principle: neither ventilation nor perfusion alone adequately characterizes lung function. Rather, the precise matching between airflow and blood flow, quantified by the ventilation-perfusion (V/Q) ratio, serves as the gold standard for evaluating regional gas exchange

efficiency (Lenfant & Okubo, 1968; West, 1968). From a radiotherapy planning perspective, this discordance creates substantial uncertainty in defining functional lung volumes for avoidance, potentially leading to suboptimal treatment plans. Furthermore, conventional pulmonary function tests (PFTs) offer only global metrics, lacking the spatial resolution necessary for voxel-level dose optimization in advanced techniques like stereotactic body radiotherapy (SBRT) (Lu et al., 2025; Zhong, Li & Cui, 2023).

1.2 Research Gaps and Rationale

Although single-modality CTVI is widely used due to no extra patient burden (Li et al., 2023) but fails to capture perfusion; The limitations inherent to single-modality imaging create several critical barriers to precision radiotherapy. First, despite the physiological primacy of the V/Q ratio, no established clinical method exists to visualize this relationship at the voxel level. Second, the documented discordance between CTVI and PETPI undermines confidence in defining reliable functional avoidance volumes. Finally, the spatial resolution gap between global PFTs and modern radiotherapy techniques hinders personalized, voxel-level dose optimization.

These considerations establish the fundamental rationale for this study: a unified imaging technique that integrates co-registered ventilation and perfusion data should provide a more physiologically complete and spatially precise assessment of lung function than either modality alone. This research proposes to address existing gaps by developing a novel ventilation-perfusion (VP) imaging method that computationally fuses 4D-CT-derived ventilation data—calculated via the Jacobian determinant from deformable registration—with PET/CT-derived perfusion data represented by a gray value matrix. This integrated approach, conceptually outlined in

the theoretical framework presented in Figure 1.2, strategically leverages routinely available clinical scans, thereby offering a practical solution for enhancing radiotherapy personalization without imposing additional imaging burdens on patients.

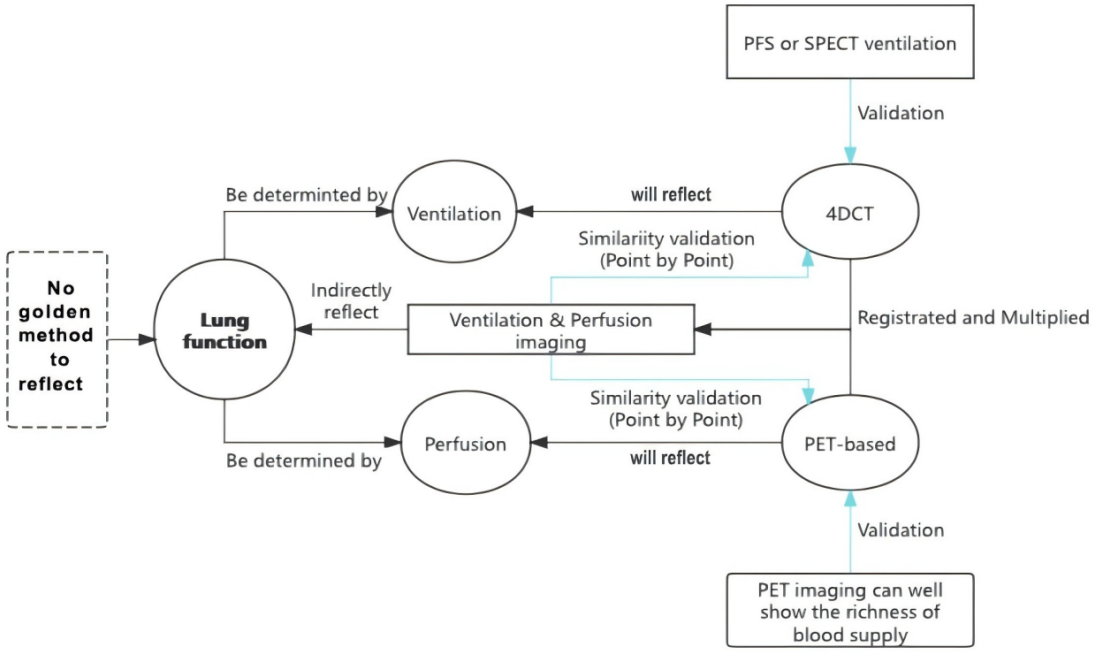

Figure 1.2 The theoretical framework of this study

1.3 Problem Statement

Radiotherapy planning for lung cancer patients necessitates a comprehensive and precise understanding of regional lung function to maximize treatment efficacy while minimizing injury to healthy tissues. Contemporary imaging techniques predominantly evaluate either ventilation or perfusion in isolation, often neglecting the complex and interdependent relationship between these two fundamental physiological processes. This fragmented approach can result in inaccurate identification of functional lung volumes, potentially leading to suboptimal radiation dose distributions and an elevated risk of clinical complications, such as radiation-induced pneumonitis (RIP).

The central challenge addressed in this research is the development of an imaging methodology capable of simultaneously capturing and integrating voxel-level ventilation and perfusion data, thereby yielding a holistic and physiologically faithful representation of pulmonary function. A modality of this kind would empower clinicians to design highly personalized radiotherapy plans that are tailored to the unique functional anatomy of each patient's lungs, ultimately contributing to improved therapeutic outcomes and reduced treatment-related morbidity.

To tackle this challenge, the present project aims to develop a novel voxel-level lung functional imaging technique based on ventilation-perfusion (VP) data. This innovative strategy seeks to overcome the inherent limitations of existing unimodal approaches by generating an integrated VP matrix that concurrently reflects both ventilation and perfusion characteristics. The project will employ advanced image processing methods, including the computation of Jacobian-based ventilation metrics derived from deformable image registration of 4D-CT data, alongside the extraction of perfusion values from pre-processed PET imaging.

The core problem being addressed is the absence of a robust and integrative technique for assessing lung function at a high spatial resolution for radiotherapy planning purposes. Through the development and validation of this novel VP-Imaging technique, the project intends to furnish clinicians with a powerful and refined tool for personalized treatment planning, thereby advancing the quality and precision of care for lung cancer patients.

1.4 Research Questions

This study aims to address the following research questions, which are designed to overcome the limitations of existing unimodal functional imaging approaches:

(1) How can ventilation data from 4D-CT and perfusion data from PET/CT be effectively integrated to generate a unified, voxel-level ventilation-perfusion (V/P) map?

(2) What is the potential impact of incorporating V/P-based functional maps into radiotherapy planning for lung cancer, particularly in terms of enabling personalized dose optimization and reducing radiation dose to high-functioning lung tissues?

The necessity of these questions is underpinned by the well-documented discordance between CTVI and PETPI functional maps. As evidenced in pathological conditions such as emphysema, neither modality alone captures the ventilation-perfusion (V/Q) ratio—the gold-standard metric for regional lung function. This fundamental limitation of current single-modality imaging hinders the precise assessment of lung function necessary for advanced radiotherapy planning.

1.5 Research Hypotheses

Based on the limitations of existing imaging modalities and the theoretical framework established above, the following research hypotheses are formulated:

(1) Enhanced Imaging Accuracy: The novel voxel-level ventilation-perfusion (VP) imaging technique, which synergistically integrates co-registered ventilation

data from 4D-CT-derived Jacobian analysis with perfusion data from PET/CT, will provide a more physiologically accurate and spatially precise depiction of regional lung function than can be achieved by either CTVI or PETPI alone. This is hypothesized because the integrated VP map directly reflects the ventilation-perfusion ratio, which is the fundamental determinant of gas exchange efficiency at the alveolar level.

(2) Improved Radiotherapy Planning: The incorporation of the proposed VP functional maps into RT treatment planning will facilitate the design of more personalized and anatomically-informed treatment strategies. It is hypothesized that by enabling explicit identification and sparing of high-functioning lung regions, this approach will lead to a significant reduction in the risk of radiation-induced pulmonary toxicity (such as pneumonitis) without compromising tumor coverage, thereby potentially improving overall therapeutic outcomes and patient quality of life.

1.6 Research Objective

This study is primarily aimed at establishing the technical viability and preliminary dosimetric advantages of fusing ventilation and perfusion signal data, forming a crucial platform for future clinical translation. To achieve this aim, the following specific research objectives have been formulated:

1.6.1 Objective 1: Development and Technical Validation of Integrated VP Imaging

To develop a robust and reproducible technical pipeline for fusing 4D-CT-derived ventilation and PET-derived perfusion data into a unified VP imaging model and construct a quantifiable VP imaging model that reflects the ventilation-perfusion balance at the voxel level.

1.6.2 Objective 2: Preliminary Validation in Clinical Radiotherapy Treatment Planning

To perform a dosimetric analysis to evaluate the potential of this novel VP model in optimizing radiotherapy plans, specifically by assessing its ability to spare high-functioning lung regions.

This involves comparing VP-based functional avoidance plans with conventional CTVI- or PETPI-based plans, and quantitatively evaluating differences in dose distributions to functional lung regions, organs at risk (OARs), and target volumes, with the goal of determining whether VP imaging facilitates improved personalization of dose delivery and reduction of predicted toxicity.

1.7 Conceptual Framework and Rationale

Figure 1.3 outlines the systematic approach linking theoretical foundations, data processing, imaging generation, and clinical application. It integrates multi-modality images registration with advanced analytical techniques to ultimately improve radiotherapy accuracy.

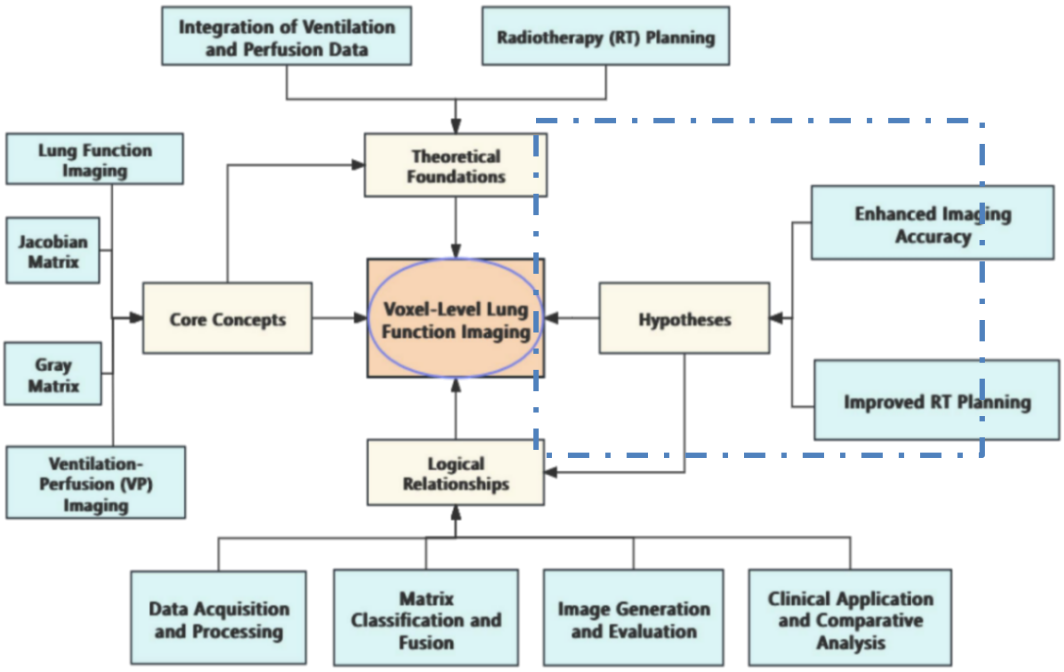

Figure 1.3 Conceptual framework of this research

The conceptual framework of this research (Figure 1.3) outlines a systematic approach linking theoretical foundations to clinical application. It integrates multi-modality image registration with advanced analytics to improve radiotherapy accuracy.

1.7.1 Core Concepts

Voxel-Level Lung Function Imaging: A high-resolution quantitative technique for assessing regional pulmonary function at the individual voxel level, enabling precise functional tissue segmentation for radiotherapy planning.

Jacobian Matrix: A mathematical construct derived from DIR of 4D-CT images. Its determinant quantifies local volume change and serves as a surrogate measure for regional ventilation.

Gray Matrix: A quantitative matrix representing perfusion characteristics extracted from PET imaging, reflecting spatial heterogeneity in pulmonary blood flow at the voxel level.

1.7.2 Theoretical Foundations

This research is grounded on two principles:

(1) Integration of Ventilation and Perfusion Data: The synergistic combination of ventilation and perfusion data yields a more complete and accurate assessment of regional lung function than either parameter alone, crucial for informed clinical decision-making.

(2) Radiotherapy Planning Optimization: Personalized treatment design is essential for maximizing efficacy and minimizing toxicity. High-resolution lung function imaging is critical for identifying and preserving functional lung subunits, thereby reducing the risk of radiation-induced injury.

1.7.3 Logical Relationships

The framework follows a coherent progression:

(1) Data Acquisition and Processing: Ventilation data is acquired via 4D-CT and DIR, while perfusion data is obtained from PET/CT scans.

(2) Matrix Classification and Fusion: The derived Jacobian (ventilation) and Gray (perfusion) matrices are classified and computationally fused to generate a unified VP matrix.

(3) Image Generation and Evaluation: Functional images are generated and rigorously evaluated using quantitative metrics for spatial agreement and clinical validity.

(4) Clinical Application and Comparative Analysis: The VP-Imaging technique is applied in RT planning, and its efficacy is evaluated by comparing dose distributions against plans using traditional V- or P-Imaging alone.

1.8 Innovation and Significance of the Research

This study introduces several key innovations that address the fundamental limitations of current functional lung imaging for radiotherapy. The novelty of this work is not merely the combination of existing imaging modalities, but lies in the methodology, integration, and clinical application of the resulting data.

1.8.1 Key Innovations

Novel VP-Image Generation: The core innovation is the development of a unified VP imaging technique. This is achieved through a novel data fusion framework that performs a Hadamard product (element-wise multiplication) of the classified Jacobian matrix (derived from 4D-CT DIR) and the classified PET Gray-value matrix. This mathematical fusion creates a new, voxel-level physiological metric that more closely reflects the gas-exchange capacity of the lung than either ventilation or perfusion alone, directly embodying the clinically pivotal V/Q ratio.

Clinical Workflow Integration without Additional Burden: A significant innovative aspect is the strategic use of routinely acquired clinical scans (4D-CT and FDG-PET/CT). By deriving both functional parameters from standard simulation and

staging scans, this method eliminates the need for additional, costly, or complex specialized functional imaging procedures (e.g., SPECT, Galligas PET). This makes the technique highly practical and readily integrable into existing clinical radiotherapy workflows.

A Practical Tool for Precision Radiotherapy: The research is innovatively targeted at generating a clinically actionable, voxel-level functional map specifically designed for treatment planning systems. The final VP-Image is processed and classified to allow for the direct contouring of functional sub-regions, enabling truly personalized, physiology-guided dose optimization in a way that was previously impractical with discordant unimodal images.

1.8.2 Significance and Contributions

This study successfully completed a full cycle from conceptual design, through technical implementation, to preliminary validation. Its significance is manifested in the following aspects:

(1) Provision of an Innovative Methodological Tool for Functional-Guided Radiotherapy. This research has established a stable and automated technical pipeline for generating ventilation-perfusion (VP) functional lung images. It provides the clinical radiotherapy community with a practical, efficient, and reproducible new tool, moving beyond the limitations of single-modality functional imaging and offering a viable technical pathway for truly implementing "functional-guided precision radiotherapy."

(2) Construction of a Physiologically More Comprehensive Lung Functional Model. By integrating ventilation and perfusion information at the voxel level,

the study has constructed a multi-parametric functional lung model that more accurately reflects the physiological essence of gas exchange. This model enables precise visualization of functional subregions within the lung, providing a more reliable imaging basis for delineating personalized lung protection zones.

(3) Preliminary Confirmation of Clinical Application Potential in Radiotherapy Optimization. Dosimetric analysis has confirmed that radiotherapy plans based on the VP model can significantly reduce the radiation dose to high-functioning lung regions. This preliminarily validates the potential of this novel imaging technique in improving the therapeutic ratio—maximizing tumor control while minimizing pulmonary toxicity—thereby providing compelling preliminary evidence for its clinical translation.

(4) Establishment of a Crucial Technical Foundation for Future Research. As a foundational "proof-of-concept" study, this work has developed a complete technical workflow from data processing to image generation. It establishes an essential platform for subsequent large-scale clinical validation, in-depth mechanism exploration, and even the development of artificial intelligence models based on multi-parametric functional data, holding substantial long-term scientific value.

1.9 Research Scope and Delimitation

The scope of this work is deliberately focused on the technical development and dosimetric validation of the VP imaging technique. This involves retrospective analysis of 4D-CT and PET/CT data from lung cancer patients, with specific attention

to algorithm development, image fusion methodologies, and comparative planning studies. The research explicitly excludes prospective clinical implementation and long-term outcome assessment, which represent logical directions for future investigation.

1.10 Thesis Structure

To ensure logical coherence, this thesis is organized as follows: Chapter 2 provides a comprehensive literature review on functional lung imaging and its application in radiotherapy. Chapter 3 details the methodology, including data processing, VP matrix generation, and treatment planning design. Chapter 4 presents the results of both technical validation and dosimetric evaluation. Finally, Chapter 5 summarizes the findings, discusses their implications, acknowledges the study's limitations, and suggests directions for future research.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter provides a comprehensive review of the literature relevant to the development and application of lung functional imaging in radiotherapy. The focus is on the technological foundations, comparative characteristics of various imaging modalities, and their integration into treatment planning and evaluation. Key areas examined include image registration techniques, the performance of different functional imaging methods, planning strategies for functional avoidance, and the metrics used for assessing both image quality and dosimetric outcomes. By synthesizing current research, this review establishes the context for the present study and highlights the advancements and remaining challenges in the field of voxel-level pulmonary function imaging.

2.2 Advancements in Lung Functional Imaging Technology

2.2.1 DIR and Algorithms Selection in Imaging Processing

In image segmentation algorithms, image registration is the process of obtaining a deformation field between a reference image and the image to be segmented. The accuracy of segmentation heavily depends on the quality of this deformation field. Within multi-atlas segmentation algorithms, the deformation parameters derived from registration can be utilized not only for segmenting the image but also for calculating weighting factors.

The volume change algorithm, a direct geometric method for calculating ventilation from lung volume change (ΔV), aims to determine specific volume changes by computing the volume of deformed elements based on the DIR transformation, using the positions of the eight vertices of each voxel (Zhou & Zhang, 2022). The volume of each tetrahedron is calculated by the formula:

$$V = (\vec{b} - \vec{a}) \cdot [(\vec{c} - \vec{a}) \times (\overrightarrow{d - \vec{a}})] / 6 \quad (1)$$

where $\vec{a},\vec{b},\vec{c},\vec{d}$ are the vertices of the tetrahedron as vectors. Summing the volumes of the six tetrahedrons from the DIR deformation matrix, we can get the volume of a given polyhedron.

In addition to direct geometric methods, Reinhardt et al. (2008) proposed an approximate method for estimating voxel volume changes by calculating the Jacobian determinant of the deformation field. The Jacobian matrix is grounded in the theory that local partial derivatives of the deformation field correlate with volume changes in lung tissue, thereby describing local volume variations due to ventilation (Yamamoto et al., 2014). The Jacobian calculation depends solely on the DIR transformation function, with the Jacobian determinant of the deformation field between different breathing phases obtained through image registration. The formula is expressed as (Castillo et al., 2019):

$$\mathrm{Ven}_{\mathrm{exh}}^{\mathrm{Jac}}(\mathrm{p}) = \begin{vmatrix} 1+\frac{\partial \mathrm{d}_{\mathrm{p}}^{1}}{\partial \mathrm{x}_{1}} & \frac{\partial \mathrm{d}_{\mathrm{p}}^{1}}{\partial \mathrm{x}_{2}} & \frac{\partial \mathrm{d}_{\mathrm{p}}^{1}}{\partial \mathrm{x}_{3}} \\ \frac{\partial \mathrm{d}_{\mathrm{p}}^{2}}{\partial \mathrm{x}_{1}} & 1+\frac{\partial \mathrm{d}_{\mathrm{p}}^{2}}{\partial \mathrm{x}_{2}} & \frac{\partial \mathrm{d}_{\mathrm{p}}^{2}}{\partial \mathrm{x}_{3}} \\ \frac{\partial \mathrm{d}_{\mathrm{p}}^{3}}{\partial \mathrm{x}_{1}} & \frac{\partial \mathrm{d}_{\mathrm{p}}^{3}}{\partial \mathrm{x}_{2}} & 1+\frac{\partial \mathrm{d}_{\mathrm{p}}^{3}}{\partial \mathrm{x}_{3}} \end{vmatrix} \quad 2$$

Where $\mathrm{d}_{\mathrm{p}}^{1}$, $\mathrm{d}_{\mathrm{p}}^{2}$ and $\mathrm{d}_{\mathrm{p}}^{3}$ represent the displacement components of pixel points along the left and right, abdomen and back, and head and foot directions respectively. $\mathrm{Vent}_{\mathrm{exh}}^{\mathrm{Jac}}(\mathrm{p})$ values between 0 and 1 indicate reduced lung volume, $\mathrm{Vent}_{\mathrm{exh}}^{\mathrm{Jac}}(\mathrm{p})$ =1 indicates no change in the volume of this area, and $\mathrm{Vent}_{\mathrm{exh}}^{\mathrm{Jac}}(\mathrm{p}) > 1$ indicates volume expansion of pixels.

Besides the Jacobian algorithm, the CT number (Hounsfield Unit, HU) method can also estimate pulmonary ventilation distribution (Zhong & Cui, 2023). This method infers lung ventilation from changes in CT values between end-inhalation and end-exhalation phases, as CT values are directly related to lung tissue density. The ventilation capacity formula related to maximum expiratory and inspiratory phases is expressed as (Zhong & Cui, 2023):

$$\mathrm{Ven}_{\mathrm{exh}}^{\mathrm{Hu}}(\mathrm{p}) = \frac{\mathrm{HU}_{\mathrm{exh}}(\mathrm{G}_{\mathrm{K1}} - \mathrm{HU}_{\mathrm{inh}}(\mathrm{X}_{\mathrm{p}+\mathrm{d}_{\mathrm{p}}}) \times \mathrm{G}_{\mathrm{K1}})}{\mathrm{HU}_{\mathrm{inh}}(\mathrm{X}_{\mathrm{p}+\mathrm{d}_{\mathrm{p}}}) + 1000} \times \mathrm{G}_{\mathrm{K2}} \quad 3$$

Where $\mathrm{HU}_{\mathrm{exh}}(\mathrm{x}_{\mathrm{p}})$ represents the CT value of each pixel in the image corresponding to the maximum expiratory phase; $\mathrm{HU}_{\mathrm{inh}}(\mathrm{x}_{\mathrm{p}+\mathrm{d}_{\mathrm{p}}})$ represents the CT value of pixel p in the image corresponding to the maximum inspiratory phase after

the action of the displacement vector; G_{k1} and G_{k2} represent Gaussian filters for image smoothing and denoising.

To explore the advantages and disadvantages of these three approaches, Castillo et al. (2010) conducted a comparative study and found that although the Jacobian-based method was more widely used, HU-based method showed a higher correlation with clinical references. However， Latifi et al. (2013) compared the three ventilation imaging algorithms and results indicated that the similarity between ΔV and Jacobian was higher than that between HU and Jacobian, and between ΔV and HU.

While some studies have indicated that the HU-based method may yield higher correlation coefficients with clinical references in specific cohorts, the Jacobian method was selected for this study due to its superior robustness. The Jacobian algorithm, being derived from the deformation field itself, is less sensitive to absolute CT Hounsfield unit values, which can be affected by scanning protocols, beam hardening artifacts, and patient-specific factors. This choice prioritizes methodological stability and theoretical clarity (direct measurement of volume change) over potential gains in correlation that might be context-dependent

2.2.2 Quantitative Analysis and the Role of Deep Learning in CT Ventilation Functional Imaging

The quantitative analysis of lung ventilation function relies on obtaining voxel-level ventilation change values and performing subsequent image segmentation and visualization. Following the derivation of ventilation-related metrics—through methods such as DIR, Jacobian determinant calculation, or HU change analysis as detailed in Section 2.2.1—the resulting deformation fields or functional matrices must be further processed to extract clinically meaningful regions. This stage involves

converting quantitative ventilation values into segmented functional maps that distinguish regions with differing levels of pulmonary function.

Image segmentation methodologies can be broadly classified into two categories based on their objectives: semantic segmentation and instance segmentation (Hegi-Johnson et al., 2017; Khan, Lee, & Lee, 2023). Semantic segmentation assigns a categorical label (e.g., "functional," "non-functional") to each pixel in the image, enabling a pixel-wise classification of lung tissue. Instance segmentation goes further by distinguishing between different objects within the same category—for example, identifying and separating individual functional sub-regions or lesions. The design of these segmentation strategies depends heavily on the availability of task-specific annotated data, which provides essential information for differentiating between anatomical or pathological regions. Common medical imaging modalities used include X-ray, CT, and MRI. Traditional segmentation techniques have included edge detection, template matching, region growing, graph cuts, active contours, and classical machine learning algorithms (Wu et al., 2021; Westcott et al., 2019; Fain, 2019).

In recent years, deep learning has become increasingly prominent in medical image analysis, offering powerful alternatives to traditional algorithms for functional image generation and segmentation (Xu S et al., 2025; S. A. A. K. Ponsingh et al., 2025). A significant application involves using expertly annotated maps as training targets, with corresponding anatomical images serving as input. For instance, deep convolutional neural networks (CNNs) and U-Net architectures have been developed to estimate ventilation images directly from 4DCT data, potentially bypassing the need for explicit DIR and its associated uncertainties (Liu et al., 2020; Zhong et al.,

2019). Recent advancements have further demonstrated the potential of transformer-based architectures and diffusion models for more accurate and robust medical image segmentation and synthesis (Karimijafarbigloo S et al., 2025; Verdicchio M et al., 2025).

Despite these promising advances, the application of deep learning to lung functional imaging remains constrained by a fundamental challenge: the scarcity of a reliable, standardized ground truth for model training and validation. Current methods often depend on heterogeneously generated functional maps derived from traditional algorithms (e.g., DIR-based methods), which inherently transfers the limitations of these methods to the deep learning models, thereby compromising generalizability and reproducibility.

This study directly addresses this critical bottleneck. The VP-Imaging technique developed here, by integrating multi-modality data into a unified, physiologically grounded framework, aims to establish a more robust and standardized reference. This novel imaging output can, in future work, serve as a superior training target and validation benchmark for deep learning models, paving the way for the development of more accurate, reliable, and automated segmentation tools for functional lung assessment.

2.3 Characteristics of Different Function Imaging Techniques

PET-based functional imaging relies on the development of perfusion imaging techniques. It has been shown that when combined with radioactive gas inhalation, PET-based imaging can roughly reflect lung blood flow and ventilation function, thereby better capturing changes in local lung function during RT (McIntosh et al.,

2021). SPECT (Single Photon Emission Computed Tomography) technology reflects lung perfusion and possesses unique advantages in lung function visualization and evaluation. Using SPECT, Hoover et al. (2014) classified lung cancer patients into non-radiation pneumonitis and radiation pneumonitis groups. They found that compared to the radiation pneumonitis group, the mean lung dose was nearly 5 Gy higher, and V20 and V30 (Vx: the volume of OAR receiving x Gy dose) were nearly 5% higher in the non-radiation pneumonitis group. Meanwhile, Matuszak et al. (2016) found that optimizing RT plans based on SPECT could reduce the mean lung dose, suggesting that SPECT-guided radiation plans can reduce the incidence and severity of radiation pneumonitis.

In addition to PET/CT, lung function imaging also includes MRI. Depending on the technique, MRI-based functional imaging primarily consists of MRI ventilation imaging, fluorinated gas MRI, pulmonary perfusion and hemodynamic imaging, and biomechanical evaluation for pulmonary functional imaging (Ohno et al., 2022).

Hyperpolarized noble gas (^{3}He or ^{129}Xe) MRI, oxygen-enhanced (O_2-enhanced) MRI, and fluorine-19 (^{19}F) MRI have been studied as potential MRI-based ventilation imaging techniques since the 1990s. They have been extensively tested for assessing disease severity and evaluating therapeutic effects of various pulmonary diseases (Chan, Stewart, Norquay, Collier, & Wild, 2018; Markstaller et al., 2002). Pulmonary perfusion and hemodynamic imaging are widely used for visualizing pulmonary vasculature and blood flow (Johns et al., 2000; Hatabu et al., 2000). MRI-based biomechanical assessment has currently been attempted mainly for radiation oncology rather than pulmonary functional imaging. Additionally, the lack of ionizing radiation makes it suitable for experimental work with healthy subjects (Kolb et al., 2016).

About the correlation between MRI-based and CT-based functional imaging in RT, A study by Carey et al. (2023) involved 34 patients who underwent Hyper polarized Helium-3 Magnetic Resonance Imaging (HP ^{3}He MRI) and CT imaging. HP ^{3}He MRI was assessed for ventilation defects using a semi-automated k-means clustering algorithm. Inspiratory and expiratory CT images were analysed using parametric response mapping (PRM) to quantify markers of emphysema and functional small airways disease (fSAD). The study concluded that on a global level, fSAD correlated well with whole lung localized ventilation defect percent (VDP) but poorly correlated with forced vital capacity (FVC)% predicted ($-0.38 \leq r \leq -0.35$, $p < 0.001$), consistent with previous work. Furthermore, Matsumoto et al. (2021) proposed a new method based on MRI, EPRI, and PET to study the tumor microenvironment. This research provides a new perspective that a multimodal instrument, such as PET-MRI, may offer another possibility for linking multiple functions.

The aforementioned functional imaging studies based on CT, PET, or MRI are relatively mature and each has its own characteristics, advantages, and inevitable drawbacks, as summarized in Table 2.1. For SPECT perfusion imaging, ^{99m}Tc-labeled radioactive aerosols are harmful and require special aerosolization equipment, and the image resolution of inert gas ^{133}Xe is not high. For MRI, ^{3}He is expensive due to source limitations and the requirement for specific inert gas polarization devices. Moreover, poor signal and contrast from solid tissue and blood vessels limit MRI registration on 3D images.

Table 2.1 summarizes the characteristics, advantages, and inherent limitations of the major functional lung imaging modalities. A critical analysis reveals a consistent and significant gap between technical capability and clinical feasibility. While

modalities like dedicated SPECT/VQ and hyperpolarized gas MRI provide valuable functional data, their clinical translation in radiotherapy is hampered by two primary factors: limited availability/integration into routine clinical workflows and prohibitive cost/resource intensity (McIntosh et al., 2021; Ohno et al., 2022). For instance, SPECT/VQ requires radioactive aerosols and specialized equipment, while MRI with ^{3}He is constrained by the high cost of the gas and the need for specific polarization devices. These barriers often relegate such techniques to specialized centers or research settings, preventing their widespread adoption in standard radiotherapy practice.

Table 2.1 Comparative characteristics of CT-, SPECT/PET-, and MRI-based functional lung imaging modalities

Function imaging	**CTVI**	**SPECT/PETCT**	**MRI**
Technical Principle	Ventilation (from4D-CT deformation)	Perfusion (from radio- tracer distribution)	Ventilation/Perfusion/ Biomechanical assessment
Key Algorithms	1 Registration algorithms 2 Jacobian & HU value analysis 3 Deep learning (Vinogradskiy Y. 2019; Bucknell NW, et al., 2018)	1Grey values matrix 2 Deep learning (McIntosh L, et al., 2021; Yamamoto T, et al., 2014)	1 Registration algorithms 2 Grey values 3 Deep learning (Mirsadraee S, et al., 2015; Eichinger M, et al.,2007)
Image Quality	1 High spatial resolution (inherent from CT) (Yamamoto et al., 2013) 2 Accuracy dependent on DIR performance (Castillo et al., 2010) 3 Reflects ventilation only (Li M, et al., 2013; Ren M, 2024)	1 Limited spatial resolution (e.g.,^{133}X) (McIntosh et al., 2021) 2 High accuracy for perfusion mapping (Yamamoto et al., 2014) 3 Reflects perfusion only; poor ventilation assessment (Le Roux et al., 2019)	1 Poor signal from solid tissue/vasculature (Mirsadraee et al., 2015) 2 Accuracy affected by long scan times & co-registration with CT (Eichinger et al., 2007) 3 Can reflect perfusion; ventilation assessment requires specialized gas (Ohno et al., 2022)

Table 2.1 Continued

Function imaging	CTVI	SPECT/PETCT	MRI
Patient Safety & Workflow	1 Minimal patient burden; no additional scans (Li et al., 2013) 2 No additional radiation dose (derived from planning 4D-CT) (Farr et al., 2015)	1 Additional scan required with radioactive tracer/ gas (Faught et al., 2017) 2 Additional radiation exposure (Faught et al., 2017; Hoover et al., 2014)	1 Additional scan required, often with specialized gas (Ohno et al., 2022) 2 No ionizing radiation (Ohno et al., 2022)
Cost & Accessibility	No additional cost for radiotherapy patients (uses standard simulation images) (Ren, 2024)	High cost (specialized equipment &radiopharmaceuticals) (Hegi-Johnson et al., 2017)	Very high cost (hyperpolarized gas, specialized hardware) (Ohno et al., 2022)
Clinical Value in Radiotherapy	1 Easily integrated & widely adopted (Castillo et al., 2017) 2 Prospective evidence of clinical benefit (e.g., reduced pneumonitis) (Farr et al., 2015)	1 Limited adoption due to cost/logistics (Hegi-Johnson et al., 2017) 3 Lacks prospective validation of clinical benefit in RT (Castillo et al., 2020)	1 Limited adoption in RT; more common in diagnostic pulmonology (Matsumoto et al., 2021) 2 Lacks prospective validation of clinical benefit in RT (Ohno et al., 2022)

Note. DIR = Deformable Image Registration; RT = Radiotherapy.

In direct response to this clinical-translational gap, our study introduces a novel imaging methodology that is both physiologically comprehensive and clinically practical. Our VP-Imaging technique is strategically designed to leverage routinely acquired clinical scans—4D-CT and FDG-PET/CT—which are already the standard-of-care for lung cancer patients undergoing radiotherapy planning. By deriving both ventilation and perfusion information from this existing data, our method eliminates the dependency on additional, costly, and complex specialized functional imaging procedures. This approach ensures high clinical practicality, cost-effectiveness, and seamless integration into existing radiotherapy workflows, thereby directly addressing the primary limitations of current unimodal and specialized functional imaging methods.

2.4 Evaluation Methods for Lung Function Imaging Processing Quality

The Dice Similarity Coefficient (DSC), a measure of set similarity, is commonly used to calculate the similarity between two samples (Yeung et al., 2023). It is frequently employed in imaging processing. The correlation between two local lung volumes, X and Y, using the DSC, is calculated by the formula:

$$\mathrm{DSC}(X, Y) = \frac{2 \times |X \cap Y|}{|X| + |Y|} \qquad 4$$

where X and Y are the two local volumes, |X| indicates the number of elements in volume X, and ∩ indicates the intersection of two volumes, i.e., the elements shared by them.