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Abstract

For patients with lung cancer undergoing curative intent radiotherapy, functional lung imaging can be incorporated into treatment planning to modify the dose distribution within non-target volume lung by differentiation of lung regions that are functionally defective or viable. This concept of functional image-guided lung avoidance treatment planning has been investigated with several imaging modalities, primarily SPECT but also hyperpolarised gas MRI, PET and CT-based measures of lung biomechanics. Here, we review the application of each of these modalities, review practical issues of lung avoidance implementation, including image registration and the role of both ventilation and perfusion imaging, and provide guidelines for reporting of future lung avoidance planning studies.

1. Introduction

Dose-intensification by isotoxic radiotherapy with accelerated regimes has the potential to improve current poor thoracic radiotherapy survival rates. However, a significant limiting factor is the risk of radiation induced lung injury (RILI) [1–3], with the clinical impact exacerbated by the pulmonary comorbidities that are usually present in lung cancer patients [4–6]. Therefore, one proposal to minimise RILI risk, and potentially allow dose escalation and thereby improve overall survival, is to take into account the extent of pre-existing pulmonary dysfunction when treatment planning by deliberately reducing dose to highly functioning regions of lung by allowing an increase in dose to less well ventilated and perfused regions.

The initial clinical motivation for using functional images of lung cancer patients undergoing radiation therapy was the prediction and detection of RILI [7–9]. Early work alluded to the potential value of incorporating functional information into treatment planning [8–10] but was initially limited by pulmonary function tests such as spirometry, which lack sensitivity to chronic disease [11,12], and planar scintigraphy images. In addition to improved detection of post-treatment RILI, the introduction of 3-dimensional (3D) functional imaging with single photon emission computed tomography (SPECT) improved assessment of pulmonary comorbidity and provided the localisation of healthy and defective tissue to enable lung dose optimisation by modifying beam orientations to avoid highly functioning lung [4,13,14].

To implement functional image-guided planning, various options currently exist for ventilation and perfusion imaging. While SPECT is still commonly used, alternative techniques such as 4-dimensional (4D) positron emission tomography/computed tomography (PET/CT) [15,16] and lung magnetic resonance imaging (MRI) have emerged that enable superior analysis of pulmonary physiology. By pre-polarising helium-3 or xenon-129 gas, exquisite images of ventilation and perfusion can be produced that have been applied to the study of respiratory diseases such as lung cancer, chronic obstructive pulmonary disease (COPD) and asthma [17,18]. Despite moves to widen the availability of hyperpolarised gas imaging, the method currently remains limited to a relatively small number of research groups around the world [19]. However, new forms of gas MRI may be more widely applicable [20] and a variety of impressive ^{1}H techniques are rapidly developing [21–23]. Although lung MRI could have a significant impact in the era of hybrid MRI radiotherapy systems, CT remains ubiquitous in radiotherapy centres. Hence, much effort has been made to develop algorithms to derive functional lung measures from CT acquired at different inhalation states [11,24,25].

The scope of this review is to summarise and discuss the use of SPECT, PET, MRI and CT imaging for functional tissue dose reduction strategies in lung cancer radiation therapy planning.

2. Functional lung imaging

2.1. SPECT and PET

Technetium-99m-labeled macroaggregated albumin (MAA) perfusion SPECT has been the most widely investigated imaging modality for providing the functional information required to perform functionally-guided lung avoidance treatment planning, with only one study using technetium-99m-labeled diethylenetriamine pentaacetate (99mTc-DTPA) ventilation [26]. However, SPECT involves ionising radiation, provides poorer spatial and temporal resolution [27] than CT, MRI or PET, with potential errors in attenuation and scatter correction [28], image registration of the functional data to CT [29], and inconsistent patient setup and breathing regimes. Ventilation SPECT can also be affected by aerosol deposition in the central airways [27].

Unlike SPECT, PET is fully quantitative and respiratory correlation is possible [15]. Ventilation imaging is performed following inhalation of Galligas (gallium-68 aerosol) and perfusion PET is acquired with gallium-68 MAA. Low-dose 4D-CT is also performed. Functional images can be reconstructed as either gated or ungated [15]. Using a PET/CT scanner, Siva and colleagues at the University of Melbourne have performed impressive work producing 4D functional images, registered to 4D-CT, that have been used for lung avoidance treatment planning [15,16].

2.2. MRI

Alternative images to emission tomography that provide improved analysis of pulmonary function, and without ionising radiation, can be acquired using MRI. Historically, MRI was beset with major drawbacks when attempting to image pulmonary features because the multiple microscopic tissue interfaces and lack of protons in the lung parenchyma significantly diminish signal-to-noise [22]. One approach to bypass such problems is to inhale an inert, non-ionising, hyperpolarised gas that can be detected using MR scanners tuned to the relevant frequency [30]. In recent years, both gas and ^{1}H lung MRI have developed rapidly.

The availability and cost of gas, the expertise required for gas imaging including access to specialist equipment, and the need for image registration to planning CT have been perceived to be limitations to clinical implementation of MR hyperpolarised gas imaging techniques in radiotherapy [31–33]. However, multi-nuclear MRI scanners are now more commonly available and use of lung MR imaging is becoming more practical, although care is required when interpreting the physiological meaning of deep inspiration images [11]. Many current research techniques have either started to be used clinically or have the potential to enter clinical use [34]. More abundant than helium-3, xenon-129 [35,36], by virtue of its solubility, follows the gas exchange pathways in the lungs [37] providing a unique tool for direct assesment of lung ventilation/perfusion (V/Q) matching [38] and diffusion capacity. Transport of gas has been shown to be feasible [39], and original MR lung imaging techniques that do not require pre-polarised gases are emerging [20]. Instrumentation for multinuclear single breath-hold imaging [40,41], along with new image acquisition protocols, have been developed to improve image registration of gas MRI to CT [42–44]. Combining gas MRI with lobar CT segmentation has the potential for quantitative lung analysis as well as benefits for functional treatment planning [45].

Greater use of MR in radiotherapy is on the horizon [46–48], from delineation of tumour and organs at risk [49,50] and assessment of lung motion [51,52] to MR-only planning [53–56]**.** Additionally, the roll-out of hybrid MR treatment machines such as cobalt systems [57] and MR-linacs [58,59] provides further incentive for the advancement of both gas and novel ^{1}H MR lung sequences that potentially offer valuable functional information [21–23].

Several groups have investigated the issues related to hyperpolarised gas MRI-based lung avoidance planning [17,60–64].

2.3. CT

CT currently remains the predominant modality in radiotherapy planning due to its high geometric accuracy and as a source of the electron density required for dose calculation. Therefore, efforts to derive functional parameters from CT may be worthwhile as the availability of CT is presently more widespread than high quality lung MRI or PET/CT. However, in the case of 4D-CT, respiratory correlation equipment and training also require a significant initial cost and level of expertise, and whole lung radiation dose is high compared with standard planning CT [65]. Low dose breath-hold CT may be a feasible alternative [66].

Since local measures of lung mechanics and intensity change have the potential to provide a sensitive test of respiratory status, various pulmonary non-contrast CT image processing techniques have also been investigated as an alternative source of functional data for lung avoidance treatment planning [24,67]. One estimate of regional ventilation is provided by the specific volume change measured using CT [11]. Breath-hold images or 4D-CT can be used, usually with deformable image registration, to generate either Jacobian [68] or Hounsfield Unit (HU) derived ventilation maps [24,67,69], although variations have also been investigated [25,67,70].

Since the emergence of registration-based non-contrast CT surrogates of ventilation, several attempts have been made to validate them against more established measures of ventilation and moderate correlations against spirometry have been found [71,72]. However, conflicting results have been reported in the literature for validation against imaging-based measures of regional ventilation. In controlled-breathing animal experiments, CT-based ventilation surrogates have demonstrated both a reasonably high level [67,68,73] and relatively low level [74] of correlation with xenon CT. Recently, high correlation has been observed in rats against Cryomicrotome imaging [75]. In human studies, comparison with other ventilation modalities is also challenging with low or moderate spatial overlap and correlations reported [31,71,76–79]. Although some studies do suggest more promising correlation results [80–82], analysis of expiration-only scans can outperform registration-based metrics and further investigation of the added value of inspiration is required [66]. The CT-based methods do not always appear to give robust voxel level functional information, which should be one of the advantages of using CT over lower resolution images [78]. Different image registration algorithms and parameter settings can significantly alter CT ‘ventilation’ values [83–85] and alternatives to image registration have been explored [79,86]. 4D-CT artefacts [83,87], CT noise [88], gravity [89,90], and breathing manoeuvre [91–93] may also have an impact on CT-based measures, and reproducibility is moderate [92,94].

Given the large variability in methods and potential for artefacts, care must be taken when attempting to compare results and further validation of the functional value of CT-based methods is essential (Figure 1). Despite this, a large scale study of ventilation defects has been conducted [95] and several attempts have been made to modify lung treatment plans based upon local volume expansion [96–99] or intensity based metrics [33,100,101].

3. Functional image-guided lung avoidance treatment planning

3.1. Planning studies

The concept of functional image-guided lung avoidance treatment planning is to apply functional planning constraints and/or beam angle optimisation to modify the dose distribution within non-target volume lung by differentiation of regions that are functionally defective or viable. Functional planning methods have developed over time in tandem with improvements to treatment planning systems, from initial SPECT studies that used conventional plans with manually modified beam orientations [4,102,103]; to conformal (3D-CRT) planning [5,16,99,104], including a comparison of coplanar and non-coplanar fields [104]; and comparison of 3D-CRT and intensity modulated radiotherapy (IMRT) [105–107]; and a number of IMRT studies that have used between 3-10 beams [5,15,17,26,33,60,96,98,100,101,104–106,108–111]; to the use of helical tomotherapy and volumetric modulated arc therapy (VMAT) [61,62,96,112]. Comparison of anatomical and functional plans has been conducted by modification of beams numbers and orientations due to functional information [5,16,17,26,33,60,98,99,104–107,110,111,97] or with fixed beam numbers and angles [15,26,96,98,100,109,113,114]. The most common approach is to threshold segment the functional image into low and high regions, although the selection of threshold is challenging [16]. Regional functional information is then utilised within commercial treatment planning systems, however voxel-wise functional planning may prove a more useful option [111,115].

Application of functional data into treatment planning has enabled new forms of dose and plan evaluation parameters to be developed, including a functional form of dose-volume histogram (DVH) [4,116–118], functional normal tissue complication probability (NTCP) [117], functional mean lung dose [5] and functional equivalent uniform dose, calculated from a dose-function histogram [119]. Most commonly used are the functional mean lung dose and functional volumes such as FV20 (the percentage volume of functional lung that receives ≥20 Gy) [104]. Absolute reductions in functional V20 range from no significant difference [104,111] and 3-7% for SPECT [107,109,110,113,114]; no significant difference [16] and 4% for perfusion PET but no significant difference when using ventilation PET [15]; 2-3% for MRI [17,60,62]; and no significant difference [99–101,112] and 5% for CT-based methods [33,96,98,97] (Table 1). However, comparison between studies is complicated by the diverse methodology employed, including patient characteristics, planning techniques, segmentation and definition of functional regions, image registration and other image processing, and a lack of consistency in the use and reporting of statistical analysis.

For example, using fixed angles may be a sensible approach to reduce subjectivity when testing the potential value of including functional data [113]. However, in some cases the optimisation of beam angles can eliminate significant differences between anatomical and functional plans obtained from fixed beam-only plans [98]. Interestingly, the largest functional V20 differences of 5-7% have been found when using fixed beams [96,98,109,113] in contrast to optimised beam angles which tend to produce 2-3% differences [17,60,99,107,97], although both methods have also produced a large number of cases with no significant difference due to additional functional data [5,98,100,104,105,111].

3.2. Clinical trials

SPECT studies have not yet tested the efficacy of including functional data on tumour control or overall survival [102] although one randomised trial has recently completed patient recruitment (ClinicalTrials.gov NCT01745484). Similarly, despite a long history of published feasibility studies on functionally modifying lung radiation treatment plans with MRI or CT data, until recently, no trials have attempted to evaluate the clinical impact of treatment with functionally adapted plans. However, at least three clinical trial protocols have recently received approval (ClinicalTrials.gov NCT02002052, NCT02528942 & NCT02308709). A randomized, double-blind trial using ^{3}He ventilation MRI functional lung avoidance techniques to assess its impact on pulmonary toxicity and quality of life is recruiting in Canada [6]. Two further research teams, in Denver and Sacramento, are currently investigating the use of CT measures of ventilation for functionally-guided radiotherapy planning and treatment. In a case report of one patient, functional V20 was reduced by 5% [33].

4. Practical implementation of lung avoidance strategies

4.1. Perfusion or ventilation

A strong case has been made in the SPECT and PET literature for using perfusion data over ventilation for functional optimisation of lung dose distribution. Perfusion defects have been shown to occur more frequently than ventilation defects, and both are more common than changes in CT [120]. Perfusion is considered a more sensitive metric for assessing lung function and RILI since reductions in ventilation will generally also cause perfusion reductions, but the inverse is less common [2]. The majority of SPECT-guided treatment planning has used pulmonary perfusion. MRI-guided planning has so far been conducted with ventilation but MR measures of perfusion are also possible [22], while CT-based metrics offer surrogate measures of regional lung ventilation [90]. For a complete representation of regional lung function, both perfusion and ventilation data are required and thus there may be benefit in analysing both defects together for functional-image guided treatment planning [121]. Notably, use of PET/CT has demonstrated that compared to anatomical-based plans, perfusion PET resulted in significantly different functionally-guided plans but ventilation-guided plans for the same group of lung cancer patients did not [15].

4.2. Image acquisition and registration protocols for functional planning

Accurate image registration is important for integration of functional data into treatment planning [17,42] but matching of SPECT to treatment planning CT can be challenging [29,102,109,122,123]. Fiducial markers [4,103,104,106,107,114] or the attenuation CT component of SPECT/CT, similar to that used for PET/CT [124], can assist functional image registration to planning CT [113]. Further, PET/CT has been registered to 4D-CT [125]. Ideally, the same immobilisation technique [4,15,113] and a flat bed [15,104,106,111] should be used for both image acquisitions.

Initially, a similar approach was adopted for integration of hyperpolarised gas MRI into lung planning, including the use of fiducial markers [17]. Subsequently, imaging protocols [62,63] and equipment have been specially modified. For example, registration is significantly improved by using an imaging protocol that enables both ^{3}He MRI and CT to be acquired with similar breath holds and body position by using a flat bed insert, an MR coil that enables the patients' arms to be in treatment position and a CT breath hold manoeuvre that mimics the ^{3}He breath hold [42]. Further improvement to registration accuracy is possible with a dual-frequency coil that enables acquisition of ^{3}He and ^{1}H MR images in a single breath hold [44] (Figure 2).

Although CT 'ventilation' has the advantage over SPECT, PET and MRI in that it can be acquired concurrently with treatment planning CT and therefore does not necessary require further image matching, the method itself can depend upon accurate 4D-CT image reconstruction and a reliable method of deformable image registration between inhalation and exhalation CT. While registration of pulmonary CT is a difficult problem and numerous algorithms exist, considerable effort has been made to improve and validate non-rigid techniques [85,126–129].

4.3. Timing of scans and patient setup

In addition to differences between acquisition methodologies, such as breathing state and patient setup, the time interval between planning CT and functional imaging can influence both image registration accuracy and the validity of image comparison [72]. For 4D-CT based methods, clearly the functional and planning CT are acquired at the same time but it is also possible to acquire SPECT [104], PET [15] or gas MRI [17] on the same day as planning CT. Furthermore, the time interval between scans is an important consideration when comparing two or more functional modalities.

4.4. Potential limitations of normal lung avoidance

The original concept of lung avoidance planning was born in the era of conventional manual planning. The gains brought about through successively more conformal and computationally optimised plans [130–132] may diminish returns from further optimisation due to functional data and several studies have shown no significant benefit for the majority of patients examined [5,98,100,104,105,111].

An assumption made when functionally weighting the treatment plan to constrain dose to healthy lung tissue is the clinical acceptance that higher dose can be targeted through poorly ventilated or perfused lung [133]. Although lung function can be reduced irreversibly by radiation therapy [4,134,135], it has also been known for many years that the tumour itself can be responsible for reduced lung function [9] when bronchial obstruction and large vessel compression create regional ventilation and perfusion defects that become tempting targets for functionally-guided dose redistribution. Therefore, a potential limitation of normal lung avoidance is that lung volumes that may have received a functionally modified, amplified dose may regain some degree of function following treatment [4]; an effect noticeable on SPECT [136], PET [135], hyperpolarised gas MRI [63,137,138] and CT-based 'ventilation' [32,139] and even part way through treatment [135,140,141]. Hence, whether defects are transient [142,143], reversible [136] or persistent [134] becomes an important issue when assigning functional and non-functional planning constraints.

In addition to the possible limitation due to post-treatment lung function improvement for a selection of patients, the biologic effect of reducing high dose volume and increasing low dose volume is not clear [105]. In a recent animal model, the dose-limiting toxicity changed from early to late dysfunction when the irradiated volume was reduced [144]. As early and late RILI are also due to different pathologies in humans, the impact of incorporating functional data to create larger low dose volumes and reducing more highly irradiated volume should be examined in future work.

4.5. Recommendations for reporting of lung avoidance studies

The inevitable inconsistency of methods and reporting of results in the literature spread over many years makes it difficult to compare studies from the different research groups that have investigated functional image-guided lung avoidance treatment planning. To assist with comparison in the future, it may be beneficial if at least the following information is included:

- Diagnosis (classification of lung cancer) and staging of patients along with tumour location and volume.
- Time interval (median and range) before treatment at which functional imaging was conducted, and after the start of treatment if repeated scans are performed.
- Time interval between different forms of functional imaging for comparative studies.
- Time between functional imaging and treatment planning CT.
- Patient setup for image acquisition: use of diagnostic or treatment position patient setup and use of flat beds and immobilisation.
- Image acquisition and reconstruction methods and parameters.
- Image registration issues: methods and validation related to the image registration of functional images to planning CT or to the generation of CT-based ventilation surrogate measures, including computational hardware used and processing times.
- Methods used for calculation of CT ventilation metrics.
- Method of functional image segmentation/thresholding.
- Details of any image processing such as filtering, interpolation or normalisation.
- Treatment prescription and fractionation scheme.
- Treatment planning system and algorithms.
- Planning constraints
- Method of constraining the plan optimization with functional data; manually fixed or optimised beam angles.
- Planning technique used: conformal, IMRT, RapidArc/VMAT etc and the method of generating plans to compare anatomical plans with the functional data; either fixed or modified beam orientations.
- Parameters used to quantify and compare plans with and without incorporation of functional data: functional volumes, mean lung dose etc.
- Reporting of absolute rather than relative measures of change.
- Use of statistical analysis to test the significance of differences.

5. Conclusions

This review highlights each of the imaging techniques that have been used to test the inclusion of functional data related to healthy tissue into lung treatment planning. However, given the large reduction to normal lung dose offered by optimised conformal planning, more fundamental, at least initially, is not the question of which modality to use to assist treatment planning but whether functional lung related data from any imaging source can have a major impact on healthy lung dose distributions and what the short and long term clinical implications of such modifications are. While reduced post-treatment function is common, the potential for improved function should also be considered within regions of lung that may receive higher dose due to functionally-guided lung dose redistribution. Evidence from clinical and simulation studies indicate that there may only be small numbers of patients with specific types of functional defects and tumour volumes and positions who will benefit from the inclusion of functional data for normal lung dose reduction. Importantly, SPECT and PET studies demonstrate that using ventilation only is not sufficient for lung avoidance. Further validation tests, planning studies and clinical trials will be required to increase our understanding of the potential benefits and long term effects of functional image-guided lung avoidance planning strategies.

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Figure 1

3He MRI (left) and CT ventilation (right), derived from inspiratory and expiratory breath-hold and computed via the intensity metric, for an example NSCLC patient. Arrows indicate spatially corresponding ventilation defects.

Figure 2

Example 3He MRI (left) and treatment planning CT (middle) acquired in the same inflation state. The fused image (right) after deformable registration of 3He MRI to CT demonstrates that anatomical locations of ventilation defects can be discerned.

Table 1

Summary of lung avoidance studies using CT, SPECT, PET and MRI.