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Overview

Functional Image-guided Radiotherapy Planning for Normal Lung Avoidance

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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 single photon emission computed tomography (SPECT), but also hyperpolarised gas magnetic resonance (MR) imaging, positron emission tomography (PET) and computed tomography (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.

Key words: CT ventilation; lung avoidance; magnetic resonance imaging (MRI); non-small cell lung cancer (NSCLC); radiation therapy planning; radiation-induced lung injury

Statement of Search Strategies Used and Sources of Information

References were identified using Scopus and PubMed searches for functional lung avoidance and radiotherapy treatment planning papers that use CT ventilation, SPECT, PET or MR. Reference lists and citation records were also checked for relevance.

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 three-dimensional functional imaging with single photon emission computed tomography (SPECT) improved the 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. Although SPECT is still commonly used, alternative

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techniques such as four-dimensional (4D) positron emission tomography/computed tomography (PET/CT) [15,16] and lung magnetic resonance (MR) imaging 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 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 MR may be more widely applicable [20] and a variety of impressive ^{1}H techniques are rapidly developing [21–23]. Although lung MR could have a significant impact in the era of hybrid MR 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, MR and CT imaging for functional tissue dose reduction strategies in lung cancer radiation therapy planning.

Functional Lung Imaging

SPECT and PET

Technetium-99m-labelled macroaggregated albumin (MAA) perfusion SPECT has been the most widely investigated imaging modality for providing the functional information required to carry out functionally guided lung avoidance treatment planning, with only one study using technetium-99m-labelled diethylenetriamine pentaacetate (99mTc-DTPA) ventilation [26]. However, SPECT involves ionising radiation, provides poorer spatial and temporal resolution [27] than CT, MR or PET, with potential errors in attenuation and scatter correction [28], image registration of the functional data to CT [29] and inconsistent patient set-up 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 acquired. Functional images can be reconstructed as either gated or ungated [15]. Using a PET/CT scanner, Siva and colleagues [15,16] at the University of Melbourne carried out impressive work producing 4D functional images, registered to 4D-CT, that have been used for lung avoidance treatment planning.

MR

Alternative images to emission tomography that provide improved analysis of pulmonary function, and without ionising radiation, can be acquired using MR. Historically, MR 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 MR 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, multinuclear MR scanners are now more commonly available and use of lung MR 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 assessment 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], together with new image acquisition protocols, have been developed to improve image registration of gas MR to CT [42–44]. Combining gas MR 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 MR-based lung avoidance planning [17,60–64].

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 MR 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 the whole lung radiation dose is high compared with standard planning CT [65]. Low dose breath-hold CT may be a feasible alternative [66].