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SPECT V/Q in Lung Cancer Radiotherapy Planning

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Curative-intent lung cancer radiation therapy either alone (RT) or combined with immunochemotherapy is associated with potential risk of serious radiation-induced lung injury. This review provides a summary of the role of SPECT ventilation perfusion (V/Q) imaging as an emerging adjunct to lung cancer RT planning and treatment dosimetry. Denoted "functional lung avoidance RT" it is hypothesized that preferential dosimetric avoidance of physiologically functional lung may reduce the frequency of radiation-induced lung injury. SPECT V/Q imaging datasets available during the planning process allows the prioritization (or "personalization') of RT dose to minimize the volume of functional lung probabilistically exposed to injurious radiation dose. Selective escalation of target dose and adaptive planning and replanning is also enabled. The emergent importance of the tumor-lung microenvironment and its biologic relationship to local immune effectors in lung cancer provides further incentive to individualize RT planning and delivery. This review examines important normal tissue dosimetric constraints that are part of current standards-of-care and the new dosimetric parameters associated with functional lung avoidance RT. SPECT V/Q has been a valuable tool in investigating the feasibility and efficacy of functional lung avoidance RT but is yet to become main stream due to the lack of large clinical trials. It is encouraging however that functional lung avoidance is feasible in RT dose-target delineation and some of the more promising studies are discussed.
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Introduction

The past decade has witnessed enormous advances in radiotherapy (RT) planning and delivery stemming from developments in cancer diagnostics (eg tissue immunophenotyping, high resolution 3D and 4D-body CT and nuclear imaging), computer algorithms, and treatment technology. From these have evolved modern RT strategies such as intensity-modulated RT (IMRT), volumetric-modulated arc therapy, and stereotactic ablative body radiotherapy.[1] The latter techniques, often combined with small (so-called targeted) molecules and/or standard chemotherapy play important roles in the current management protocols of non-small-cell-lung cancer.[2] Ideally (and ultimately) these therapeutic advances offer the opportunity for "personalized" or risk-adaptive cancer care. Although improvements in the treatment planning process and RT delivery have had largely positive impacts on loco-regional tumor control and overall survival,[3] minimizing severe acute pulmonary toxicity and chronic health morbidity have become major therapeutic themes. Uniquely in NSCLC management, lung tissue is both an RT target for high dose exposure, and an organ-at-risk (OAR) for RT avoidance or dose minimization.

Functional lung avoidance RT is an emerging concept in the treatment of locally advanced NSCLC.[4-7] Functional lung avoidance RT prioritizes delivery of high radiation dose to the lung cancer gross tumor volume (GTV) while minimizing, through treatment planning system (TPS) optimization algorithms RT dose to uninvolved and functional lung. In the locally advanced (inoperable) NSCLC setting the GTV often also includes regional lymph node metastases. The resultant

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complex volume RT (primary tumor + regional lymph nodes) necessitates the use of high resolution 3D or preferably 4D-CT and co-registered functional lung imaging to aid target and OAR delineation. Delineation of the GTV also involves defining a "motion envelope" comprising the clinical tumor volume (CTV) or internal tumor volume and finally the constitutive planning target volume (PTV) margins. Consideration of a lung function map in this process has the potential to reduce historical large population-based CTV/internal tumor volume to PTV isotropic expansions to margins that are more personalized (or anisotropic to functional lung).[8] This paradigm when integrated with respiratory motion management has the potential to leverage target dose escalation against significant sparing of functional lung.[9]

Whilst there have been many investigations into dose-volume factors associated with radiation-induced lung injury (RILI) using various functional imaging modalities, SPECT V/Q is the most widely used, perhaps due to its availability and relatively low cost.[5,6,10,11] Several investigations in the potential use of SPECT V/Q in RT planning has shown promising results.[7,12-15] Some clinical trials have been completed and others are underway with the aim of assessing the efficacy of functional imaging in minimizing lung toxicity.[16-19] In this article we describe the applications of SPECT V/Q in the development of the new concept of functional lung avoidance RT primarily focusing on locally advanced NSCLC.

Rationale for the Use of Functional Lung Avoidance RT

Improving Tumor Control With the Use of Higher Doses Without Increasing Toxicity

The standards-of-care for patients of good performance status and unresectable nonmutation-addicted NSCLC is concurrent chemo-radiation therapy (C-RT) or conformal radiation therapy followed by immunotherapy (IC-RT).[20] These strategies however often fail to achieve good tumor control within the chest (eg RTOG 0617 2-year local failure rates 31%-39%)[21] and have poor median (20-29 months), progression-free (10-17 months),[20-22] and overall survival rates (5-year: 15%-20%).[20-22] C-RT and IC-RT are associated with substantial risk of pulmonary toxicity and in the case of IC-RT this risk is yet to be fully elucidated.[20-23] Overall serious RILI occurs in up to 15%-40% of patients.[24] Many of these patients also have reduced pulmonary reserve due to current cigarette smoking, suffer other respiratory comorbidities, or are elderly.[25-27] Improving the quality of NSCLC control mandates the use of higher RT doses without increasing the frequency or severity of RILI.

Results from dose modeling studies and early phase dose escalation trials have suggested a steep radiation dose −response curve (certainly from 40 Gy to 60 Gy) and possibly up to 103 Gy.[28,29] based on effective lung volume as summarized by Hong and Salama.[30] A recent multicenter dose escalated (60 Gy vs 74 Gy) phase III C-RT trial (RTOG-0617) however closed randomization to dose escalation prematurely in 2011 due to futility.[21] As initially suggested in an editorial by Cox (2012)[31] and later in a planned post hoc analysis by the investigators,[30] RT-induced acute cardiopulmonary toxicity reduced the therapeutic impact of the higher RT dose[31] and may have resulted in clinically meaningful differences in survival (2-year overall survival: 45% vs 58%).

We posit therefore that the future use of higher than conventional dose (60 Gy) fractionated lung cancer RT particularly in the setting of concurrent chemotherapy (including targeted molecules), should incorporate functional lung imaging for the purpose of lung avoidance dosimetry.

Predicting RILI as RILI Is Associated With Irradiation of Functional Lung

The majority of lung cancer patients present with respiratory comorbidities which result in heterogenous lung function.[25-27] The current dose-volume predictors and mean lung dose (MLD) for the development of radiation pneumonitis in this cohort have significant collinearity (eg MLD < 7-13 Gy, V20 < 25%, V30 < 13%, and V50 < 10%) creating difficulties in risk prediction.[5,24] De Jaeger et al using SPECT perfusion (Q) has found that irradiation of nonperfused lung regions contributed less to functional damage and hence, suggested that radiation treatment beams should be directed preferentially through hypoperfused lung regions.[32] Other studies have shown the relationship between dose and perfusion loss post-RT and patients with relatively poor pre-RT lung function are more likely to experience toxicity than those with better lung function.[6,15,33,34] These studies suggest an association with the frequency of RILI and irradiation of functional lung, therefore, the use of functional lung avoidance RT could predictably minimize RILI. Functional lung maps identified by SPECT V/Q imaging and co-registered with the simulation CT could be implemented in RT planning process.

Accounting for Recoverable Nonfunctioning Lung Regions During RT

Yuan et al (2012) demonstrated using SPECT V/Q that RT-induced tumor volume reduction can cause functional lung recovery.[35] An assessment of function mid-treatment revealed changes in the V/Q functional map.[7,35] Additionally, they found that patients with central tumors had improvements in the ipsilateral lung which they proposed was related to the tumor GTV reduction.[35] The possibility of interval changes in V and Q during RT supports the need for functional imaging mid-treatment for RT plan re-optimization. Further, functionally adapted RT treatment plans based on recovery of pre-RT SPECT perfusion defects may identify nascent functional regions within the CTV and allow appropriate editing of planning contours particularly within IMRT/volumetric-modulated arc therapy plans.[5] These findings support the utilization of SPECT functional imaging in the

RT planning of NSCLC to enable dynamic reductions functional lung exposures (eg in functional V20, FV20; mean functional lung dose, MFLD).[36]

Models of Care in Lung Cancer RT Planning

Current Standard Care in Lung Cancer RT Planning—Anatomical-Based Planning

Current standard practice in radiation oncology treatment planning is based on doses delivered to the anatomical lung which has been defined by CT. TPS are used to optimize beam arrangements in such a way that fits with the planning constraints for minimal toxicity to OARs, in particular, the "normal lung." Commonly used radiation pneumonitis dosimetric constraints are to limit the percentage of lung receiving greater than 20 Gy (V20) to ≤30%-35% and the MLD to ≤20-23 Gy.[37] The TPS provide a means to predict the dose delivered to each voxel in a volume of interest. Numerous plan options are made available and the best possible plan is chosen, one which provides the highest therapeutic ratio (highest tumor control with least normal tissue complications). A useful tool used to compare plans is the dose-volume histogram (DVH). DVH represents a condensed summary of the plan in a 2D plot, with the y-axis being the amount of volume of a particular region of interest receiving a specified dose (x-axis). Utilizing this method implies that functional activity is distributed homogeneously throughout the lung. The majority of lung cancer patients however have heterogeneous lung function caused by local tumor effects or comorbid lung disease so this methodology may not be suitable[4] within a particular volume of interest. Ideally the RT planning should exploit regional differences in lung function.[36]

Emerging Concept in Lung Cancer RT Planning

Functional Lung Avoidance Planning Utilizing SPECT V/Q

In functional lung avoidance planning, the SPECT information is used to increase the weight of radiation beams through nonfunctional lung regions and avoid functional lung without compromising the plan in terms of satisfying established criteria for tumor coverage and normal tissue sparing. In perfusion weighted optimization data obtained from SPECT perfusion is used to weigh the MLD with the perfusion (this is the same ventilation weighted optimization). Corresponding functional metrics to those in anatomical-based planning are[1] functional volume irradiated to 20 Gy (FV20) and[2] functional mean lung dose.[32,38] The standard DVH is thus transformed to a functional DVH or DFH.[37]

Functional volume is defined on the voxel level where SPECT V/Q signal exceeds a certain threshold; however, there is currently no evidence-based consensus on what this threshold should be. Various threshold values have been used for functional volume, eg, 10%,[39], 30%,[5] 80%,[38] 90%,[40] however, the 40%-60% region has been suggested to be the "most clinically relevant" by some reseachers.[13,14] Current treatment-planning systems are still developing tools to allow the direct inclusion of functional imaging data and for the most part functioning lung contours are manually created externally to treatment planning systems. Functional lung contours are based on percentile of SPECT function where a histogram equalization technique is applied to the SPECT images to equalize the lung volume (trachea and bronchi not included) under each SPECT pixel intensity bin.[40] This also provides an easy means of removing any focal hot spots. These functional contours are then integrated into the RT plans where plan optimization includes constraints for moderate to high percentile lung function. Figure 1 shows a comparison of an anatomical RT plan (a) with a functional RT plan (b) in the axial and coronal views.[40] The patient has a large PTV in the upper right lung and functional plans were weighted with perfusion information. Functional lung at the 50 and 90-percentile perfusion levels (F50 lung and F90 lung, respectively) were defined as the top 50% and 10% of the normal lung volume, respectively. The isodose distribution shows that both the functional plan and the anatomical plan had good coverage of the PTV. In the functional plan, isodose lines 5−20 Gy spared more F50 and F90 lung in both ipsilateral and contralateral lungs compared with those in the anatomic plan. Figure 2 is a comparison of the dosimetric parameters of the anatomical plan vs the functional plan for the patient in Figure 1.[40] Figure 2a shows a 5.1% and 6.5% reduction in the V20 for the F50 and F90 functional lung, respectively. The reduction in the mean functional lung dose was 3.1 Gy, 4.2 Gy, and 1.6 Gy for the F50 lung, F90 lung, and total lung, respectively. In Figure 2b the DFH of the functional plan shows a reduction of 12.5%, 15.0%, and 5.0% for lung receiving 5 Gy, 10 Gy, and 20 Gy, respectively, compared with that of the anatomic plan.

Potential Impact of Functional Lung-Based Planning

Several dosimetric studies have been performed to assess the feasibility of SPECT functional-weighted optimization in decreasing dose to functional lung regions. Studies have compared the performance of the type of SPECT functional imaging and the type of RT techniques. Results from these studies are still inconclusive due to the limitation in most single center studies due to the difficulty associated with recruiting patients. Nevertheless, these single center studies have shown the feasibility of directing dose away from functional lung.

SPECT V/Q

Most studies have utilized Q-SPECT imaging alone, some studies have utilized both SPECT V/Q imaging and only one study was found to have utilized V-SPECT imaging alone. Munawar et al (2010) studied the impact of V-SPECT in

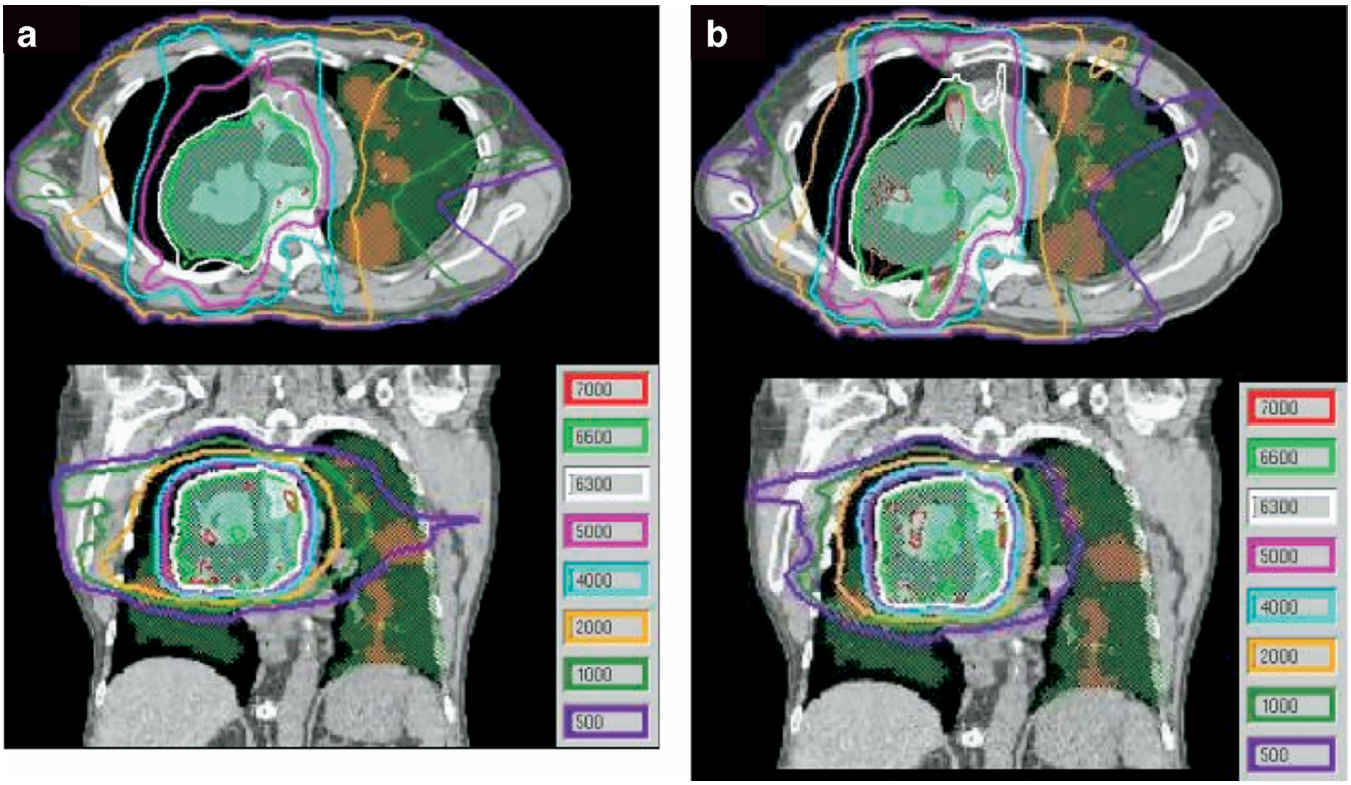

Figure 1 Anatomical-based plan (a) vs functional-based plan (b) (with permission from Shioyama et al 2007).

functional lung avoidance RT planning and found that dose to the ventilated lung could be reduced when there was little overlap of the PTV and the ventilated lung and that the PTV is not surrounded by the ventilated lung.[41] Perfusion-weighted optimization planning have shown better correlation with dosimetric parameters than ventilations-weighted optimization planning.[6,15] Some researchers have suggested that this finding is possibly due to ventilation imaging artefacts such as radioaerosol clumping in the airways typical in a NSCLC patients and the lower activity in the lungs with ventilation.[6] On the other hand, recently published studies have suggested that the use of both V/Q SPECT in RT

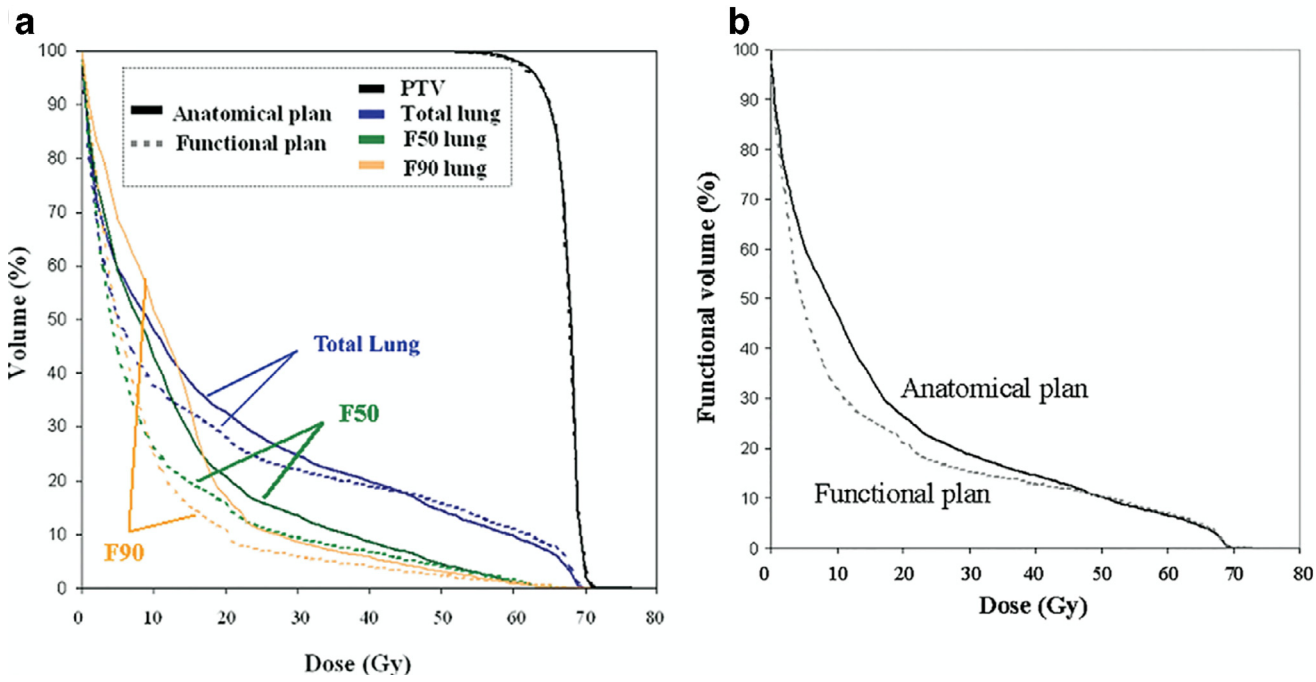

Figure 2 DVH vs DFH for patient in Figure 1 (with permission from Shioyama et al 2007).

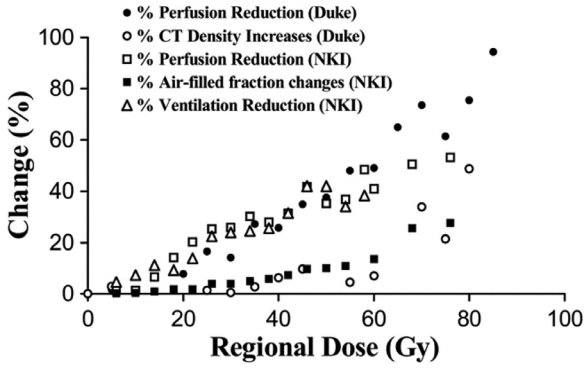

Figure 3 Dose–response curve showing radiographic changes in the lung as a function of regional lung dose. (with permission from Evans et al 2007).

planning may provide a more comprehensive analysis of lung function for patients with heterogenous lung function as they can have mismatched V/Q.[42,43] Yuan et al (2011) found that V/Q SPECT provided additional information over Q-SPECT alone in 39% of patients (20 of 51) which could alter the RT planning.[42]

SPECT perfusion-weighted optimization planning studies have demonstrated the feasibility to decrease functional parameters such as FLV20 as much as 14% and functional mean lung dose by approximately 3%.[12,13] Shioyoma et al (2007) optimized functional lung avoidance plans to achieve dose reductions of 1.1 Gy to total lung and 4.2 Gy to lung regions with 90th percentile function.[40] Shioyama et al (2007) also reported that the functionally adapted plans resulted in reduced coverage of the PTV minimum dose.

IMRT vs 3DCRT

There are several studies that have compared IMRT to 3D conformal radiation therapy (3DCRT) in terms of optimizing functional lung avoidance CT planning. IMRT is proving to be more effective than 3DCRT in enabling radiation beam optimization for sparing functional lung particularly when the targets are of complex shape.[14,44] Studies have demonstrated that IMRT is capable of obtaining a 6%-15% decrease of V20 compared to 3-DCRT.[14,45] The benefit of IMRT in reducing irradiation of functional volume appears to be more pronounced in patients with late stage disease with heterogenous lung function.[14] IMRT is showing advantages in terms of applying safe dose escalations whilst keeping to within dosimetric constrainsts.[14]

Prediction of RILI

The clinical significance of functional lung avoidance RT is still unclear, thus the advantage of utilizing functional metric parameters has yet to be validated in well-designed large prospective clinical trials. The few small clinical trials that studied the association of SPECT-based functional parameters with RILI have found a positive correlation with RILI.[7,46,47] Q-SPECT parameters are proving to be more sensitive than V-SPECT in assessing RILI (Fig. 3).[6,48] Xiao et al (2017) found that V-SPECT showed better correlation with RILI for patients with COPD and poor baseline PFTs whilst Q-SPECT showed better correlation with RILI for patients with PFTs and without COPD.[43] In addition, they found patients with central-type NSCLC have better V-SPECT correlation with RILI, whilst patients with peripheral-type NSCLC have better Q-SPECT correlation with RILI.[43]

Conclusion

SPECT V/Q has played a major role in the development of functional lung avoidance RT in the treatment of NSCLC patients. Q-SPECT combined IMRT is showing promising results in minimizing functional lung whilst allowing dose escalation to the target. There is a growing interest in this area and several clinical trials are underway to assess the efficacy of SPECT V/Q in functional avoidance RT planning.[21,49-51]

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