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A comparison of two methods for segmentation of functional volumes in radiotherapy planning of lung cancer patients

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ABSTRACT

Background: In radiotherapy (RT) of lung cancer, dose to functional lung (FL) volumes segmented with two different methods (perfusion SPECT (Q-SPECT) and 4D-CT (4D) ventilation (V)) have been shown to correlate with the incidence of radiation pneumonitis (RP). This study aims to compare the FL volumes identified by both methods.

Material and methods: Thirty lung cancer patients had a 4D and Q-SPECT prior to treatment. Seventeen of these patients also had a ventilation SPECT (V-SPECT). FL sub-volumes were segmented automatically, using cut-off values. The volumes were compared in terms of overlap fraction (OF) relative to the minimal volume, and intersection fraction (IF) of the FL volume relative to the total lung volume (V_{Lung}).

Results: Cut-off values suggested in literature for Q-SPECT and 4D-V resulted in volumes differing in size by a median 18% [6%;31%], and a median OF and IF of 0.48 [0.23;0.70] and 0.09 [0.02;0.25], respectively. Segmenting volumes of comparable size of about 1/3 of V_{Lung} (FL-m(1/3), m = method) resulted in a median OF and IF of 0.43 [0.23;0.58] and 0.12 [0.06;0.19], respectively. Twenty-five patients (83%) had a reasonable overlap between FL-Q(1/3) and FL-4D-V(1/3) volumes, with OF values above 0.33. IF increased significantly ($p = .036$) compared to using fixed cut-off values. Similarly, volumes of comparable size of about 1/3 V_{Lung} were produced for V-SPECT, and FL-Q(1/3), FL-V(1/3), and FL-4D-V(1/3) were compared. The overlaps and intersections of FL-V(1/3) with FL-Q(1/3) volumes were significantly ($p < .001$) larger than the corresponding overlaps and intersections of FL-Q(1/3) with FL-4D(1/3) and FL-V(1/3) with FL-4D(1/3).

Conclusion: The Q-SPECT and 4D-V methods do not segment entirely the same FL volumes. A reasonable overlap of the volumes along with the findings of other studies that both correlate to RP incidence, suggests that a combination of both volumes, e.g. using the IF, may be useful in RT treatment planning.

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Introduction

Chemotherapy combined with radiotherapy (cRT) is the standard treatment for locally advanced non-small cell lung cancer (NSCLC). However, frequent local recurrences (25–35%) and five-year survival rates of 30–35%, necessitate more aggressive treatment strategies [1–3]. Possibilities are limited, however, as cRT in its current form results in grave toxicities in many patients. The most prominent is radiation pneumonitis (RP) having severe effect on the quality of life for the patient and being potentially lethal [2,4,5].

The treatment planning strategies used in clinical routine are based on limiting the dose to the *entire* lung, regardless of verifiable inhomogeneous regional air and blood flow, i.e. lung function. It has been shown that radiation of non-perfused regions contributes less to radiation induced damage than radiation of well-perfused regions [6]. A reduction in RP may thus be achieved by actively avoiding the best

functioning volumes of the lung [7,8]. This idea has been investigated in many studies focusing either on regional perfusion (Q) or regional ventilation (V) of the lungs to identify the functional lung (FL) volume [9–15].

The clinical gold standard for determining regional lung function is ventilation/perfusion single-photon emission computed tomography (V/Q-SPECT), a well-established nuclear medicine modality using inhaled and injected radioisotopes to measure pulmonary air flow and blood flow, respectively [16,17]. However, the inhaled macromolecules used in ventilation SPECT (V-SPECT) examinations tend to cause clumping in the airways, exaggerating the functionality of the voxels in these regions [18,19]. One prevalent method for correlating the incidence of RP to the dose to the FL therefore uses Q-SPECT solely as the modality to define FL [9,10]. The work by Farr et al. showed strong correlation between dose to the FL as defined by Q-SPECT and the risk of RP.

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Another method to define the FL volume extracts pulmonary ventilation information from 4D-CT scans routinely acquired for RT planning, thus avoiding the additional radiation dose from the nuclear medicine examination. A ventilation map (V-map) of the lungs is generated from the breathing cycle phases of a 4D-CT either by deformable registration [11–13] or by comparison of the Hounsfield units (HU) of corresponding regions of lung tissue [15,17]. Both methods have been shown to produce ventilation FL volumes that are more predictive of RP than the total lung [14,15], indicating that dose sparing of well-ventilated lung volumes also impacts the risk of RP. Hereby, Q-SPECT and 4D-CT V-maps both predict a correlation between FL volumes and RP. Treatment planning may take this into account by selecting beam angles avoiding FL [20]. However, no studies have compared the FL regions obtained by Q-SPECT and 4D-CT in order to investigate if the two methods point at identical regions. Additionally, no consensus exists on the choice of the best modality [20].

In the present study, we have compared FL volumes obtained from Q-SPECT and 4D-CT to determine if the methods identify overlapping functional volumes. The aim was to identify regions in the lungs having high perfusion and high ventilation making these regions objects for decreased radiation dose. Additionally, FL volumes obtained from V-SPECT and 4D-CT were compared.

Material and methods

Patients and pre-treatment scans

Thirty consecutive NSCLC patients undergoing standard treatment of 60–66 Gy in 30–33 fractions were selected for this study. The patients were included in a prospective trial and details on patient characteristics, scanning and treatment planning have formerly been described [9,10]. In brief, all patients had a Q-SPECT and a 4D-CT scan prior to RT treatment. Seventeen of the patients additionally had a V-SPECT. All images were acquired with the patient immobilized in supine position with arms above the head while breathing freely.

The thoracic SPECT scans were obtained on a dual-head SPECT-CT camera with a low-energy-high-resolution collimator (Siemens Symbia T 16, Siemens Healthcare GmbH, Erlangen, Germany) with pixel size 9.6×9.6 mm, matrix size 64×64 pixels, 5 s/view and 128 projections. The associated CT scan (AC-CT) (110 kV, 40 mAs) had a pixel size of 9.8×9.8 mm, and slice thickness 5 mm. The scans were acquired in median one day before treatment start with a range of 11 days before and three days after treatment start. In patients for whom both SPECT scans were acquired, V-SPECT was imaged just before the Q-SPECT scan in the same frame of reference. The V-SPECT patients inhaled an aerosol of 35 MBq ^{99m}Tc -labelled solid graphite particles (Technegas, Dupharma, Kastrup, Denmark) in sitting position. After approximately 15 min the patients were imaged in the supine position. Immediately before the Q-SPECT scan the patients were injected with 200 MBq ^{99m}Tc macro-

aggregated albumin (MAASOL, GE Healthcare, Milan, Italy). The duration of each of the scans was approximately 20 min.

The pre-treatment 4D-CT scan (Philips BrillianceTM CT Big Bore, Philips Healthcare, Amsterdam, Netherlands, with Varian RPM system, Varian Medical Systems, Palo Alto, CA, USA) with voxel size $1.17 \times 1.17 \times 3$ mm, $512 \times 512 \times 97$ voxels, encompassed the entire thoracic region and the images were binned into 10 respiratory phases. The inhale ($4D_{\text{inhale}}$) and exhale ($4D_{\text{exhale}}$) phases were selected based on a visual inspection of the diaphragm motion throughout the 4D-CT motion loop, so that the lung volume on $4D_{\text{inhale}}$ would always be the largest and the lung volume on $4D_{\text{exhale}}$ would be the smallest of the 10 phases. The scan was acquired a median [range] 8 [0,18] days before the SPECT scan.

Functional lung segmentation

For Q-SPECT, the FL volumes were defined as the voxels within the total lung volume, $V_{\text{FL-Q}(x\%)}$, with values exceeding a threshold x of 20%, 30%, 40%, 50%, 60%, 70%, and 80% of the maximum perfusion counts, giving the largest volume for the smallest value of x . For V-SPECT, the best functioning third of the lungs was segmented ($V_{\text{FL-V}(1/3)}$). The total lung volume (V_{Lung}) (excluding the visible tumor) was defined on the associated AC-CT scan, and $V_{\text{FL-V}(1/3)}$ was segmented using patient individual threshold values resulting in FL volumes of approximately $1/3 V_{\text{Lung}}$.

For the 4D-CT scans, the FL volumes were calculated following the methodology of Vinogradskiy et al. [14,21]. V_{Lung} was segmented on the $4D_{\text{exhale}}$ ($V_{\text{Lung-ex}}$) phase of the 4D-CT. $4D_{\text{inhale}}$ (source image) and $4D_{\text{exhale}}$ (target image) were deformably registered using a free form intensity based deformable image registration (DIR) algorithm (MIMv6.7, MIM Software Inc., Cleveland, OH, USA), focusing on the thoracic region. The precision of the deformation in the thoracic region has been reported by Piper et al. [22]. The Jacobian determinant of the deformation vector field (J_{DVF}) was calculated. The J_{DVF} ventilation map describes the ratio of local volume change in the deformed image, and values above 1 indicate an expansion from the target to the source image. For J_{DVF} above 1 within the $V_{\text{Lung-ex}}$, multiple functional sub-volumes, $V_{\text{FL-4D}(y\%)}$, were segmented by including voxels with a value of J_{DVF} above a threshold y of 5%, 10%, 16%, 20%, 30%, 40%, 50%, and 60% of the maximum J_{DVF} value, giving the largest volume for the smallest value of y . The threshold value was calculated as $y(J_{\text{DVFmax}} - 1) + 1$. The 16% threshold was included as this was the threshold identified by Faught et al. as the value most predictive of RP [15]. Additionally, for the 17 patients who also had a V-SPECT, the best ventilated third of the lung was segmented ($V_{\text{FL-4D}(1/3)}$) similarly to $V_{\text{FL-V}(1/3)}$. The volumes of all segmented regions were determined.

Comparison of FL volumes between modalities

Volume comparison was performed using the mid-ventilation (mv) phase of the 4D-CT scan. Therefore, the V-SPECT and Q-SPECT images were deformably registered to the 4D-CT

image using the AC-CT image. The DIR algorithm used for producing the 4D-CT V-map was used. All segmented $V_{FL-V(1/3)}$ and $V_{FL-Q(x\%)}$ contours were propagated to the 4D-CT image. The V_{FL-4D} were deformably propagated to the mv-phase.

The volume ratio, $R_{FL-m(x\%;y\%)}$, between the FL and V_{Lung} for each modality m was determined as:

$$R_{FL-m(x\%;y\%)} = V_{FL-m(x\%;y\%)} / V_{Lung}$$

for threshold x or y and V_{Lung} determined on the 4D-CT scan.

The FL volumes obtained by Q-SPECT were compared to the FL volumes obtained by 4D-CT using the overlap fraction (OF), $OF_{FL-Q(x\%)4D(y\%)}$, defined as [23]:

$$OF_{FL-Q(x\%)4D(y\%)} = ((V_{FL-Q(x\%)} \cap V_{FL-4D(y\%)}) / \text{Min}[V_{FL-Q(x\%)}, V_{FL-4D(y\%)})])$$

evaluating the overlap compared to the smallest of the two segmented volumes.

The OF was calculated in all patients for $x = 40\%$ and $y = 16\%$, being the values formerly shown to predict RP [9,10,15]. Various recommendations for a Q-SPECT cut-off value can be found in literature, but as this patient cohort was a part of the cohort studied by Farr et al., $x = 40\%$ was chosen.

Additionally, the intersection between FL volumes in Q-SPECT and 4D-CT was determined as a fraction of V_{Lung} :

$$IF_{FL-Q(x\%)4D(y\%)} = (V_{FL-Q(x\%)} \cap V_{FL-4D(y\%)}) / V_{Lung}$$

The absolute FL volumes obtained for $x = 40\%$ and $y = 16\%$ may differ considerably. Therefore, comparison of FL volumes of nearly identical size for each patient was also made. For Q-SPECT and 4D-CT, values of x and y segmenting approximately $1/3$ of V_{Lung} ($1/3 V_{Lung}$) were selected for each patient, followed by calculation of $OF_{FL-Q(1/3)4D(1/3)}$ for all patients. For patients where no segmented volumes were close to $1/3 V_{Lung}$ by use of the preselected values for x and y for one or both modalities, comparable sized segmented volumes closest to $1/3 V_{Lung}$ were selected.

In all patients with V-SPECT scans, $V_{FL-V(1/3)}$ was compared to $V_{FL-4D(1/3)}$, calculating $OF_{FL-V(1/3)4D(1/3)}$, and $IF_{FL-V(1/3)4D(1/3)}$. Furthermore, the FL volumes of Q-SPECT and V-SPECT were compared. For Q-SPECT, the already segmented volume identifying approximately $1/3 V_{Lung}$ was used. Both $OF_{FL-Q(1/3)V(1/3)}$ and $IF_{FL-Q(1/3)V(1/3)}$ were calculated.

Statistics

Differences in R , OF and intersection fraction (IF) between the three modalities were pairwise investigated with a Mann-Whitney U test for continuous variables using Matlab (Version 2019a, The Mathworks Inc., Natick, MA, USA). $p < .05$ was considered statistically significant.

Results

The cut-off values of $x = 40\%$ for Q-SPECT and $y = 16\%$ for 4D-CT produced volume ratios of widely different sizes: the median [range] $R_{FL-Q(40\%)}$ and $R_{FL-4D(16\%)}$ was 0.39 [0.09;0.57]

and 0.25 [0.06;0.43], respectively. $R_{FL-Q(40\%)}$ was significantly ($p = .0053$) larger than $R_{FL-4D(16\%)}$. Within each patient, the volumes differed by a median of 0.18 [0.06;0.31] with $V_{FL-Q(40\%)}$ being the largest in 21 patients (70%) and $V_{FL-4D(16\%)}$ the largest in nine patients (30%).

For all patients, values of $R_{FL-Q(40\%)}$, $R_{FL-4D(16\%)}$, $OF_{FL-Q(40\%)4D(16\%)}$, and $IF_{FL-Q(40\%)4D(16\%)}$ are shown in Figure 1(a,b). The median [range] $OF_{FL-Q(40\%)4D(16\%)}$ and $IF_{FL-Q(40\%)4D(16\%)}$ were 0.48 [0.23;0.70] and 0.09 [0.02;0.25], respectively. In 11 patients (37%), R was less than 0.2 for one or both modalities, leading to IF values less than 0.1. However, in three of these patients, the OF was larger than 0.5 due to the smaller of the two segmented volumes being mostly contained in the larger volume. This is illustrated in Figure 2(a) for patient 2. On the other hand, if a small volume was segmented by both modalities, only minor overlap was obtained as seen for patient 20 (see Figure 2(b)). Another six (20%) patients had IF values less than 0.1 even though R was more than 0.2 for both modalities. For these patients, OF values were never above 0.5, indicating that different functional volumes were found by the two methods.

Volume ratios of segmentations of approximately $1/3 V_{Lung}$ are shown for all patients in Figure 1(c). No statistical difference ($p = .88$) was seen between $R_{FL-Q(1/3)}$ and $R_{FL-4D(1/3)}$. The $OF_{FL-Q(1/3)4D(1/3)}$ and $IF_{FL-Q(1/3)4D(1/3)}$ are shown in Figure 1(d). Median values were 0.43 [0.23;0.58] and 0.12 [0.06;0.19], respectively. As the OF was normalized to the minimum of the two volumes, OF decreased compared to $OF_{FL-Q(40\%)4D(16\%)}$ when approximately $1/3 V_{Lung}$ was segmented, as this generally led to larger, but more inter-patient comparable, minimum volumes, without including too much noise from low-functioning lung areas. Twenty-five patients (83%) had a reasonable overlap between volumes, with OF values above 33%. $IF_{FL-Q(1/3)4D(1/3)}$ increased significantly ($p = .036$) compared to $IF_{FL-Q(40\%)4D(16\%)}$, and only seven patients (23%) had IF values below 0.1. This increase is illustrated for both patient cases in Figure 2, where Q-SPECT and 4D-CT both identify large coherent areas of FL, with high $OF_{FL-Q(1/3)4D(1/3)}$ values of 0.45 and 0.58, and $IF_{FL-Q(1/3)4D(1/3)}$ values of 0.19 and 0.17, respectively, showing good overlap between the segmented regions of the two modalities. In five patients (17%), $OF_{FL-Q(1/3)4D(1/3)}$ was less than 33% due to a low overlap between the FL segmented by Q-SPECT and 4D-CT. The low $OF_{FL-Q(1/3)4D(1/3)}$ resulted from a low breathing amplitude giving a noisy 4D-CT V-map and patchy $FL_{4D(1/3)}$ volumes (four patients), and large breathing amplitude and motion artifacts (one patient), negatively affecting the deformable registration (see Supplementary material).

For the 17 patients who received V-SPECT and 4D-CT, values for $R_{FL-V(1/3)}$, $R_{FL-4D(1/3)}$, $OF_{FL-V(1/3)4D(1/3)}$, and $IF_{FL-V(1/3)4D(1/3)}$ are shown in Figure 3(a,b), respectively. Comparison of $V_{FL-V(1/3)}$ and $V_{FL-4D(1/3)}$ resulted in median [range] $OF_{FL-V(1/3)4D(1/3)}$ of 0.38 [0.27;0.69] and $IF_{FL-V(1/3)4D(1/3)}$ of 0.13 [0.08;0.20]. The OF and IF values between FL-4D and FL-V were not significantly different ($p = .55$ and $p = .41$, respectively). Segmentations of FL-V(1/3) and FL-4D(1/3) in two patients are shown in Figure 4. For patient 21 (Figure 4(a)), both methods identify large contiguous areas of high functionality,

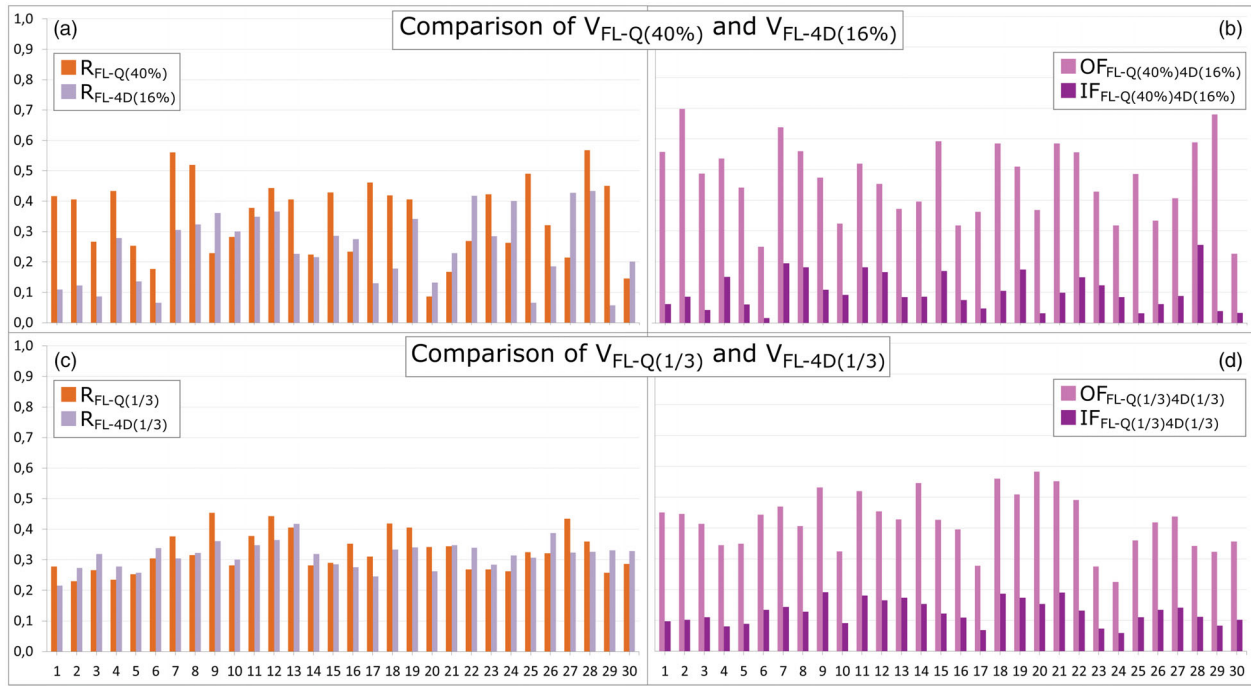


Figure 1. Comparison of 4D-ventilation to Q-SPECT. Patients 9 and 25 have had one lung removed. (a) Volume ratios $R_{FL-Q(40\%)}$ and $R_{FL-4D(16\%)}$ and (b) overlap fraction $OF_{FL-Q(40\%)4D(16\%)}$ and intersection fraction $IF_{FL-Q(40\%)4D(16\%)}$. (c) Ratios $R_{FL-Q(1/3)}$ and $R_{FL-4D(1/3)}$, and (d) overlap fraction $OF_{FL-Q(1/3)4D(1/3)}$ and intersection $IF_{FL-Q(1/3)4D(1/3)}$. For some patients with very inhomogeneous functionality, a volume close to 1/3 of the total lung volume was not segmented. The highest volume giving comparable volumes with the two modalities was selected.

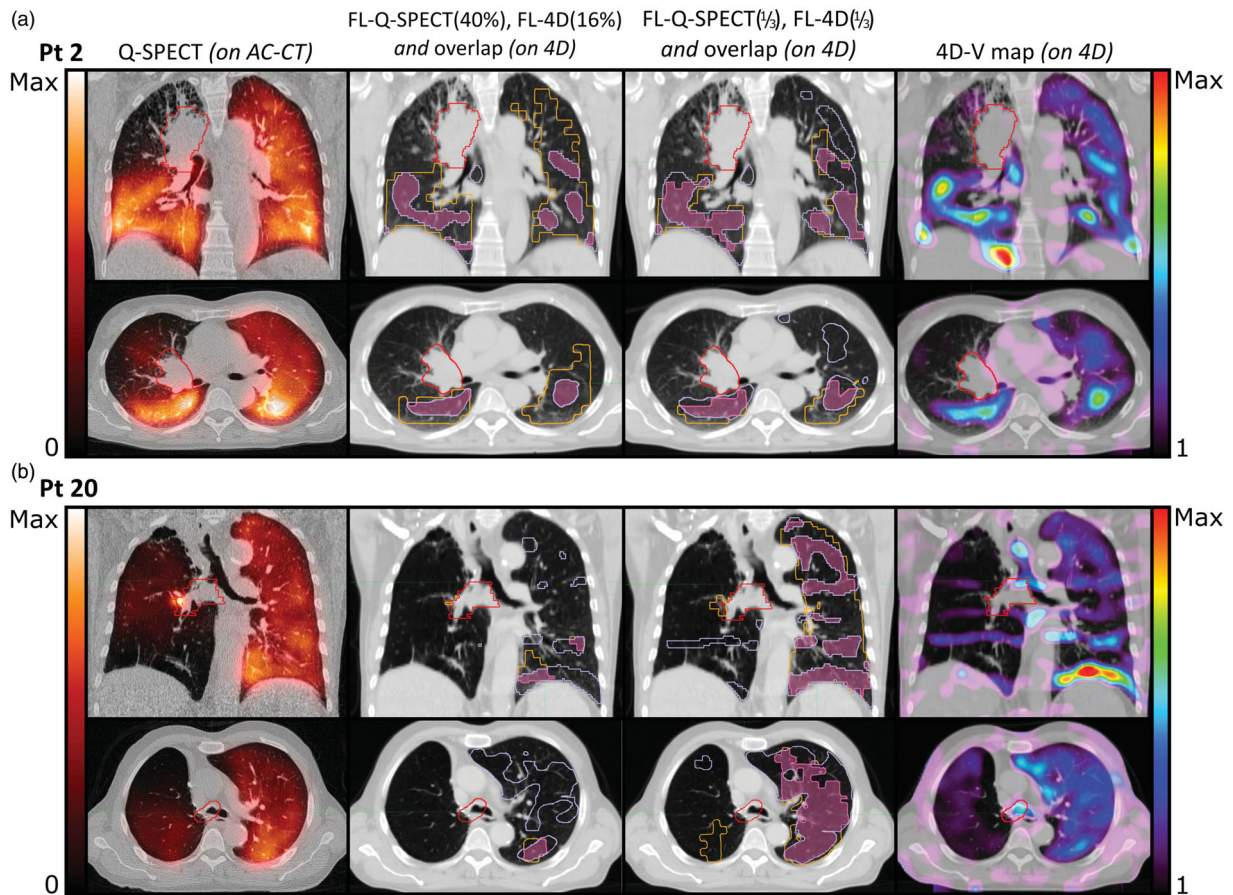


Figure 2. Frontal and transversal planes of (from left to right): AC-CT with Q-SPECT (orange hues), showing values from 0 to maximum counts; 4D-CT with overlay of functional volumes $V_{FL-Q(40\%)}$ (orange) and $V_{FL-4D(16\%)}$ (light purple), and the overlap between the two (pink); 4D-CT with overlay of functional volumes $V_{FL-Q(1/3)}$ (orange) and $V_{FL-4D(1/3)}$ (light purple), and the overlap between the two volumes (pink); 4D-CT with 4D-CT V-map (rainbow heat map) showing Jacobian values from 1 to maximum value. Primary tumor in red. (a) Patient 2. The cut-off values of 40% for Q-SPECT and 16% for 4D-CT produce volumes of very different size, $R_{FL-Q(40\%)}$ is 0.41 and $R_{FL-4D(16\%)}$ is 0.12, with $OF_{FL-Q(40\%)4D(16\%)}$ = 0.70 and $IF_{FL-Q(40\%)4D(16\%)}$ = 0.09. $OF_{FL-Q(1/3)4D(1/3)}$ is 0.45 and $IF_{FL-Q(1/3)4D(1/3)}$ = 0.10. (b) Patient 20. $R_{FL-Q(40\%)}$ is 0.09 and $R_{FL-4D(16\%)}$ is 0.13, with $OF_{FL-Q(40\%)4D(16\%)}$ = 0.37 and $IF_{FL-Q(40\%)4D(16\%)}$ = 0.03. $OF_{FL-Q(1/3)4D(1/3)}$ = 0.58 and $IF_{FL-Q(1/3)4D(1/3)}$ = 0.15.

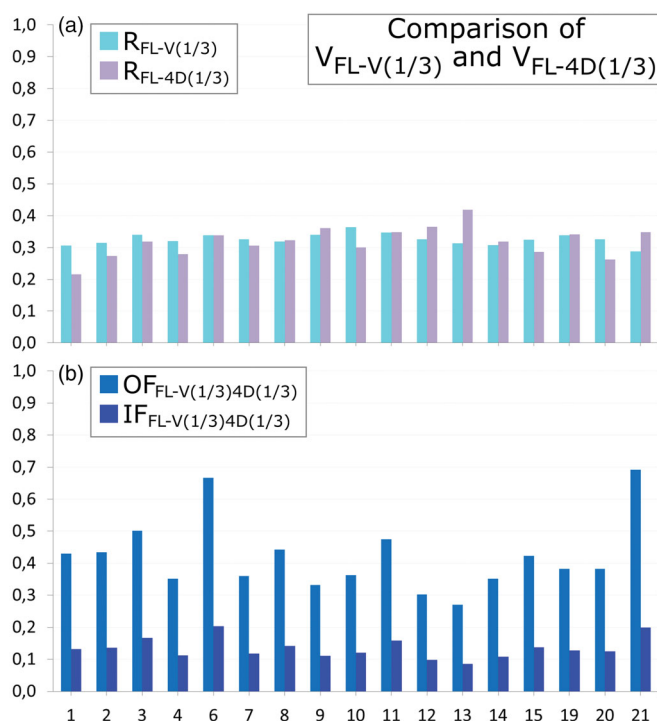


Figure 3. Comparison of 4D-V to V-SPECT. Seventeen patients with a V-SPECT scan are shown (patients 1–4, 6–15, and 19–21). Patient 9 has had one lung removed. (a) Ratios $R_{FL-V(1/3)}$ (cyan) and $R_{FL-4D(1/3)}$ (light purple) and (b) overlap fraction $OF_{FL-V(1/3)4D(1/3)}$ (light blue), and intersection $IF_{FL-V(1/3)4D(1/3)}$ (dark blue).

with an $OF_{FL-V(1/3)4D(1/3)}$ of 0.69 and $IF_{FL-V(1/3)4D(1/3)}$ of 0.20, and agree on a low functionality of the upper right lung near the tumor. On the contrary, for patient 12 (Figure 4(b)), $OF_{FL-V(1/3)4D(1/3)}$ is 0.30 and $IF_{FL-V(1/3)4D(1/3)}$ is 0.10, as both methods find only dispersed areas of high functionality. This indicates a generally low functionality, and both methods are likely influenced by noise in the functional images.

Finally, Figure 5 shows $R_{FL-V(1/3)}$, $R_{FL-Q(1/3)}$, $OF_{FL-V(1/3)Q(1/3)}$, and $IF_{FL-V(1/3)Q(1/3)}$ for the same 17 patients, with a median [range] $OF_{FL-V(1/3)Q(1/3)}$ of 0.68 [0.46;0.81] and $IF_{FL-V(1/3)Q(1/3)}$ of 0.20 [0.13;0.31]. The overlaps and intersections of FL-V(1/3) with FL-Q(1/3) volumes were significantly ($p < .001$) larger than the corresponding overlaps and intersections of FL-Q(1/3) with FL-4D(1/3) and FL-V(1/3) with FL-4D(1/3).

Discussion

The inclusion of functional information has been shown to correlate with the risk of RP in former studies [9,10,15]. The functional information on perfusion and/or ventilation may be obtained from several imaging modalities including SPECT, MRI, PET, and 4D-CT [20].

In this study, we aimed at investigating if two techniques, SPECT and 4D-CT, pointed at the same regions. We compared the overlap in FL volumes obtained from perfusion using Q-SPECT and ventilation using 4D-CT. Cut-off values of 40% for Q-SPECT and 16% for 4D-CT, formerly shown to be predictive for RP [9,10,15], resulted in significantly larger FL volumes segmented by Q-SPECT, and 37% of the patients had less than 20% of the lung identified as functional by one or both methods. The median $OF_{FL-Q(40\%)4D(16\%)}$ was 0.48

[0.23;0.70], and $IF_{FL-Q(40\%)4D(16\%)}$ was 0.09 [0.02;0.25], meaning that 9% of V_{Lung} was found to be functional by both methods. Seventeen patients had an IF value below 0.1.

Functional volumes were determined using the total lung volume. This was chosen despite the potential inhomogeneous functionality between the ipsilateral and contralateral lung induced, e.g. by the tumor itself, as current RT planning strategies are based on limiting the dose to the entire lung, regardless of verifiable inhomogeneous functionality. As no consensus exists on the cut-off values [20], we further segmented approximately 1/3 V_{Lung} for both modalities. This fraction was chosen to obtain reasonably large inter-modality, intra-patient comparable functional volumes, which could be used for treatment planning based on FL avoidance. Furthermore, the median $R_{FL-Q(40\%)}$ and $R_{FL-4D(16\%)}$ were 0.39 [0.09;0.57] and 0.25 [0.06;0.43], respectively. Thus, $R_{FL-Q(40\%)}$ and $R_{FL-4D(16\%)}$ segment FL volumes of different sizes. A value of 1/3 for both modalities secures segmentation of identical volumes with a ratio in-between $R_{FL-Q(40\%)}$ and $R_{FL-4D(16\%)}$. Hereby, more inter-patient comparable volumes were obtained, with a median $OF_{FL-Q(1/3)4D(1/3)}$ of 0.43 [0.23;0.58] and a median $IF_{FL-Q(1/3)4D(1/3)}$ of 0.12 [0.06;0.19], meaning that 12% of V_{Lung} was found to be functional by both methods, while only seven patients had an IF value below 0.1. This indicates large overlap of well-ventilated and well-perfused regions and points at a possibility of dose sparing of both well-ventilated and well-perfused parts of the lungs, hereby decreasing the risk of RP. This aligns with a former study of 60 patients having both Q-SPECT and 4D-CT, showing that the clinical correlation with RP was stronger in the ventilation and perfusion matched region than ventilation or perfusion alone [24]. A complete picture of lung function however includes imaging both physiological processes, especially in lung cancer patients, where pulmonary abnormalities lead to spatial lung function heterogeneity [9]. The findings in this study support this fact, and one would not expect the two methods to overlap to higher extent.

As the SPECT scans were acquired over several minutes and hence several breathing cycles, the functionality of single voxels affected neighboring voxels during breathing. Thus, identification of individual functional voxels in the lungs becomes uncertain and segmentation of small volumes should be avoided. In some patients, for instance patient 20 in Figure 2(b), the 40% cut-off value for Q-SPECT produced small dispersed areas of high activity due to a very inhomogeneous albumin-deposit which resulted in an $OF_{FL-Q(40\%)4D(16\%)}$ of 0.37 and $IF_{FL-Q(40\%)4D(16\%)}$ of only 0.03. For the same patient, the $OF_{FL-Q(1/3)4D(1/3)}$ was 0.58, and $IF_{FL-Q(1/3)4D(1/3)}$ was 0.15 showing much larger overlap between FL-Q and FL-4D.

V/Q-SPECT is the golden standard for imaging regional lung function. SPECT imaging is mainly used as a qualitative grey-level based diagnostic tool due to the frequent occurrence of artifacts and uneven distribution of the radioactive agents, making quantification challenging. The V-SPECT signal generally has a lower activity than the Q-SPECT signal, resulting in noisy V-SPECT images that may be hard to interpret quantitatively [20]. For the V-SPECT scans in this study,

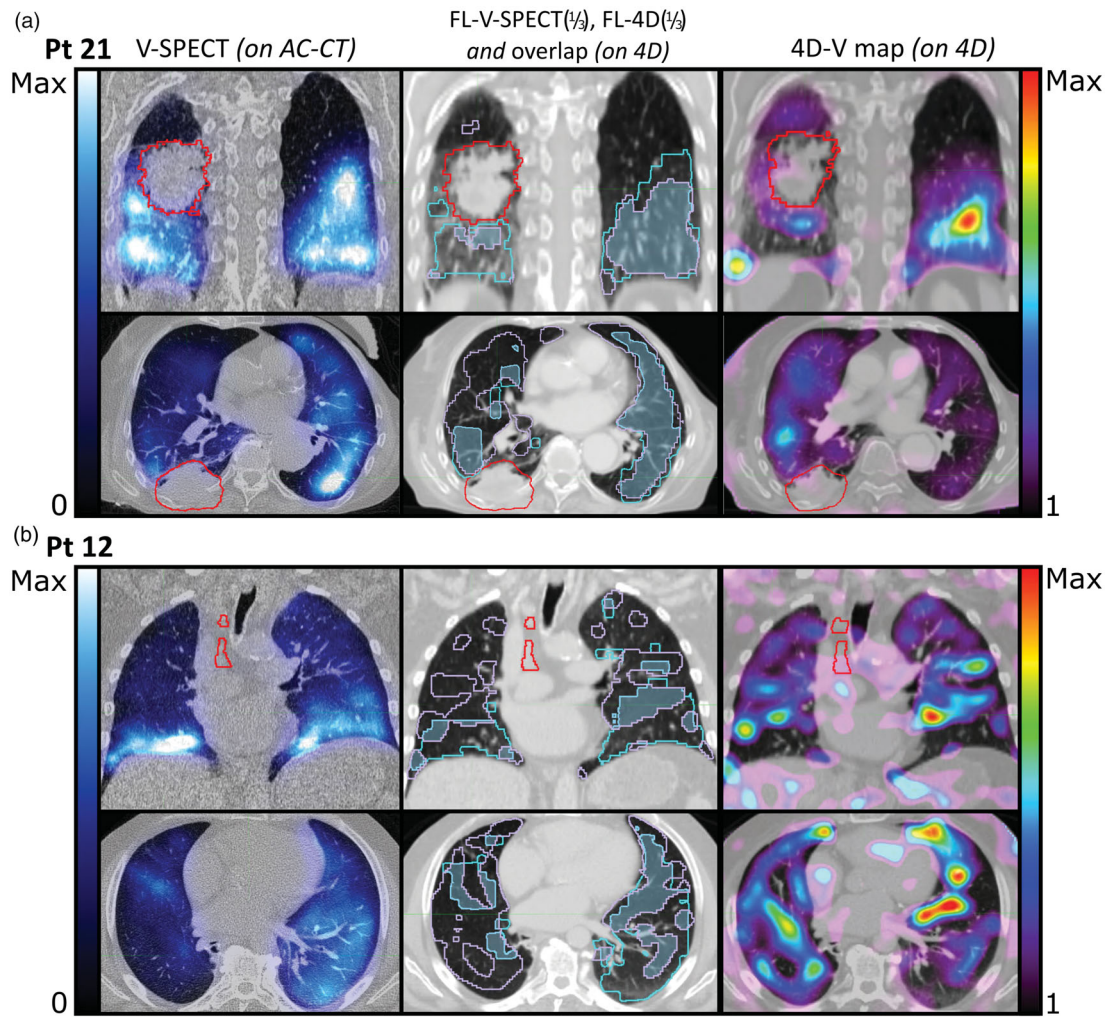


Figure 4. Frontal and transversal planes of (from left to right): AC-CT with V-SPECT (blue hues), showing values from 0 to maximum counts; 4D-CT with overlay of functional volumes $V_{FL-V(1/3)}$ (cyan) and $V_{FL-4D(1/3)}$ (light purple), and the overlap between the two (blue); 4D-CT with 4D-CT V-map (rainbow heat map) showing Jacobian values from 1 to maximum value. Primary tumor in red. (a) Patient 21. $OF_{FL-V(1/3)4D(1/3)}$ is 0.69 and $IF_{FL-Q(1/3)4D(1/3)}=0.20$. (b) Patient 12. $OF_{FL-V(1/3)4D(1/3)}$ is 0.44 and $IF_{FL-Q(1/3)4D(1/3)}=0.14$. In both modalities, the functional images have a high level of noise.

patients were inhaling the radioactive agent in upright position while the imaging was performed in the supine position. Contrary to this, the agent used for Q-SPECT was injected into the veins of the patient and distributed through the blood flow while the patient was in the supine position, also being the position used for imaging both V- and Q-SPECT. In a study administering SPECT agents to healthy volunteers either in the upright, supine or prone posture, the regional blood flow and ventilation was redistributed by gravity in the upright posture. Hereby, activity was increased in the caudal regions. Much less influence was seen in the supine and prone postures [25]. In accordance with this, we generally saw the highest V-SPECT activity levels caudally and dorsally in the patients. For patients receiving both a V- and a Q-SPECT, the two examinations were carried out sequentially, causing remaining activity from the prior scan to influence activity levels in the latter, sometimes causing artifacts in the Q-SPECT scan. This is the case in patient 20 in Figure 2(b) where residual activity from V-SPECT resulted in extremely high activity just outside the right bronchus in the Q-SPECT image.

The 4D-CT method gives a strictly mechanical evaluation of the elasticity of the lung tissue. Voxels in an elastically flexible volume will be deemed functional regardless of lung tissue being inaccessible to air from the bronchi due to emboli or a tumor blocking its way. The 4D-CT method is sensitive to the breathing motion, as small breathing amplitudes during the 4D-CT scanning are often linked to minor motion of the voxels between the inhale and exhale phases causing a high level of noise in the V-map. This effect can be seen in Figure 4(b) where patient 12 with a very low breathing amplitude shows disjunct and poorly overlapping FL-V(1/3) and FL-4D(1/3) areas within the lungs. In both methods, this is probably the result of generally low lung functionality. The 4D-CT method is sensitive to 4D-image quality and artifacts as well as the precision of the DIR algorithm used [26,27]. In patient 20 in Figure 2(b) motion artifacts in the 4D-CT image give rise to an almost striped appearance of FL-4D(1/3). Despite the many artifacts in both the Q-SPECT and the 4D-CT V-map, both methods agree on high functionality in the left lung, and a mostly non-functioning right lung. Segmentation of large volumes minimizes the effects

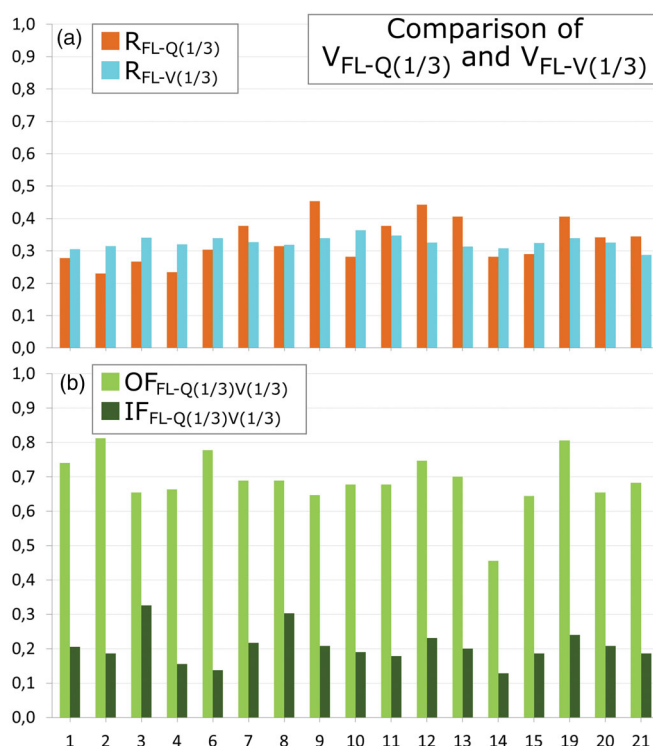


Figure 5. Comparison of Q-SPECT to V-SPECT. Seventeen patients with a V-SPECT scan are shown (patients 1–4, 6–15, and 19–21). Patient 9 has had one lung removed. (a) Ratios $R_{FL-Q(1/3)}$ (orange), $R_{FL-V(1/3)}$ (cyan); (b) overlap fraction $OF_{FL-Q(1/3)V(1/3)}$ (green) and intersection $IF_{FL-Q(1/3)V(1/3)}$ (dark green).

of artifacts but increases sensitivity to noise for patients with low perfusion on Q-SPECT or minor changes in breathing volume (see [Supplementary material](#)).

The OF and IF between FL-Q(1/3) and FL-V(1/3) were found to be significantly higher than those between FL-4D(1/3) and FL-Q(1/3) or FL-V(1/3). A high correlation between Q-SPECT and V-SPECT is likely as well-ventilated lung volumes are typically also well-perfused [19]. In a study of 11 patients, similarly the correlation between Q-SPECT and V-SPECT was found to be better than between SPECT and 4D-CT [17]. The OF and IF between FL-4D(1/3) and FL-Q(1/3) or FL-V(1/3) was found not to be significantly different. In a study of 12 patients comparing PET-Galligas-ventilation and 4D-CT, a modest correlation was found [28]. In a subsequent multi-institutional study, a huge variability was seen for the correlation between the two modalities [29]. However, in a study of 98 lung cancer patients, good global agreement between pulmonary function tests and 4D-CT ventilation was seen, indicating that 4D-CT ventilation provides a reliable assessment of lung function [13].

Treatment planning for FL avoidance is based on pre-treatment images. However, patient anatomy may change during the treatment course of five to six weeks duration [30,31]. One example might be a tumor blocking blood supply to part of the lung before RT treatment. During the treatment course, tumor shrinkage may increase blood supply to inferiorly FL volumes, which may in turn emerge as well-functioning at treatment completion. These anatomical changes should be considered by re-imaging and re-planning the patient in case of major anatomical changes [32,33]. Furthermore, ventilation and perfusion have been shown to

improve during the RT course making adaptive planning based on SPECT during RT beneficial to allow for sparing of functionally recoverable lung tissue [34,35].

In conclusion, the Q-SPECT and 4D-CT methods roughly agree on the main functional areas of lung in each patient when using larger volumes of comparable size, but the optimal cut-off value for segmentation of FL varies from patient to patient. Great care must be taken when 4D-images contain artifacts, or if the patient has small breathing amplitude. As both methods produce FL volumes that have been shown to correlate with RP incidence, a combination of both may reduce the impact of image noise (Q-SPECT) and artifacts (4D-CT) further.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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