Utility of single photon emission computed tomography perfusion scans in radiation treatment planning of locally advanced lung cancers

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ABSTRACT

Purpose: Lung perfusion scan provides a map of the spatial distribution of lung perfusion. This can be used to design radiation portals to spare functional lung (FL), potentially reducing lung toxicity. The purpose of this study was to assess the utility of lung perfusion single photon emission computed tomography (SPECT) in treatment planning for lung cancer patients. **Materials and Methods:** Radiotherapy treatment planning computed tomography (CT) scans and SPECT scans of 11 patients of lung cancer suitable for external radiotherapy were co-registered. Conventional treatment plans (anatomic plan) and plans with FL information (functional plan) was generated. The difference in dose volume parameters (V_{20}, V_{30} and mean lung doses) due to these two plans were compared using Bland-Altman plots. **Results:** Functional plans produced a more favorable plan compared with anatomic plan in all except three cases. FL V_{20} values and FL mean lung dose were reduced for all patients by an average of 5.45 Gy and 7.72 Gy respectively which were statistically significant. **Conclusions:** Lung perfusion scans provide functional information which is not provided by CT scans. SPECT-guidance aids in reducing the dose delivered to highly perfused regions which could reduce the incidence of pneumonitis.

Keywords: Lung cancer, radiation therapy, single photon emission computed tomography, treatment planning

INTRODUCTION

Radiation pneumonitis is a dose-limiting complication for patients undergoing radiation therapy for lung cancer. The incidence of grade II radiation pneumonitis is relatively low for prescribed standard doses up to 65 Gy, but dose escalation is likely to increase the incidence of radiation pneumonitis.[1] The dose parameters like mean lung dose and the volume of lung receiving greater than 20 Gy, 25 Gy, or 30 Gy are used to estimate the incidence of radiation pneumonitis.[2-4] Besides the development of radiation pneumonitis, reduction in overall pulmonary function or lung perfusion due to the treatment can be a complication as well. The amount of pulmonary function loss is especially important for patients, with medically inoperable non-small-cell lung cancer, who often have a reduced lung function before treatment because of chronic obstructive pulmonary disease (COPD), intra-thoracic tumor or because they are heavy smokers. The extent of damage to the lung due to these pre-existent diseases is not always reflected in computed tomography (CT) images. Single photon emission computed tomography (SPECT) lung perfusion scans provide additional information in three dimensions about local functionality of lung tissue and might give additional benefit to design the plan that minimizes the complication risk for perfusion damage for an individual patient.[5,6]

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Changes in overall lung perfusion correlate with reduction in pulmonary function tests for patients of lung cancer.[7] Marks *et al*., suggested that the perfusion weighted dose–volume histogram (where the volume receiving a certain dose is weighted with the average perfusion in that dose-region) could be a valuable tool in designing the optimal radiotherapy plan.[8]

Patients of non-small lung cancers commonly present in locally advanced stage. The purpose of this study was to evaluate the

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utility of perfusion SPECT in conventional radiation treatment planning for locally advanced non-small cell lung cancers. We first evaluated the accuracy of co-registering CT and SPECT data in phantom using a public domain freeware. Thereafter, co-registered data were used in patients to evaluate the change in dose volume histogram parameters due to information of functional lung (FL).

MATERIALS AND METHODS

Twelve patients of locally advanced non-small cell lung cancer suitable for radical radiotherapy consented for the study. One patient declined SPECT scan due to fatigue.

Phantom study

The phantom study was performed to assess the accuracy of CT and SPECT co-registration. The Jaszczak phantom cylinder interior dimension of 8.5" diameter × 7.32" heights (21.6 cm × 18.6 cm) containing variable dimension cold rods and solid spheres were used in this study. The phantom was filled with water and labeled with Technetium 99 m (Tc^{99m}) of 15 mCi. The SPECT study was carried out in the gamma camera (Sofa Vision Medical (SMV) DSTXL, GE Health Care) with low-energy high resolution collimators. The SPECT study was performed with 64 projections, matrix size of 128 × 128, and a pixel resolution of 4.6 mm. The radiotherapy planning CT (Picker PQ 5000 CT scanner, Philips Medical System) of the phantom performed in the same orientation with the slice thickness 5 mm, matrix size of 512 × 512 pixels, and 430 mm field of view correspond to a pixel resolution of 0.84 mm. The SPECT matrix was re-sampled to 512 × 512 matrixes as per the CT data and then co-registered using the Statistical Parametric Mapping Software (SPM 2) developed by Department of Neurosciences, University of London Software in the MatLab Platform. The co-registration accuracy between the SPECT and the CT data was <2 mm.

Patient data imaging and co-registration

Radiotherapy planning CT scans were acquired using three CT/SPECT compatible markers (multi-modality markers) on the patient's chest in the treatment position using a flat board. Scans were obtained with slice thickness of 5 mm and FOV 430 mm. Lung perfusion SPECT images were acquired in a separate session with the same markers at the same position tattooed during CT images. Lung perfusion scans were acquired after an intravenous injection of 200 MBq of ^{99m}Tc labeled macro-aggregated albumin using gamma camera on a flat couch, in free breathing. All scans had sufficient coverage to include the total lung volume. Thereafter both CT and SPECT images were co-registered using SPM 2 software (Statistical Parametric Mapping) under MatLab 7 platform. The registration method used here is based on rigid-body model work by Collignon *et al.*[9] A rigid-body 3D transformation can be parameterized by three scalar translations and rotations matrix perpendicular to each other. The CT data were kept as a reference and the transformed SPECT image was processed and re-sliced to a series of registered images so that they match the first image selected voxel-for-voxel. The accuracy of the co-registration was assessed by superposition of the markers in both the images. The co-registered CT data with SPECT was opened using MRIcro software and the region of interest (ROI) were delineated (areas of perfused lung). The SPECT data was viewed in the spectrum color setting. This produced a multi-colored image, which allowed more accurate volume contouring around a chosen color. The threshold level was adjusted individually for each patient to match the size of the SPECT image to the lung volumes defined on CT. The ROIs were overlaid on the CT and the data set was transferred on to the treatment planning system (ISIS 3D, Technology Diffusion, France) for designing the beam portals. A phantom study was performed to validate the accuracy of the registration algorithm [Figures 1 and 2a-d].

Target volume definition

For treatment planning purposes, the following areas were outlined for each patient on the co-registered images in the planning system; gross tumor volume, body outline, anatomic whole lung (WL) lung volume based on CT images as a single organ excluding gross target volume (GTV), functional whole lung based on lung volumes visible on SPECT images (FL), right lung and left lung, and normal structures. The clinical target volume was created using a 2 cm uniform margin around the GTV. Planning target volume (PTV) was created with an additional 1.5 cm margin for beam characteristics, setup uncertainties, and organ motion. FL outlines drawn using the SPECT images were validated by a nuclear medicine expert in functional imaging.

Treatment planning and evaluation of plans

Conventional treatment plans were designed to deliver 60 Gy to the PTV with an intent to minimize the dose to the CT defined whole lung (anatomical WL) or SPECT defined whole lung (FL) to a dose less than 20 Gy or 30 Gy. Two treatment plans were created for each patient, one an anatomic plan based on CT scan data alone and the other a functional plan with the incorporation

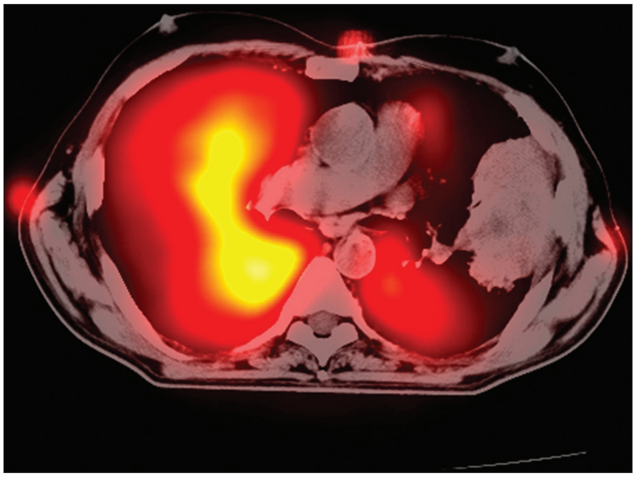

Figure 1: The accuracy of the registration was evaluated by the superposition of the fiducial markers of the single photon emission computed tomography overlaid image on the computed tomography

of FL information [Figure 3 a-d]. Plan comparison was done using dose volume parameters, V_{20} (volume of lung receiving 20 Gy), V_{30} (volume of lung receiving 30 Gy), and mean lung dose (MLD). For each patient the following data were computed: GTV, whole lung volume (WLV), Functional lung volume (FLV), PTV95 (% volume of PTV covered by the 95% isodose). Dose volume parameters recorded due to CT-based plan were WL_V_{20}, WL_V_{30}, and mean lung dose (WLMLD). Due to SPECT-based plan the following data were computed: FL_V_{20}, FL_V_{30}, and mean lung dose functional lung mean lung dose (FLMLD).

Data analysis

The difference between dose volume parameters for the anatomic and functional plans was compared using Bland-Altman plots.[10] In Bland-Altman plots, the differences between the methods that were compared were plotted against their means and gave an unbiased estimate of systematic differences between the modalities.[11]

RESULTS

The phantom study validated the qualitative accuracy of the registration algorithm [Figures 1 and 2a-d]. The mean GTV volume was 282.76 cm^3 (range: 82.4-571 cm^3). The mean PTV volume was (range: 303.9-1,096 cm^3). All patients had a smaller FLV when compared with the WLV [Table 1]. The mean difference between WL and FL was 824.7 cm^3 (range: 1-1,618 cm^3) [Table 2]. Most of the perfusion defects were in the region of tumor and or adjacent to the tumor. Perfusion was either non-uniform with considerable inhomogeneity of FL often due to pre-existing chronic lung dysfunction (due to old tuberculosis) or demonstrating specific defects usually due to local atelectasis and COPD. Dose volume data (V_{20}, V_{30}, MLD) for both anatomic and functional plans are given in Table 1. It is intuitive that a large GTV and large PTV would yield higher V_{20}, V_{30} and MLD as seen in all anatomic plans. Tumors in upper lobe or periphery had lower dose volume parameters than those at hilum, lower or middle lobe. Due to functional plan, dose volume parameters decreased in all patients except in patient 1 and 9 [Table 1]. The mean difference in all the dose volume parameters is depicted in the Bland-Altman plots [Figure 4] [Table 2] (mean change in WL_V_{20}:7.94 Gy, FL_V_{20}:6.05 Gy, WL_V_{30}:7.05 Gy, FL_V_{30}:7.55 Gy, WLMLD: 7.36 Gy, FLMLD: 7.94 Gy [Table 2].

The mean follow-up of all patients was 9 months. Only four of the evaluable patients were alive at the time of reporting. Among these four patients, three were alive with progression of disease at 16, 6, and 10 months follow-up, and one patient was disease-free at a follow-up of 10 months. A follow-up SPECT scan in those with disease progression did not reveal any change in perfusion, whereas in the patient with disease-free status reperfusion in area adjacent to the region of target was observed.

DISCUSSION

The main aim of this study was to assess whether the incorporation of FL information into conventional radiotherapy

Table 1: Comparison of anatomical and functional plan

PTV	Anatomical plan	Functional plan	Anatomical plan	Functional plan	Anatomical plan	Functional plan	Anatomical plan	Functional plan	Anatomical plan	Functional plan	Anatomical plan	Functional plan
	WLV_{20}	FLV_{20}	WLV_{30}	FLV_{30}	WLMLD	FLMLD	WLV_{20}	FLV_{20}	WLV_{30}	FLV_{30}	WLMLD	FLMLD
303.9	23	23	14.5	11.5	29.58	26.17	23	23	15.5	14	26.17	28.10
1096	48	50	18	12	44.9	39.62	45	43	37	26	39.05	33.51
415	48.5	45.5	47.5	44.5	60.48	58.2	41.5	25.6	40	36.5	52.87	49.72
773	28	26.5	26.5	25	36.51	34.27	27.5	27	15	13	28.6	27
599	52	57	47.5	55	30.2	35.9	51	57	47.5	55	30	33.02
503	60	54	57	50	33.54	35.59	30	30	28	28	20.88	20.97
870	19	17.5	15	15	24.55	22.35	13.5	10.5	12	9.5	9.56	8.14
753	51	50.5	50	50	64.1	58.54	40	37	37	35	48.57	41.11
575	28	27	20	18.5	37.6	37.49	26	28	0	0	31.03	30.31
522	33	34	32	33	41.57	41.99	30.5	29.5	24.5	23.5	36.89	35.63
1046	29.5	40.5	26.5	39	37.14	51.68	25.5	45	20.5	30	35.57	46.98

PTV: Planning target volume, WLV_{20}: Anatomical lung V_{20}, FLV_{20}: Functional lung V_{20}, WLV_{30}: Anatomical lungV_{30}, FLV_{30}: Functional lung V_{30}, WLMLD: Anatomical lung mean lung dose, FLMLD: Functional lung mean lung dose

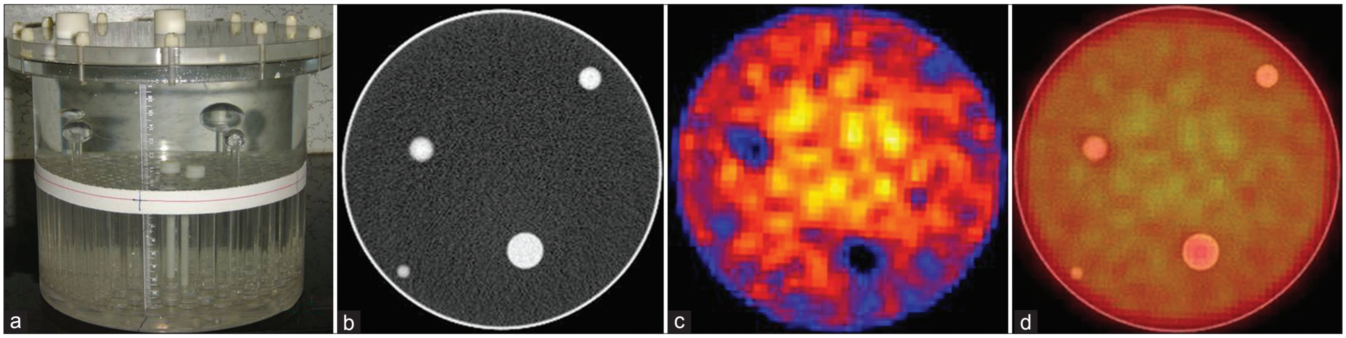

Figure 2: The accuracy of the registration was evaluated using a phantom. (a) Jaszezak phantom, (b) Computed tomography (CT) image, (c) Single photon emission computed tomography (SPECT) image, and (d) fused CT SPECT image

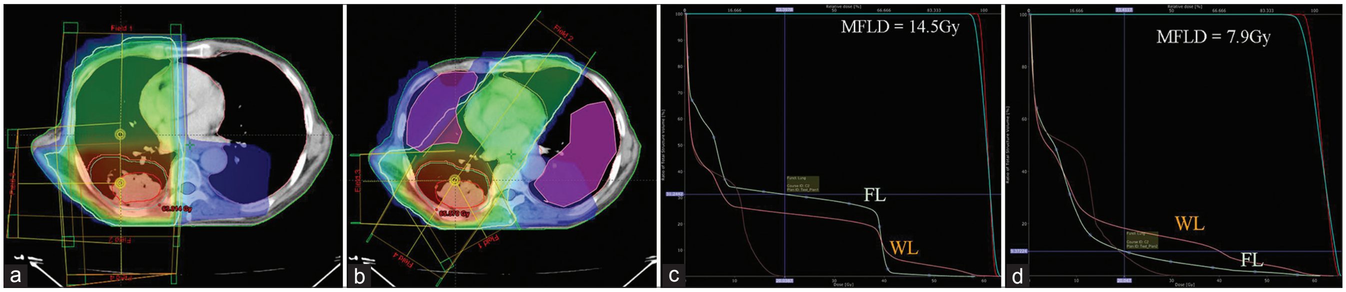

Figure 3: Comparison of the dose distribution of (a) anatomic and (b) functional plan along with the respective Dose Volume Histograms (c and d)

Table 2: Comparison of anatomical and functional plan: Mean difference in all parameters

Parameter	Anatomical plan	Functional plan	Difference	*P* value
WLV$_{20}$	45.5 (19-60)	32.13 (13.5-51)	5.86 (0-30)	0.041
FLV$_{20}$	38.68 (17.5-57)	32.32 (10.5-57.0)	5.45 (0-24)	0.087
WLV$_{30}$	32.22 (14.5-57)	25.36 (0-47.5)	7.59 (0-29)	0.045
FLV$_{30}$	32.13 (11.5-55.0)	24.59 (0-55.0)	7.54 (0-18.5)	0.034
WLMLD	40.01 (24.55-64.10)	33.95 (9.56-52.87)	7.76 (0.2-15.53)	0.002
FLMLD	40.20 (22.35-58.54)	32.22 (8.14-49.72)	7.72 (2.88-17.43)	0.001

WLV$_{20}$: Anatomical lung V$_{20}$, FLV$_{20}$: Functional lung V$_{20}$, WLV$_{30}$: Anatomical lung V$_{30}$, FLV$_{30}$: Functional lung V$_{30}$, WLMLD: Anatomical lung mean lung dose, FLMLD: Functional lung mean lung dose

planning could result in reduction of dose to healthy functioning lung. The validity of the dose-volume data depends on the method of co-registering SPECT lung perfusion images with CT images. The phantom study showed reasonable qualitative matching of fiducial markers of SPECT and CT images. Other authors have matched images using visual iterative methods or by co-registration.[12] Co-registration of images using public domain software has its utility in developing country like ours where procurement of co-registration software involves dear investments.

As previously shown and confirmed in this study, not all regions of the anatomic lung defined by CT scans are of equal physiologic importance.[13,14] Most of the patients had perfusion defects in the region of the tumor (54%) or in and adjacent to tumor region (36%), a non-functioning lung in the entire ipsilateral hemithorax in the rest. Since most of the perfusion defects are in the tumor-bearing lung, in principle one should attempt to direct all beams through the ipsilateral lung to avoid unnecessary irradiation of opposite lung. This principle can be brought to an advantage even in centers which do not have the facility of FL imaging as in most of the radiotherapy centers in our country.

The incorporation of FL information into the conventional treatment plans aided in diversion of the beams away from the FL. Functional plans resulted in reduction of all dose-volume parameters. These observations need to be validated in a larger sample size. Seppenwoodle demonstrated the feasibility of perfusion-weighted optimization of treatment plans and suggested improvement in mean lung doses by an increase in the weights of those beams that were directed through hypoperfused lung regions.[15] He concluded that perfusion-weighted optimization should result in clinical benefit in patients with large perfusion defects and larger target volume. SPECT perfusion information has also been incorporated in inverse radiotherapy planning for lung cancer and it was found that SPECT was warranted only in those patients with large perfusion defects.[16] Mcguire reported a methodology for using SPECT to deliver intensity-modulated radiation therapy (IMRT), by segmenting healthy lung into four regions on the basis of SPECT intensity and they found a reduction in V$_{20}$ and V$_{30}$ values of 15.5% and 10.5% respectively.[17] The use of IMRT when compared with 3-DCRT

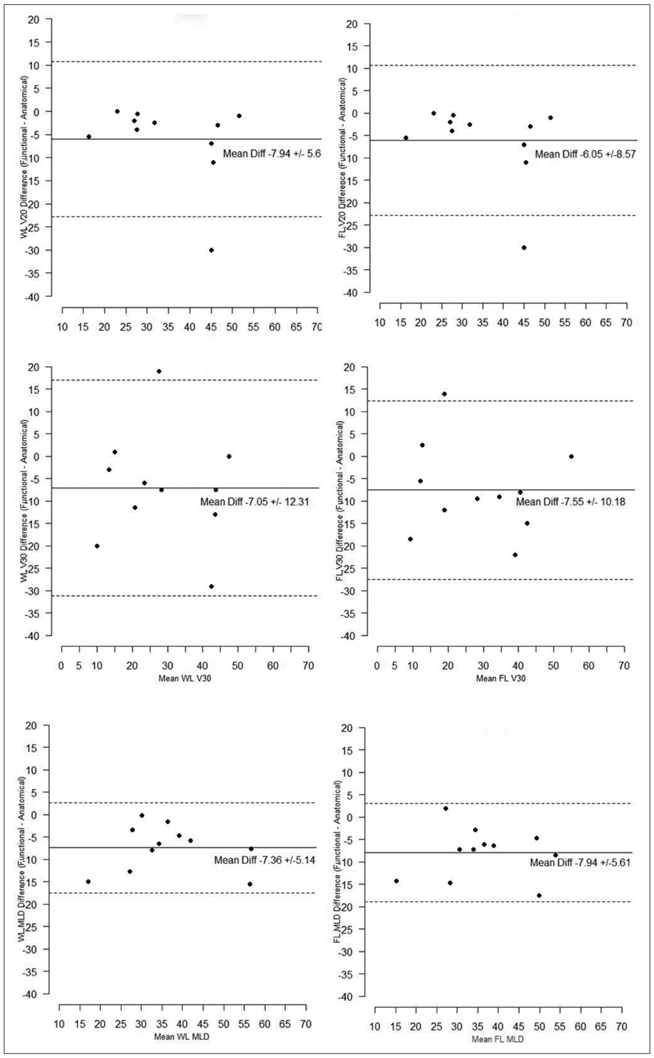

Figure 4: Bland-Altman plots representing the mean value of various dose volume parameters plotted on *x*-axis and the difference in parameter between anatomic and functional plan on *y*-axis

improved the avoidance of FL defined by perfusion SPECT scan in selected patients and IMRT allowed for effective dose escalation by specific avoidance of FL.[18,19]

Incorporation of functional information seems to be beneficial as far as planning studies are concerned. But its utility in the clinic needs to be defined according to different presenting stage. Almost all the patients attending our clinic were stage III or IV patients with target volumes almost three to eight times than those reported by other authors. Many of these patients could have been upstaged to stage IV disease with the availability of PET, which explains the shorter survivals (9 months mean follow-up) in our setup when compared with other studies where reported median survivals were 15-18 months. By the time we expect radiation pneumonitis to manifest (3-6 months or more) our patients have either succumbed to disease or have had progression of disease or recurred. Hence the clinical benefit of perfusion SPECT in inoperable locally advanced lung cancer could not be ascertained. It should be beneficial in patients with smaller target volumes with large perfusion defects. Perhaps intensity-modulated radiotherapy in appropriately staged III patients with a constraint on FL could result in clinical benefit in these patients. Moreover, a larger sample size would strengthen this conviction.

CONCLUSION

SPECT perfusion images can be accurately co-registered with radiotherapy planning CT scans using public domain software. Information regarding FL does aid in diverting beams away from the FL which might minimize radiation pneumonitis.

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