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

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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

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
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 $\times$ 7.32” heights (21.6 cm $\times$ 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 Tc-99m m 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 $\times$ 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 $\times$ 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 $\times$ 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 Tc-99m 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. 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 of perfusion.

![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.](image-url)
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), PTV\(_{95}\) (% volume of PTV covered by the 95% isodose). Dose volume parameters recorded due to CT-based plan were \(W_{L-V_{20}}\), \(W_{L-V_{30}}\), and mean lung dose (WLMLD). Due to SPECT-based plan the following data were computed: \(F_{L-V_{20}}, F_{L-V_{30}}\), 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. 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.

**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 \(V_{30}, V_{20}\) 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 \(W_{L-V_{20}}, W_{L-V_{30}}, W_{L-MLD}\), \(F_{L-V_{20}}, F_{L-V_{30}}, F_{L-MLD}\), \(WLMLD\), Functional lung mean lung dose).

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
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. 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. Most of the patients had perfusion deficits 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 deficits 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. Seppenwoole 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. 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. 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. The use of IMRT when compared with 3-DCRT
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. 

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.

**REFERENCES**

1. Graham MV, Purdy JA, Emami B, Harms W, Bosch W, Lockett MA, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small-cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323-9.
2. Marks LB, Munley MT, Bentel GC, Zhou SM, Hollis D, Searfose C, et al. Physical and biological predictors of changes in whole-lung function following thoracic irradiation. Int J Radiat Oncol Biol Phys 1997;39:563-70.
3. Kwa SL, Lebesque JV, Theuwss JC, Marks LB, Munley MT, Bentel G, et al. Radiation pneumonitis as a function of mean lung dose: An analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 1998;42:1-9.
4. Marks LB, Spencer DP, Bentel GC, Ray SK, Sherouse GW, Sontag MR, et al. The utility of SPECT lung perfusion scans in minimizing and assessing the physiologic consequences of thoracic irradiation. Int J Radiat Oncol Biol Phys 1993;26:59-68.
5. Marks LB, Spencer DP, Sherouse GW, Bentel G, Closh R, Vann K, et al. The role of three dimensional functional lung imaging in radiation treatment planning: The functional dose-volume histogram. Int J Radiat Oncol Biol Phys 1995;33:65-75.
6. Wernly JA, DeMeester TR, Kirchner PT, Myerowitz PD, Oxford DE, Golomb HM. Clinical value of quantitative ventilation-perfusion lung scans in the surgical management of bronchogenic carcinoma. J Thorac Cardiovasc Surg 1980;80:535-43.
7. Fan M, Marks LB, Lin P, Hollis D, Woel RT, Bentel GG, et al. Relating radiation-induced regional lung injury to changes in pulmonary function tests. Int J Radiat Oncol Biol Phys 2001;71:311-7.
8. Marks LB, Sherouse GW, Munley MT, Bentel GC, Spencer DP. Incorporation of functional status into dose-volume analysis. Med Phys 1999;26:196-9.
9. Collignon A, Maes F, Delaere D, Vandermeulen D, Suetens P, Marchal G. Automated multi-modality image registration based on information theory. In: Bizais Y, Barillot C, Di Paola R, editors. Proc. Information Processing in Medical Imaging. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1995. p. 263-74.
10. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999:8:135-60.
11. Bland JM, Altman DG. Comparing methods of measurement: Why plotting difference against standard method is misleading. Lancet 1995;346:1085-7.
12. Marks LB, Munley MT, Spencer DP, Sherouse GW, Bentel GC, Hopperworth J, et al. Quantification of radiation-induced regional lung injury with perfusion imaging. Int J Radiat Oncol Biol Phys 1997;38:399-409.
13. Burton GH, Seed WA, Vernon P. Computer analysis of ventilation-perfusion scans for detection and assessment of lung disease. Thorax 1985;40:519-25.
14. Susskind H, Avededo JC, Iwai J, Rasmussen DL, Heydingen DK, Pati HR, et al. Heterogeneous ventilation and perfusion: A sensitive indicator of lung impairment in nonsmoking coal miners. Eur Respir J 1988;1:232-41.
15. Seppenwoolde Y, Engelsman D, De Jaeger K, Muller SH, Baas P, McShan DL, et al. Optimizing radiation treatment plans for lung cancer using lung perfusion information. Radiother Oncol 2002;63:165-77.
16. Christian JA, Parrtridge M, Noutsikou E, Cook G, McNair HA, Cronin B, et al. The incorporation of SPECT functional lung imaging into inverse radiotherapy planning for non-small cell lung cancer. Radiother Oncol 2005;77:271-7.
17. McGuire SM, Zhou S, Marks LB, Dewhirst M, Yin FF, Das SK. A methodology for using SPECT to reduce intensity-modulated radiation therapy (IMRT) dose to functioning lung. Int J Radiat Oncol Biol Phys 2006;66:1543-52.

18. Lavrenkov K, Christian JA, Partridge M, Niotsikou E, Cook G, Parker M, et al. A potential to reduce pulmonary toxicity: The use of perfusion SPECT with IMRT for functional lung avoidance in radiotherapy of non-small cell lung cancer. Radiother Oncol 2007;83:156-62.

19. Shioyama Y, Jang SY, Liu HH, Guerrero T, Wang X, Gayed IW, et al.

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