RESEARCH ARTICLE

Spect-guidance to Reduce Radioactive Dose to Functioning Lung for Stage III Non-small Cell Lung Cancer

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Abstract

Objective: To investigate the treatment effect of additional information obtained by single photon emission computed tomography (SPECT) lung perfusion imaging (LPI) in the radiotherapy planning process for patients with stage III non–small cell lung cancer (NSCLC). Methods: 39 patients with stage III NSCLC were enrolled. Gross tumor volume (GTV) was outlined by SPECT/CT images, SPECT-LPIs being used to define functional lung (FL) and non-functional lung (NFL) regions. Two sets of IMRT plans were designed to deliver 64Gy to PTV. One was a regular IMRT plan using CT images only (Plan 1), and the other was a corresponding IMRT plan using co-registered images (Plan 2). FL_{Vx} (the % volume of functional lung receiving ≥x Gy) and WL_{Vx} (% volume of whole lung to receive ≥x Gy) were compared by paired Student's t test. Kendalls correlation was used to analyze the factor (s) related with the FLV20 decrease. Results: Compared with plan 1, both WL_{Vx} and FL_{Vx} were decreased in plan 2. WL_{V10}, WL_{V15}, WL_{V20}, WL_{V25}, WL_{V30} and WL_{V35} decreased 9.7%, 13.8%, 17.2%, 12.9%, 9.8% and 9.8%, and FL_{V10}, FL_{V15}, FL_{V20}, FL_{V25}, FL_{V30} and FL_{V35} decreased 10.8%, 14.6%, 17.3%, 14.5%, 14.5% and 10.5%. FL_{Vx} decreased significantly compared with WL_{Vx}. There were significant differences in WL_{V10}, WL_{V15}, WL_{V20}, WL_{V25}, WL_{V3} and FL_{V10}, FL_{V15}, FL_{V20}, FL_{V25}, FL_{V30} between plan 1 and plan 2 (P=0.002, 0.000, 0.000, 0.005, 0.027 and 0.002, 0.000, 0.000, 0.006, 0.010). According to Kendall correlation analysis, NFL had a negative relation with the percentage FLV20 decrease (r=-0.559, P<0.01), while the distance of PTV and NFL center had a significantly positive relation with the percentage of FLV20 decrease (r=0.768, P<0.01). Conclusion: Routine use of SPECT-LPI for patients undergoing radiotherapy planning for stage III NSCLC appears warranted.

Keywords: Non-small cell lung cancer - functional images - single photon emission computed tomography

Asian Pacific J Cancer Prev, **14 (2)**, 1061-1065

Introduction

Lung cancer is the leading cause of cancer related mortality worldwide (Parkin et al., 2005). Patients with locally advanced non-mall lung cancer (NSCLC) are appropriately treated with radiotherapy (RT) (Mornex, 2004). Despite radical RT, the 5-year survival rate is 5-14% in patients with locally advanced stage IIIA-B disease (Byhardt et al., 1998; Sause et al., 2000; Socinski et al., 2004). Although survival can be improved by intensifying radiotherapy (Partridge et al., 2011), attempts at dose escalation are limited by radiation damage of normal lung in the form of radiation pneumonitis. The incidence of radiation pneumonitis is dose and volume dependent, and is related to lung volume receiving >20 Gy (V20) with a risk of pneumonitis of over 10% when V20 exceeds 30% (Kwa et al., 1998; Graham et al., 1999; Seppenwoolde et al., 2003). A benefit can be enhanced in some cases with intensity modulated radiotherapy (IMRT) compared to three-dimensional conformal radiotherapy (3-DCRT), which may allow for improving planning target volume (PTV) coverage and better selective avoidance of normal tissues, particularly when the targets are of complex shape lying in close proximity to critical structures. In IMRT, intensity modulation within individual beam inlets is designed on the basis of the target prescription and a set of dose constraints for organs at risk using inverse planning algorithms. Recently published data report a 6-15% absolute decrease of V20 when using IMRT compared to 3-DCRT (Grills et al., 2003; Liu et al., 2004; Murshed et al., 2004).

RT has been transformed with the incorporation of 3D imaging into treatment planning software. With the vast amount of dose-distribution data that can now be generated, dose-volume histograms (DVHs) have become a useful method of reducing the volume of information. However, in creating a DVH, there is an implied assumption that homogeneity of function exists for a particular volume of an organ. In other words, treatment planning software does not depend on functional information but anatomical

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information provided by computer tomography images. Patients undergoing radiotherapy for NSCLC frequently have pre-existing lung damage may be far from uniform, especially for locally advanced stage patients. Lung cancer may cause pulmonary function changes, e.g. tumour-associated atelectasis or a tumour has destroyed an area of lung tissue (De Jaeger et al., 2003). Three dimensional single photon emission computed tomography (SPECT) lung perfusion imaging (LPI) provides information about the functioning of pulmonary vascular/alveolar subunits where 99mTc labeled albumin adheres to the functional vasculature of the pulmonary vessels. SPECT- LPI is thought to be a reasonable surrogate for lung function based on phantom (Osborne et al., 1982) and animal (Osborne et al., 1985) experiments. Lung function requires both perfusion and ventilation of alveoli. However, ventilation SPECT is more difficult than perfusion SPECT because of the inability to deposit high volumes of aerosol in the lung and rapid clearance. In addition to the practical considerations, perfusion imaging is clinically relevant to lung function because ventilation without perfusion is more common than perfusion without ventilation (West, 1992).

Only a few studies have incorporated SPECT-LPI images into the treatment-planning process for lung tumors (Marks et al., 1997; Garipagaoglu et al., 1999; Woel et al., 2002), and no study analyze the factors correlated with the better treatment plan. The current work presents an methodology for using SPECT-LPI to reduce dose to functioning lung. In this paper we investigated whether the additional information obtained by SPECT-LPI in the treatment planning process resulted in better treatment plans for patients with stage III NSCLC, and we investigated which factors were correlated with the better treatment plan according to using SPECT-LPI guidance.

Materials and Methods

Patient

39 patients with stage III NSCLC were enrolled from March 2006 to May 2009. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Shandong Cancer Hospital. Written informed consent was obtained from all participants. The median volume of PTV was 289 cm^3 (342±289 cm^3), and the median distance of PTV and NFL center was 2.50 cm (2.96±1.90 cm). The patients' demographic and clinical characteristics are summarized in Table 1. The staging of the tumors was based on the 1997 International Union Against Cancer (UICC) criteria (Sobin and Fleming, 1997).

Imaging and image co-registration

Simulation computer tomography was acquired with 4.5 mm-thick slices in a supine position on a PET/CT scanner (Discovery ST, GE Healthcare, Waukesha, WI). A vacuum pillow and a board with an arm-holding device were used to improve reproducibility of positioning. All scans had sufficient coverage to include the total lung volume during free breathing. Prior to the PET/CT scan, three '+' shape needle markers and aqueous 99mTc were

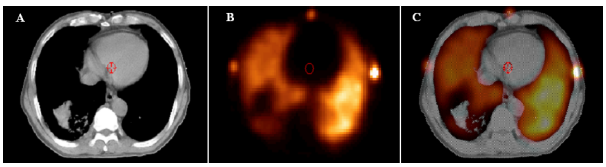

Figure 1. Marks in Three Kinds of Images. A) Marks in PET/CT images. B) Marks in SPECT images. C) Marks in co-registered images

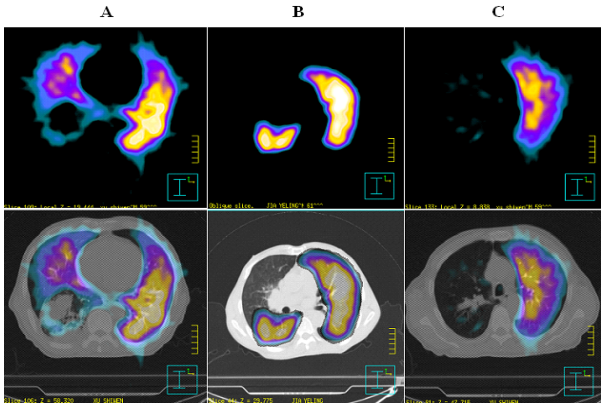

Figure 2. SPECT-LPI Lung Perfusion Deficit Grade. A) Grade 1. B) Grade 2. C) Grade 3

positioned on bony landmarks over the anterolateral surface of the patient's chest. Immediately following PET/CT, an intravenous injection of 200 MBq of 99mTc labeled macroaggregated albumin (MAA) was given and SPECT-LPI scans were acquired (Philips Medical Systems Fortee gamma camera) using low energy, high resolution collimators in the same position as that of the PET/CT simulation by lying in the same vacuum pillow. The pixel values of the SPECT-LPI, which were corrected for attenuation of the 99mTc 140-keV photon emissions, were directly proportional to the concentration of MAA trapped in the microvascular bed in the pulmonary parenchyma and, thus, are representative of relative pulmonary perfusion (Abratt et al., 1995; Boersma et al., 1995; Marks et al., 1997; Lavrenkov et al., 2007). The PET/CT and SPECT-LPI were co-registered manually in the Pinnacle3 version 7.4f (Philips Radiation Oncology Systems, Milpitas, CA) planning system (Figure 1).

Target volume definition

The PET/CT images were used to define the gross tumor volume (GTV) where the standardized uptake value (SUV) >2.5 (Hong et al., 2007). Body outline, whole lung (WL) as a single organ (excluding GTV), heart, esophagus and spinal cord were also outlined. The threshold level of the SPECT data was adjusted individually for each patient in order to match the size of the SPECT-LPI image to within the lung volumes defined on PET/CT. Functional lung (FL) refer to the region of ≥30% maximum radioactive counts and the other region was non-functional lung (NFL). Then SPECT-LPI were classified by comparing SPECT-LPI deficit with area of radiological abnormality. Grade 1 referred to the area of lung perfusion deficit similar to the size of radiological abnormality. Grade 2 referred to the area of lung perfusion bigger than the size of radiological abnormality, and extends to 1 pulmonary lobe. Grade 3 referred to the area

of lung perfusion deficit exceeding 1 pulmonary lobe (Figure 2).

Radiotherapy planning

IMRT plans were designed to deliver 64Gy to PTV using five equidistant coplanar or non-coplanar 15-MV X-ray beams. We designed two sets of IMRT plans for each patient. One was a regular IMRT plan using CT images only (Plan 1), and the other was a corresponding IMRT plan using co-registered images (Plan 2). In the plan 1, inverse planning was performed to minimize the volumes of normal lung, heart, esophagus, and spinal cord irradiated above their tolerance levels.In the plan 2, inverse planning was designed to minimize the volumes of functional lung in addition to the other planning objectives in the regular plan. Dose constraints and objectives are described in Table 2. Multiple iterative processes were involved until the objective functions were minimized and the treatment planning goals were met in both sets of plans.

Data collection and assessment of plans

The primary endpoint of this study was to compare the dose to FL for the two plans and to analyze the factors correlated with the treatment plan. according to using SPECT-LPI guidance. This would assess whether adding functional information to inverse planning for stage III NSCLC could bring about a significant reduction in the dose to the FL. For each patient, the grade of the SPECT-LPI deficit was collected. For each plan the following data was calculated: FLVx (the % volume of functional lung receiving ≥x Gy); WLVx (% volume of whole lung to receive ≥x Gy). To evaluate the quality of the plans in treating the lung tumors, the conformity index (CI) and heterogeneity index (HI) were computed on the basis of DVHs of the PTVs (Seppenwoolde et al., 2003). For the other thoracic structures, the volume of the esophagus irradiated to ≥55 Gy (EV55), heart to ≥40 Gy (HV40), and spinal cord to ≥45 Gy (SCV45) and maximal dose to them were also calculated in the dosimetric comparison of the two plans (i.e. Edmax, Hdmax, SCdmax). Data mean values were compared using paired Student's t test. Kendall correlation was used to analyze the factors related with the FL_{V20} decrease. The dosimetric parameters of the two sets of plans described were compared using descriptive statistics. Differences were reported to be statistically significant at P≥0.05. Statistical analysis was performed using SPSS software version 11.0.

Table 1. Patient Characteristics

Characteristics		Case (n)
Gender	Male	35
	Female	4
Age (y)	Median	61
	Range	34-77
Histologic type	Adenocarcinoma	12
	Squamous cell carcinoma	27
Stage	IIIA	20
	IIIB	19
Location	Right upper lobes	15
	Right middle lobes	2
	Right lower lobes	6
	Left upper lobes	12
	Left lower lobes	0
	Hilar areas	4
SPECT-LPI	1	14
deficits grade	2	13
	3	12
The number of NFL	Single	27
	Multiple	12

Results

Imaging FL

Thirty-nine patients were consented for the study; all of these patients accomplished the simulation CT and the SPECT-LPI scan and co-registered manually in the Pinnacle3 version 6.0 m planning system. The accuracy of the co-registration was very important for the plan 2. Because the SPECT images were functional, no anatomic sign could be used to co-register. In our study, simulation CT and SPECT-LPI were co-registered by the markers which were positioned on the same bony landmarks over the anterolateral and lateral surface of the patient's chest before the PET/CT and SPECT-LPI scanned. The study should be performed to improve the accuracy even though the co-registration images were approving. In our study, all patients had lung perfusion deficits, the grade of lung perfusion deficits see Table 1.

Parameters comparison

Seventy-eight RT plans of 39 patients were available for analysis. In the SPECT-guidance plan 2, both WLVx and FLVx were decreased. WL_{V10}, WL_{V15}, WL_{V20}, WL_{V25}, WL_{V30} and WL_{V35} decreased 9.7%, 13.8%, 17.2%, 12.9%, 9.8% and 9.8%, while FL_{V10}, FL_{V15}, FL_{V20}, FL_{V25}, FL_{V30} and FL_{V35} decreased 10.8%, 14.6%, 17.3%, 14.5%, 14.5% and 10.5%. Thus the FLVx was decreased more significantly. There were significant difference in WL_{V10}, WL_{V15}, WL_{V20}, WL_{V25}, WL_{V30} and FL_{V10}, FL_{V15}, FL_{V20}, FL_{V25}, FL_{V30} between the plan 1 and plan 2 (P=0.002, 0.000, 0.000, 0.005, 0.027

Table 2. Table 2. Inverse Planning Objectives When no SPECT-LPI Information is Incorporated-used for Plans Land SPECT-LPI Information for Plans 2

Objective	
Plans 1	Minimize whole lung volume receiving ≥20Gy
Plans 2	Minimize functional lung volume receiving ≥20Gy
Constraints	
PTV	64Gy to 90% of PTV
Spinal cord	Maximum dose <45Gy
Heart	mean dose <40Gy
Esophagus	Maximum dose <60Gy

Table 3. The WL_{Vx} , FL_{Vx} and OAR of Patients Between Plan 1 and Plan 2 ($\bar{\chi}$±s)

Plan	WL_{V10} (%)	WL_{V15} (%)	WL_{V20} (%)	WL_{V25} (%)	WL_{V30} (%)	WL_{V35} (%)	FL_{V10} (%)	FL_{V15} (%)	FL_{V20} (%)	FL_{V25} (%)	FL_{V30} (%)	FL_{V35} (%)	H_{V40} (%)	E_{V55} (%)	E_{dmax} (cGy)
1	51.29±10.73	37.13±6.73	28.33±4.75	22.58±4.78	18.58±4.41	14.92±4.70	48.21±11.28	33.17±8.75	24.63±6.04	19.63±5.93	16.46±5.88	13.00±5.63	6.93±1.30	13.97±2.50	5018±184
2	46.33±10.72	32.00±6.40	23.46±3.79	19.67±3.64	16.75±3.77	13.46±3.66	43.00±11.81	28.33±7.98	20.38±4.49	16.79±4.54	14.08±4.21	11.63±4.40	7.36±1.39	14.38±2.58	5070±170
t	3.479	5.095	5.119	3.122	2.366	1.821	3.503	5.468	4.779	3.047	2.827	1.925	0.929	1.693	0.711
P	0.002	0	0	0.005	0.027	0.082	0.002	0	0	0.006	0.01	0.067	0.359	0.099	0.482

and 0.002, 0.000, 0.000, 0.006, 0.010). Compare with plan 1, EV55, SCV45, HV40, Edmax, Hdmax and SCdmax increased in plan 2, but all of them had no significant difference between plan 1 and plan 2 (Table 3).

Factors analysis

According to Kendall correlation analysis, agenda, age, histologic type, stage, location, SPECT-LPI deficits grade and PTV volume had no relation with the percentage of FL_{V20} decrease. The number of NFL had negative relation with the percentage of FL_{V20} decrease significantly (r=-0.559, $P<0.01$), while the distance of PTV and NFL center had positive relation with the percentage of FL_{V20} decrease significantly (r=0.768, $P<0.01$).

Discussion

The primary aim of this study was to assess whether the incorporation of functional lung information into radiotherapy planning could be exploited by an inverse planning system to create IMRT plans which would reduce the dose to 'healthy' functioning lung, the secondary aim of this study was to find the factor which could reduce the dose to functional lung significantly according to using SPECT-LPI guidance. The validity of the dose-volume data in this study depended on the accuracy of co-registering the two sets images of PET/CT and SPECT-LPI, because the purpose of IMRT planning was to minimize the dose to FL defined by SPECT-LPI. This study matched images using a visual iterative manual technique according to the scans of three external skin markers. To ensure the same position for both scans and treatment, a vacuum pillow was used for patient immobilization. Of course, there was some limit in this method. We were studying the method to improve the accuracy of matching the two sets images, for example, using more than three external skin markers in different lateral skin.

The threshold settings for SPECT-LPI are uncertain when they are to be registered to CT images. Finding the correct setting is crucial particularly when used for radiotherapy planning, as accurate volume definition is required. This study had taken a similar pragmatic approach as other authors by adjusting the threshold level to match the lung contours until the best fit is obtained. Similar volume definition issues arise when FDG-PET is used in combination with CT for radiotherapy planning where the tumour size using PET may be over-estimated rather than underestimated (Kubota et al., 1992) although an attenuation-corrected method may be used to improve the accuracy of tumour measurements (Zasadny et al., 1996). Furthermore, the threshold settings for FL are very important because the primary aim of this study was to reduce the dose to functioning lung provided by SPECT-LPI exploited by an inverse planning system to create IMRT plans. Some authors thought that <30% of the maximum perfusion counts areas were poorly function (Kwa et al., 1998; Seppenwoolde et al., 2000), thus the FL referred to the region of ≥30% maximum perfusion counts and the other region was (NFL) in this study.

All patients had a reduction in volume, when the whole lung volume was compared to the volume of the lung that was deemed 'functional' on SPECT-LPI, ie, all patients had lung perfusion deficits. In this study, of them, 14 patients with grade 1 damage, 13 patients with grade 2 damage, and 12 patient with grade 3 damage. This implies that none of the SPECT-LPI were entirely normal and in each patient it reflected a level of lung dysfunction, perhaps due to atelectasis or underlying chronic lung disease. With the addition of accurately co-registered functional information to the radiotherapy planning CT data, significant reduction in the dose to the whole lung and functional lung was found when this was specified as the main objective during inverse planning, especially FL_{V20} and WL_{V20} which were the major factor correlated with radiation pneumonitis. So it might be helpful to decrease the percentage of radiation pneumonitis. Although the dose to organ at risk increased in plan 2 compared to plan 1, all of them had no significant difference. In order to select those patient benefited from the SPECT-LPI incorporated into PET/CT, the study explored the factor correlated with the decrease of FL_{V20} furthermore. This study appeared to the reduction of FL_{V20} correlated with the distance of PTV and NFL center, i.e., the farther distance of NFL from the tumor, the more obvious reduction in WLVx and FLVx. It would seem reasonable that large defects allow the inverse planning system to find alternate sites of entry and exit for the radiotherapy beams. Without SPECT-LPI information available to the inverse planning system, the beams passed through a large area of functional contralateral lung (Plan 1). Incorporating functional lung data into the inverse planning protocol, the area of functional lung can be avoided (Plan 2). (see Figure 1 and 2). In Plan 2, the rate of reduction was greater for FL_{V10}, FL_{V15}, FL_{V20}. It indicated that lower radiation dose to the normal lung tissue gained better protection. Yuan et al. (2011) found that it was difficult to generate detailed conclusions about which patients are most likely to benefit from CT and SPECT-LPI fusion during radiotherapy planning, and most of patients, perfusion defects were patchy and non-uniform, so it was usually not possible to find beam directions that can adequately avoid the functioning tissue and deliver dose through the non-functioning tissue. This study implied more obvious reduction in FL_{V20} with the simple NFL than multiple NFL.

In a word, the routine use of SPECT-LPI for patients undergoing radiotherapy planning for stage III NSCLC was warranted, especially for simple NFL and more distance of PTV and NFL center.

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