RESEARCH COMMUNICATION

Feasibility of Shrinking Field Radiation Therapy through 18F-FDG PET/CT after 40 Gy for Stage III Non-Small Cell Lung Cancers

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Abstract

<u>Objective</u>: To explore the feasibility of shrinking field technique after 40 Gy radiation through 18F-FDG PET/CT during treatment for patients with stage III non-small cell lung cancer (NSCLC). <u>Methods</u>: In 66 consecutive patients with local-advanced NSCLC, 18F-FDG PET/CT scanning was performed prior to treatment and repeated after 40 Gy. Conventionally fractionated IMRT or CRT plans to a median total dose of 66Gy (range, 60-78Gy) were generated. The target volumes were delineated in composite images of CT and PET. Plan 1 was designed for 40 Gy to the initial planning target volume (PTV) with a subsequent 20-28 Gy-boost to the shrunken PTV. Plan 2 was delivering the same dose to the initial PTV without shrinking field. Accumulated doses of normal tissues were calculated using deformable image registration during the treatment course. <u>Results</u>: The median GTV and PTV reduction were 35% and 30% after 40 Gy treatment. Target volume reduction was correlated with chemotherapy and sex. In plan 2, delivering the same dose to the initial PTV could have only been achieved in 10 (15.2%) patients. Significant differences (p<0.05) were observed regarding doses to the lung, spinal cord, esophagus and heart. <u>Conclusions</u>: Radiotherapy adaptive to tumor shrinkage determined by repeated 18F-FDG PET/CT after 40 Gy during treatment course might be feasible to spare more normal tissues, and has the potential to allow dose escalation and increased local control.

Keywords: Radiotherapy - 18F-FDG PET/CT - non-small cell lung cancer - shrinking field radiation

Introduction

Non-small cell lung cancer (NSCLC) is one of the most common malignant diseases. At diagnosis, a large number of patients were in Stages IIIa or IIIb. For these patients with tumors unresectable or not radically resectable or inoperable for medical reasons, combined chemoradiotherapy is the standard of care, but the prognosis remains dismal, and many patients died with loco-regional failure or distant metastasis (Kim et al., 2005). Higher radiation doses result in a higher probability of local tumor control and hence prolonged survival (Rengan et al., 2002; Rengan et al., 2004). Every 1 Gy above the conventional prescription dose would improve the 3- to 5-year survival rate by approximately 1% and would decrease the hazard from death by 3% (Kong et al., 2005). However, dose escalation is limited because of several vital normal tissues toxicity (Bradley et al., 2005; Belderbos et al., 2006), such as lung, esophagus, spinal cord, heart and so on.

Modern radiotherapy technologies, such as three-dimensional conformal radiation therapy (3D-CRT) and intensity modulation radiation therapy (IMRT), have the potential to provide a dose distribution to the target with a much steeper dose gradient, which increases the dose to the target and minimises the irradiated volume of normal tissue. Continuous tumor regression during the course of conventionally fractionated radiotherapy or combined chemoradiotherapy for locally advanced NSCLC is well known (Britton et al., 2007; Guckenberger et al., 2011). This shrinkage of the gross tumor volume (GTV) indicates that irradiation field shapes and field sizes could or should be adapted during the treatment course, thus NSCLC patients are re-imaged and re-planned during the treatment is a possible strategy to improve treatment delivery. It is reported that if GTV decreases by greater than 30% at any point in the first 20 fractions of treatment, i.e., 40Gy, it may be appropriate to adapt the plan to improve sparing of normal tissues, adaptive planning is appropriate to further improve the therapeutic ratio (Woodford et al., 2007).

On the other hand, acurate delineation of the primary tumor and involved lymph nodes is a key requisite for

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Table 1. Patient and Clinical Characteristics

Characteristics		N (%)
Gender	Male	55 (83.3)
	Female	11 (16.7)
KPS	70-80	25(37.9)
	90-100	41(62.1)
Type of cancer	Central	39(59.1)
	Peripheral	27(40.9)
Pathology	Squmous cell carcinoma	36(54.5)
	Adenocarcinoma	20(30.3)
	Non-small cell without further specification	10(15.2)
TNM stage*	Stage IIIa	27(40.9)
	Stage IIIb	39(59.1)
T stage	T1	8(12.1)
	T2	14(21.2)
	T3	8(12.1)
	T4	36(54.5)
N stage	N0	5(7.5)
	N1	6(9.1)
	N2	35(53.0)
	N3	20(30.3)
Adjuvant	Yes	61(92.4)
chemotherapy	No	5(7.6)

KPS, Karnofsky performance status; *TNM, stage consulting the new 7th edition of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) tumor-node -metastasis (TNM) lung cancer staging

precise radiotherapy. It is demonstrated that 18F-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET) can help delineating the target volume accurately for radiation therapy planning (Nestle et al., 2006; van Baardwijk et al., 2007). The reason is that 18F-FDG PET can reveal the malignant aggressiveness of a tumor based on preferential FDG accumulation in malignant tissues with increased glucose uptake and metabolism. It is thought to assist in differentiating malignant pulmonary nodules from benign nodules and in detecting regional lymph nodes (N-staging) or distant metastasis (M-staging) (Gilman et al., 2005). Therefore, during the clinical practice of radiation therapy for patients with Stage III NSCLC in our institution, 18F-FDG PET is regularly applied in target volume delineation. In the current study, we sought to quantify the degree of tumor volume change during radiotherapy course, with the goal of assessing the feasibility of individualized shrinking field technique in sparing normal tissues during treatment.

Materials and Methods

Patients

The current study was based on 66 consecutive patients (55 male, 11 female), with the median age of 62 years (range, 34 -82 years), treated in Shandong Cancer Hospital, between May 2008 and March 2011. All the patients satisfied the following rules: (1) histologically or cytologically confirmed proof; (2) clinical stages of IIIa or IIIb; (3) Karnofsky performance status (KPS) ≥70; (4) no prior therapy; (5) lung function satisfying vital capacity ≥70% and forced expiratory volume ≥60%. Exclusion criteria were patients with distance metastasis. All of the patients recruited into this study were treated with 3D-CRT or IMRT. Among the primary, advanced-stage NSCLC

66 patients, 61 patients were treated with concurrent chemoradiotherapy with a cisplatin-based regimen, while the other 5 cases received radiotherapy only. Patients and tumor characteristics are summarized in Table 1.

18F-FDG PET/CT image and target delineation

18F-FDG PET/CT (Discovery LS PET/CT system; GE Healthcare) was used before treatment for staging and treatment planning. All patients fasted and rested for at least six hours before undergoing PET/CT. Serum glucose level was measured to ensure the value was less than 6.6 mmol/L. Patients didn't received urinary bladder catheterization, oral muscle relaxants or CT contrast agents. Forty-five to sixty minutes after the intravenous injection of 370 MBq (10 mCi) of 18F-FDG, PET emission images were acquired from the level of the middle skull to the proximal thigh for 5 minutes per field of view, each covering 14.5 cm, at an axial sampling thickness of 4.25 mm per slice. The spiral CT component was performed with an x-ray tube voltage peak of 120 kV, 90 mA, a 6:1 pitch, a slice thickness of 4.25 mm, and a rotation speed of 0.8 s per rotation. A full-ring dedicated PET scan of the same axial range followed. Both the PET and the CT scans were obtained during normal tidal breathing. The total acquisition time varied between 25 and 35 min per patient. PET images were reconstructed with CT-derived attenuation correction using the ordered-subset expectation maximization (OSEM) algorithm. The attenuation-corrected PET images, CT images, and fused PET/CT images displayed as coronal, sagittal, and transaxial slices were viewed on a Xeleris workstation (GE Healthcare). 18F-FDG PET/CT scanning was repeated after 4 weeks treatment, i.e., 40Gy of radiation therapy.

PET/CT images were transferred to the Eclipse treatment planning system (TPS, Varian Medical Systems, Palo Alto, CA, USA) via DICOM. The gross tumor volume (GTV) was delineated on the CT images, combined with FDG metabolism of PET images. The primary tumor was delineated on a lung window setting (-600 HU, 1000 HU) and the lymph nodes on mediastinal setting (40 HU, 400 HU) and central necrosis within the tumor was not excluded from GTV. Lymph nodes were defined to be involved if the short axis was larger than 10 mm on CT, or if they had high FDG-avidity in PET images, and the edge of the lesion was established by an the standard uptake value (SUV) contour of 2.5 (Hong et al., 2007). To consult our previous study (Li et al., 2011), the clinical target volume (CTV) was auto-generated by adding 5 mm to GTV in all directions for squamous cell carcinoma, and 7 mm for adenocarcinoma or other types of NSCLC. The planning target volume (PTV) was CTV plus a 5 mm margin in all planes. And the PTV of lymph nodes was defined as involved nodes plus 8 mm in all directions. No elective irradiation of the lymphatic regions was conducted. The same steps were performed on the first images of treatment planning as well as on the images taken after 40Gy. The targets would be modified adapting to tumor volume change. Total lung was contoured by combining single photon emission computed tomography (SPECT) lung perfusion and PET-CT images. Lung with the maximum radioactive counts ≥30% was defined as

functional lung (Seppenwoolde et al., 2000), and was evaluated in the current study. The esophagus included from pharynx to the cardiac. The spinal cord included the entire levels of scanning. The heart included the apex of both atria to the most caudal part of the left ventricle and excluded the great vessels.

Treatment planning

An IMRT plan was implemented when a 3D-CRT plan could not meet the treatment planning goals, and SPECT lung perfusion imaging was used to optimize the plans. The total dose was from 60 to 78 Gy (median 66 Gy) individually, according to the medical or psychological conditions of the patients in our study. Plan 1 was delivering a dose of 40 Gy to the initial PTV followed by a boost of 20-38 Gy to the shrunken targets, and both the two phases treatment were implemented by 2.0 Gy/fraction, 5 fractions a week. Plan 2, a dose of 60-78 Gy prescribed to the initial PTV in one phase, using the same time dose fractionation and the same planning methods as plan 1, but it was optimized without shrinking field technique. Dose was prescribed to the 90% isodose line with lung correction for inhomogeneity, which encompassed at least 95% of the PTV. Using a surface-based algorithm of deformable image registration, accumulated doses were calculated in the PET/CT images acquired during the treatment course. The use of deformable image registration for dose accumulation allows for voxel-based ''tracking'' of delivered doses across varying anatomic states.

Accepted measures in normal tissue toxicity included a maximum dose to the spinal cord (SCmax) of 45 Gy and to the esophagus of 75 Gy, the volume percentage of esophagus exceeding 60 (V60) $\leq$ 30%(Kim et al., 2005), total mean lung dose (MLD) $\leq$ 20 Gy, the volume percentage of normal lung exceeding 20 Gy (V20) (both lungs minus PTV) $\leq$ 35% for patients receiving radiotherapy only, $\leq$33% for patients treated with chemoradiotherapy, the volume percentage of the whole heart exceeding 65 (V65) and 45 (V45) $\leq$33% and 67%, the volume percentage of liver exceeding 35 (V35) $\leq$ 50%, and the maximum dose to the gastric of 50 Gy.

The chemotherapy regimens used for 61 patients in this study were cisplatin/gemcitabine, cisplatin/docetaxel, cisplatin/vinorelbine, and cisplatin/pemetrexed. These chemotherapy regimens were known to possess similar activity and effectiveness for treatment of NSCLC and were combined with radiotherapy.

Data collection and statistical analysis

Target volumes (including GTV and PTV), prior to and after 40 Gy radiotherapy, were calculated by the treatment planning system (Pinnacle version 8.0). A statistical analysis was performed using commercial software SPSS for Windows (version 16.0). The correlation between the reduction of target volume and the patient/tumor related factors was investigated using multi-factor analysis of variance. A wilcoxon signed-rank test was used to compare parameters of dose-volume histogram (DVH) between the two plans. The statistical difference was considered significant at p <0.05.
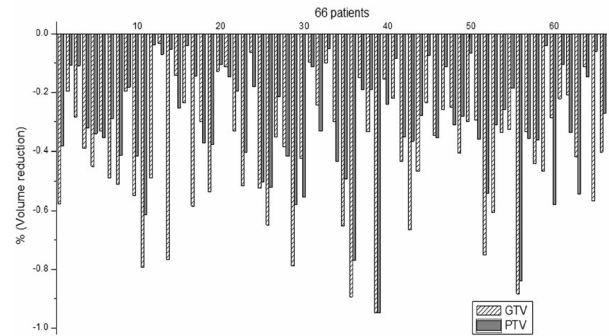
Figure 1. Percentage of Reduction in Gross Tumor Volume (GTV) and Planning Target Volume (PTV) Following 40 Gy (when Compared to Pre-Treatment Values)
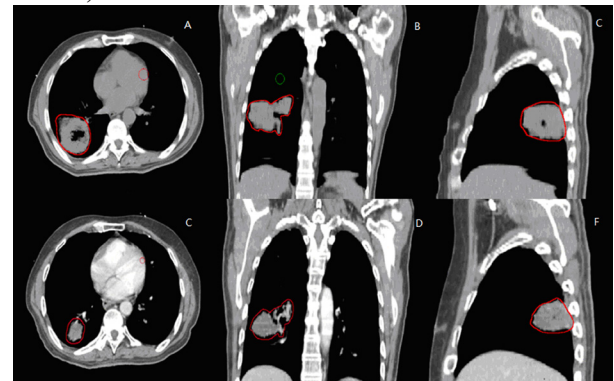

Figure 2. Example of Patient with Tumor Volume Reduction. The patient's initial (A, B, C) and subsequent (C, D, E) gross tumor volume (GTV) were 328 and 219 cm , respectively. The GTV reduction was 33.2%

Results

Tumor shrinkage led to the reduction of target volume during treatment, which was observed in all patients and shown in Figure 1. The median PET/CT-delineated initial GTV (tumor and lymph nodes) was 167 cm^3 (range, 14-968 cm^3) and this reduced to 87 cm^3 (range, 10-766cm^3) when 40Gy delivered to the targets, with a median reduction of 35% (range, 3-95%). The median PTV reduced from initial 505 cm^3 (range, 82-1350 cm^3) to 330 cm^3 (range, 51-896 cm^3) after 40 Gy irradiation, with a median reduction of 30% (range 4-95%). Figure 2 was an example who had significant shrinkage of tumor volume.

The correlation between the reduction of target volume and the patient/tumor related factors was investigated. Only chemotherapy and sex were correlated with PTV reduction (p=0.037, 0.038), none of other analyzed variables, including age, KPS, type of cancer, pathology and TNM stage, was significantly (multi-factor analysis of variance) associated with the reduction of target volume. Through comparing the two plans, delivering the same total dose to the initial PTV without shrinking field technique after 40 Gy, could have been achieved in 15.2% (10/66) patients. Of the remaining 56, it would exceed normal tissue tolerance parameters, for lung 42.4% (n = 28), esophagus 21.2% (n = 14), heart 3.0% (n = 2), and spinal cord 51.5% (n = 34). Table 2 compared the

Table 2. DVH Parameters of Plan 1 and Plan 2 (n=66)

Parameters	Plan 1		Plan 2		p value[*]
	Mean	Median	Mean	median	
MLD (Gy)	15.9	15.5	17.2	16.9	0.039
V20 of the lung (%)	29.4	31	31.6	32.1	<0.001
V60 of the esophagus (%)	19.9	19	22.8	22	<0.001
SCmax (Gy)	40.2	43.4	43.3	46	<0.001
V45 of the heart (%)	15	14.3	15.5	14.7	0.012
V65 of the heart (%)	2.3	2.7	2.5	3	0.033

DVH, dose-volume histogram; MLD, mean lung dose; Vx, the volume percentage of normal tissue exceeding x Gy; SCmax, the maximum dose of the spinal cord; [*]p values result from a Wilcoxon signed-rank test comparing plan 1 and plan 2

parameters collected from DVH for plan 1 and plan 2, and the mean and median values were shown. Due to the partial normal distribution of the DVH parameters in the two plans, a wilcoxon signed-rank test was used. All the dose volume parameters of plan 2 were higher than plan 1 (p<0.05). By the way, the maximal prescription dose to PTV of plan 1 was 68.5 Gy ± 8.2 Gy, while that of plan 2 was 61.9 Gy ± 8.6 Gy.

Discussion

Unresectable, locally advanced, stage III NSCLC remains a therapeutic challenge to radiation oncologists. In curative radiotherapy, modern techniques have been used to deliver high doses to the target and spare the normal tissues. In order to generate highly accurate radiation treatment plans, precise target delineation is essential. There is a strong case for the routine use of FDG-PET in radiation therapy planning for NSCLC, and the two most important and consistent reasons for applying PET in target volumes in NSCLC were listed (MacManus et al., 2009). On one hand, FDG-PET significantly changed lymph node staging in the thorax, usually by showing more positive nodes than CT. On the other hand, in cases with atelectasis, PET helped to demarcate the border between tumor and collapsed lung, allowing a smaller volume of lung to be treated (Nestle et al., 1999). On the basis of high FDG-avidity, the target volumes for the initial and after 40 Gy irradiation were delineated in the fused PET/CT images, we expected to verify that shrinking field technique after 4 weeks' radiation therapy would be feasible to reduce doses to normal tissues. In our results, applying repeated PET/CT scanning for NSCLC patients in the course of radiotherapy, we have recorded substantial reductions in the radiologic extent of disease occurring after 40 Gy during treatment. The median GTV reduction was 35%, range between 3% and 95%, at receiving treatment dose of 40 Gy. Similar results have been obtained before. Fox et al. (2009) showed in their study that the GTV had a median reduction of 24.7% at dose of 30 Gy and of 44.3% at dose of 50 Gy. In addition, Guckenberger et al. (2011) reported continuous tumor regression by 1.2% per day was measured in CT images of 13 patients treated for NSCLC, which was in very good agreement with the data of Kupelian's research (Kupelian et al., 2005).

It was concluded that the treatment outcomes were more promising to lung cancer patients if being treated with chemoradiotherapy than receiving radiotherapy alone (Kim et al., 2002). Similarly, our result showed that patients receiving concurrent chemoradiotherapy would have more significant reductions in target volumes than those who were treated with radiotherapy alone. However, Fox et al. (2009) reported no difference in tumor regression between radiotherapy and chemoradiotherapy. We have only five patients treated with radiotherapy only, thus it needed to be further researched. On the other hand, our data also suggested PTV reduction rate was more significant in male patients than female, which also required further studying due to the small sample size of female patients.

Incidence rates of complications rise with increasing dose, but fall with decreasing irradiated volume. Shrinking field radiation allowed substantial dose escalation to be achieved using modern techniques (Guckenberger et al., 2011), without raising the incidence of these complications beyond acceptable levels. In the current study, the same dose to targets in plan 2 would be limited due to normal tissues exceeding their constraints. Thus tumor shrinkage determined by the second FDG PET/CT during treatment was thought to be beneficial to protect organs at risk and result in improvement on dose escalation, which was also suggested by Gillham (2008). The Radiation Therapy Oncology Group (RTOG) 94-01 trial established that 60 Gy was the optimal dose for local advanced NSCLC, with 4-year survival rate of 21% and median survival rates of approximately 17 months (Curran et al., 2003). Several recent studies (Curran et al., 2003; Blackstock et al., 2006) suggested that 74 Gy delivered to locally advanced NSCLC with concurrent chemotherapy may be safe and feasible, with improved survival time and acceptable toxicity rates. It indicated that dose escalation to the primary tumor was necessary. Moreover, in our study, the shrinking field technique allowed a prescription dose escalation of the PTV from 61.9 Gy ± 8.6 Gy to 68.5 Gy ± 8.2 Gy. The benefits to treatment outcome of shrinking field radiotherapy after 40 Gy are being further studied as another part. To our knowledge, this is the first study using shrinking field technique after 40 Gy radiation based on PET/CT imaging.

There are several limitations to this study. Firstly, shrinking field radiation therapy after 40 Gy might lead to omission of some small positive lymph nodes irradiation. Secondly, concurrent chemoradiotherapy was given to 61 patients. Chemotherapy may have lead to a marked reduction in FDG-avidity (Eschmann et al., 2007) and this would have potentially increased the risk of a geographical radiotherapy miss. To handle the above two problems, careful contrast of initial and repeated PET/CT images were conducted by at least two experienced oncologists. Thirdly, because of the small sample size, large clinical randomized controlled trials would be necessary.

In conclusion, during the treatment course, radiation treatment planning change adapting to tumor shrinkage, as determined by repeated FDG PET/CT after 40 Gy, might be feasible to spare more normal tissues, and has the potential to allow dose escalation and increased local control.

Acknowledgements

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