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Original article

# Differences in lung injury after IMRT or proton therapy assessed by $^{18}$FDG PET imaging

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ABSTRACT

*Background and purpose:* To compare lung injury among non-small cell lung cancer (NSCLC) patients treated with IMRT or proton therapy as revealed by $^{18}$F-FDG post-treatment uptake and to determine factors predictive for clinically symptomatic radiation pneumonitis.

*Material and methods:* For 83 patients treated with IMRT or proton therapy, planning CT and follow up $^{18}$F-FDG PET-CT were analyzed. Post-treatment PET-CT was aligned with planning CT to establish a voxel-to-voxel correspondence between PET and planning dose images. $^{18}$F-FDG uptake as a function of radiation dose to normal lung was obtained for each patient. PET image-derived parameters as well as demographic, clinical, treatment and dosimetric patient characteristics were correlated with clinical symptoms of pneumonitis.

*Results:* The dose distributions for the two modalities were significantly different; V5 was higher for IMRT, whereas V60 was higher for protons. The mean lung dose (MLD) was similar for the two modalities. The slope of linear $^{18}$F-FDG-uptake – dose response did not differ significantly between the two modalities. The MLD, slope, and 95th percentile of SUV were identified as three major factors associated with radiation pneumonitis.

*Conclusions:* Despite significantly different dose distributions for IMRT and for protons, the slope of the SUV–dose linear regression line previously shown to be associated with RP did not differ between IMRT and protons. Patients who developed radiation pneumonitis had statistically significantly higher MLD and higher slope regardless of treatment modality.



Lung cancer remains the most morbid cancer worldwide [1,2]. The results of standard treatment are quite poor except for early-stage disease and localized tumors. In patients with advanced-stage disease, radiation therapy in combination with chemotherapy is considered a modality of choice but is unfortunately successful in only 45–55% of the patients due in part to a high rate of local recurrence [3]. The effectiveness of radiotherapy may be improved with escalation of radiation dose, however, treatment associated toxicities often diminish the gain. The major toxicity that occurs in nearly 30% of patients receiving chemotherapy and radiation therapy for advanced non-small cell lung cancer (NSCLC) is radiation pneumonitis (RP) [4].

RP is an inflammatory reaction to ionizing radiation with infiltration of macrophages, leak of fluid to the alveoli in the irradiated area. The $^{18}$F-fluoro-2-deoxyglucose (FDG) positron emission computed tomography (PET/CT) is an effective method for visualizing the inflammatory process. Pulmonary inflammation manifests on FDG PET/CT as enhanced $^{18}$F-FDG uptake, which enables quantitative assessment of RP [5,6]. Although increased $^{18}$F-FDG uptake in the lungs is linked with several inflammatory processes [7–9], high and diffuse uptake after the completion of radiation therapy had been reported for patients who developed RP [10,11] suggesting that $^{18}$F-FDG uptake could be considered as a surrogate measure of lung injury.

Proton therapy offers better sparing of normal organs distal to the target due to much lower exit dose, and it is therefore a promising modality to reduce the risk of RP. At the same time, proton range uncertainty requires increased margins around the target, reducing conformity of dose distribution making the benefit of proton therapy for locoregional NSCLC debatable [12,13]. Recently, a phase II multi-center Bayesian randomized trial of image-guided adaptive conformal photon vs. proton therapy with concurrent chemotherapy for locally advanced NSCLC was

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completed [14]. The data collected in the trial offered an opportunity for quantitative analysis to assess radiotherapy toxicity and compare treatment outcome of the two modalities.

In this study, we correlated lung injury that gives rise to inflammatory processes manifested by increased $^{18}$F-FDG uptake with clinical symptoms of radiation pneumonitis, and focused on comparison of magnitude of that inflammatory response after either intensity modulated radiation therapy (IMRT) or passively scattered proton therapy.

## Material and methods

### *Patients*

Eighty-three patients treated at the University of Texas MD Anderson Cancer Center for lung cancer between August 2009 and June 2014 were selected for this retrospective study. They were enrolled into the randomized trial on comparative assessment of IMRT and proton therapy for advanced NSCLC. Eligibility for this study included inoperable stages II–III and a subset of stage IV patients defined with a single or oligo-metastasis to the brain that was treated with either resection or stereotactic radiosurgery, and those with local or loco-regional recurrence after surgery for the original tumor. They were treated with fractionated standard dose radiotherapy and chemotherapy of curative intent. The patients were randomized into two groups by Bayesian randomization [15,16]; one group treated with IMRT and another group treated with passively scattered proton therapy. All patients had planning CT and follow up $^{18}$F-FDG PET-CT imaging. Follow up PET-CT scans were acquired at median 48 days (25–116 days) after completion of radiotherapy.

Clinical symptoms of pneumonitis were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 (CTCAE v3). RP was scored for 12 months from the completion of radiotherapy. The consensus of up to six clinicians was used for scoring each patient. Clinically symptomatic pneumonitis was defined as grade 2 or higher by CTCAE v3; please also refer to the NCT00915005 for the details of RP scoring.

### *Treatment planning*

The trial protocol required treatment plans for 74 Gy/37 fractions for both IMRT and proton therapy for each patient before randomization. Relative biological effectiveness (RBE) was set to 1.1 for protons. Patients were eligible for randomization only if both plans achieved target coverage greater than 95% while dose constraints of organs-at-risk were met at the same prescription dose of 74 Gy; if the constraints could not be met, the prescription dose was reduced to 66 Gy. The planning constraints for the organs-at-risk, common for the two arms, are listed in Supplementary Material Table S1.

The internal gross tumor volume (iGTV) was defined on the maximum intensity projection of the 4DCT to take into account tumor motion associated with respiration. The internal clinical target volume (iCTV) was created by adding a margin of 0.8 cm to iGTV. The iCTV was then modified to remove overlap with the heart and vertebral bodies.

Proton treatment planning was performed using a passive scattering method on Varian's Eclipse proton therapy system (Varian Medical Systems, Palo Alto, CA). Brass aperture blocking was used with 1.3 cm expansion of iCTV; the margins were adjusted to achieve a desired coverage of the target. The custom range compensators were made with a 5 mm drill bit. The distal range margin was defined as distal range $\times$ 3.5% + 2 mm, the proximal margin was defined as (distal range – spread-out Bragg peak (SOBP)) $\times$ 3.5% + 2 mm [17]. The compensators were smeared to account for range variations. Additionally, CT image intensities inside iGTV were replaced by 50 HU to compensate for the density variation due to breathing motion [18]. IMRT plans were generated in Pinnacle (Philips Radiation Oncology Systems, Fitchburg, WI). The planning target volume (PTV) was created by adding 0.5 cm to iCTV.

### *Image analysis*

The image processing was performed using open-source platform 3D Slicer [19] and our in-house software package Plastimatch [20]. The lung label-map was taken from the planning CT, and then

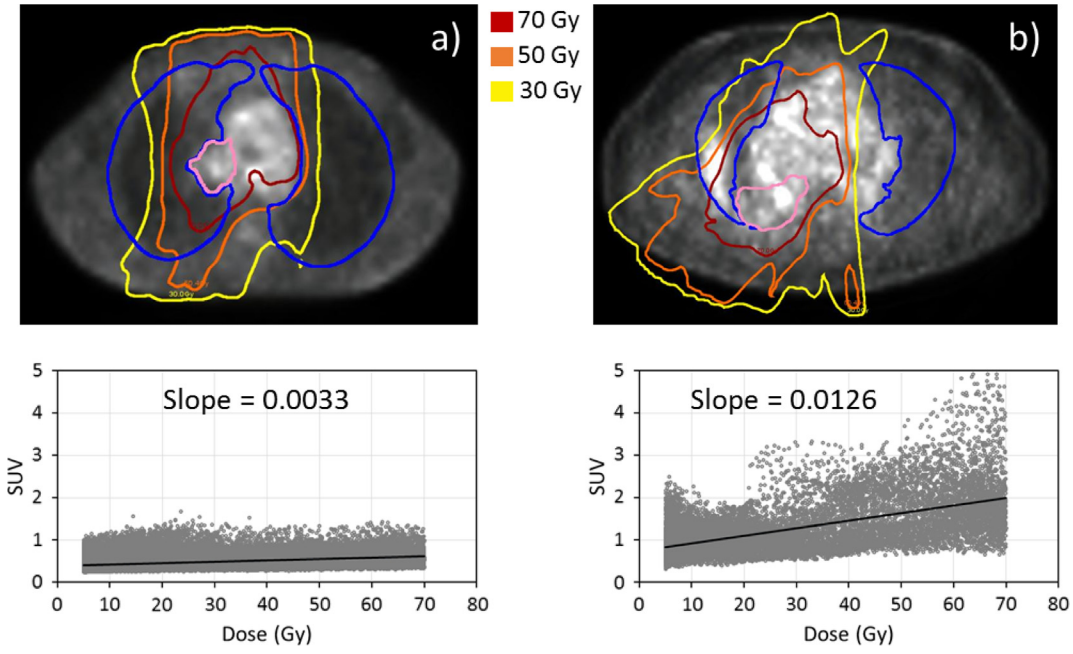


**Fig. 1.** $^{18}$F-FDG PET image overlaid with isodose lines of planning dose distribution (upper row) and SUV vs. dose dependence with a linear regression line (lower row) for two patients treated by IMRT (a) showing Grade I symptoms of radiation pneumonitis and (b) showing Grade II symptoms of radiation pneumonitis. Lung contours are shown in blue and GTV contours are shown in pink. The slope of linear regression line of $^{18}$F-FDG PET response is higher for the patient exhibiting higher grade symptoms of RP. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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