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[¹⁸F]-FDG UPTAKE DOSE RESPONSE CORRELATES WITH RADIATION PNEUMONITIS IN LUNG CANCER PATIENTS

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Abstract

Purpose—To quantify the post-radiotherapy 2-[¹⁸F]-fluoro-2-deoxyglucose (FDG) pulmonary uptake dose-response in lung cancer patients and determine its relationship with radiation pneumonitis symptoms.

Methods and Materials—The data from 24 patients treated for lung cancer with thoracic radiotherapy who received restaging PET/CT imaging between 4 and 12 weeks after radiotherapy completion were evaluated. Their radiation dose distribution was registered with the post-treatment restaging PET/CT. Using histogram analysis, the voxel average FDG-PET uptake versus radiation dose was obtained for each case and linear regression was performed. The resulting slope, the pulmonary metabolic radiation response (PMRR), was used to characterize the dose-response. The Common Toxicity Criteria version 3 was used to score clinical pulmonary toxicity symptoms. Receiver operating characteristic (ROC) curves were used to determine the level of FDG uptake v. dose, MLD, V₅, V₁₀, V₂₀, and V₃₀ that can best predict symptomatic and asymptomatic patients.

Results—The median time between radiotherapy completion and FDG-PET imaging was 59 days (range, 26–70 days). The median of the mean SUV from lung that received 0–5 Gy was 1.00 (range, 0.37–1.48), 5–10 Gy was 1.01 (range, 0.37–1.77), 10–20 Gy was 1.04 (0.42–1.53), and > 20 Gy was 1.29 (range, 0.41–8.01). Using the dose range of 0 Gy to the maximum dose minus 10 Gy, hierarchical linear regression model of the radiation dose and normalized FDG uptake per case found an adequate fit with the linear model. Pneumonitis scores were: Grade 0 for 13, Grade 1 for 5, Grade 2 for 6, and Grade 3, 4 or 5 for none. Using a PMRR threshold of 0.017 yields an associated true positive rate of 0.67 and false positive rate of 0.15 with average error of 30%. A V₅ threshold of 57.6 gives an associated true positive rate of 0.67 and false positive rate of 0.05 with a 20% average error.

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Conclusion—The metabolic radiation pneumonitis dose response was evaluated from post-treatment FDG-PET/CT imaging. Statistical modeling found a linear relationship. The FDG uptake dose response and V_5 correlated with symptomatic radiation pneumonitis.

Keywords

Radiation pneumonitis; Pulmonary injury; Computed tomography; Positron emission tomography

INTRODUCTION

Radiation pneumonitis is the dose-limiting toxicity in thoracic radiotherapy (RT) for lung cancer^{1,2}. Severe radiation pneumonitis is often fatal, with a mortality rate approaching 50%³. Radiation pneumonitis is an inflammatory reaction within irradiated lung tissue in response to injury^{4,5} and occurs beginning after the initiation of RT for up to 6 months characterized by cough, shortness of breath, fever, and changes in pulmonary function^{6,7}. Development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change are associated with fatal pneumonitis⁸. Radiation pneumonitis has been reported in a wide range of doses to normal lung. Dosimetric parameters, such as the percentage of lung volume irradiated ≥ 20 Gy (V_{20}) and the mean lung dose (MLD), provide a guide to assess the risk of radiation pneumonitis in the treatment planning process. These parameters have poor predictive power for individual risk^{2,9,10} and their range for the asymptomatic versus symptomatic overlap^{9,11}. Radiographically, radiation pneumonitis results in changes within the irradiated lung on imaging studies.

Radiographic changes on chest-ray following “intensive roentgenization” was first reported by Hines et al.¹². For a historical review of these studies see Libshitz et al.¹³. The appearance of radiation lung injury on computed tomography (CT) imaging was reviewed by Libshitz¹⁴. Their appearance is characterized by an early and a late phase, corresponding to presumed radiation pneumonitis and subsequent fibrosis response¹⁵. Ma et al.¹⁶ quantified the relationship between radiation dose and lung density changes on CT, finding a dose-dependent density increase at all time points. Loss of local pulmonary perfusion and ventilation were evaluated and quantified using planar projection and single photon emission computed tomography (SPECT) by comparing pre- with post-irradiation imaging^{17–20}. SPECT perfusion changes with up to 12 years follow-up have been reported²¹. The early appearance of a variable hypermetabolic activity within the irradiated lung on [¹⁸F]-2-fluoro-2-deoxyglucose positron emission tomography (¹⁸F-FDG PET) imaging post-irradiation for lung cancer was described by Hicks et al.²². These radiation induced changes were subjectively scored on a scale from 0 to 3. Guerrero et al.²³ found a linear correlation between the radiation dose and enhanced ¹⁸F-FDG uptake within the irradiated lung in each patient studied. This metabolic dose response was found to vary widely between individuals and correlate with symptoms for esophagus cancer patients²⁴. In this study we characterize the ¹⁸F-FDG PET dose response for a lung cancer cohort.

¹⁸F-FDG PET imaging can assess pulmonary inflammation, which appears as enhanced ¹⁸F-FDG uptake in response to inflammatory stimuli^{25–27}. The metabolic response to radiation has been reported to begin early in the RT course²⁸ and reach its peak response ~ 3 months after completion²⁹. This metabolic response of normal lung tissue, called the pulmonary metabolic radiation response (PMRR), was found to correlate with clinical symptoms²⁴. Notably, the PMRR combines with treatment-planning parameters to better distinguish symptomatic from asymptomatic patients than either alone. In a retrospective study of 139 esophageal cancer patients, those who received taxane-based chemotherapy as part of induction and concurrent chemotherapy had significantly higher PMRR than did patients without any taxane-based treatment³⁰. These studies were performed in patients with

esophageal cancer with no pulmonary involvement of malignancy. In the recent paper by MacManus et al., a nuclear medicine physician assigned a radiotoxicity score to each of the follow-up PET scans in a cohort of 88 lung cancer patients. The observer was asked to subjectively score the uptake from 0 to 3 based on visual appearance. They found that the visual scoring system showed significant correlation with the presence and severity of radiation pneumonitis³¹.

For the present study, 24 lung cancer patients were retrospectively evaluated for radiation pneumonitis based on their clinical symptoms. Lung cancer patients who received restaging FDG-PET/CT imaging approximately 6 weeks after chemoradiotherapy at the Roger Maris Cancer Center were studied. Their PMRR was determined from their radiation dose distributions registered to their post-treatment ¹⁸F-FDG PET imaging. The correlation of clinical symptoms with the quantitative PMRR values for this lung cancer cohort is reported here.

METHODS AND MATERIALS

Twenty four patients treated at the Roger Maris Cancer Center (Fargo, ND) for lung cancer between May 1, 2004 and December 31, 2008 were selected for this study. Patients who had undergone CT treatment planning and follow-up PET-CT imaging between 25 and 85 days after radiotherapy completion at the Roger Maris Cancer Center were included. Patients whose imaging studies were obtained with their arms at the side or whose PET/CT contained image artifacts were excluded. The patient identifiers were removed in accordance with a Roger Maris Cancer Center and University of North Dakota institutional review board-approved retrospective study protocol and Health Insurance Portability and Accountability Act (HIPAA) regulations were strictly enforced. Each patient underwent a treatment planning session in which CT images of the entire thorax and upper abdomen were obtained at 2.5-mm slice spacing on a General Electric Discovery ST PET/CT scanner (GE Medical Systems, Waukesha, WI). The treatment planning CT scans were obtained during free breathing. Post-treatment restaging FDG PET/CT imaging was obtained on the same scanner.

The treatment plan for each patient was imported into a research dosimetry workstation and evaluated with the Pinnacle³ version 7.6c or 8.0u treatment-planning system (Philips Medical Systems, Andover, MA). The radiation dose distributions were all recalculated using lung heterogeneity corrections³². The restaging FDG PET/CT was imported into the Pinnacle treatment-planning system and spatially registered to the planning CT scan by using the Syntegra image fusion software version 1.2b (Philips Medical Systems, Andover, MA). Manual segmentation of the vertebral column was performed on each CT volume. A CT-to-CT six-degrees-of-freedom rigid-body registration of the vertebral column was performed between the treatment planning CT and the PET/CT CT images by using a mutual information algorithm³³. The registered images were visually verified, and minor adjustments of less than 1 cm along each axis were made to improve the registration of the lung regions.

The images, registration parameters, and dose distribution were exported for analysis. A pulmonary segmentation algorithm based on histogram segmentation and connectivity (available on-line at www.dir-lab.com) was applied to each treatment planning CT image set³⁴. The resulting lung parenchyma region of interest was used in the subsequent analysis. The lung segmentation was also applied to the CT scan from the restaging PET/CT scan and used in analysis of the pulmonary standard uptake values (SUVs).

The standard uptake values (SUV) were calculated from the PET count rate by using the following equation³⁵:

$$\text{Standard Uptake Value} = \frac{{}^{18}\text{F-FDG count rate per mL} \times \text{body weight (g)}}{\text{decay-corrected } {}^{18}\text{F-FDG injected dose (Bq)}} \quad (1)$$

The mean SUV within the pulmonary tissue was obtained for each case. Using the registration between the treatment-planning CT and the CT from the PET/CT, the mean SUV values in the lung tissue were obtained for each case over the dose ranges 0–5 Gy, 5–10 Gy, 10–20 Gy, and subsequently in 10-Gy intervals to 60 Gy. The median of SUV mean values and the range of the means for the 24 cases were determined. The maximum SUV value within pulmonary tissue irradiated above 5 Gy was found for all cases.

Using the registered dose and PET images, histograms were formed of the FDG-PET count rate vs. the radiation dose using single-voxel values, resulting in an average count rate per voxel at each dose. The upper limit was case-specific and was set at 10 Gy below the prescription dose. Inspection of treatment plans showed this upper limit avoided inclusion of the planning target volume (PTV)³⁶. The FDG uptake was normalized to the non-irradiated lung tissue as an internal control²³ as follows:

$$\text{Normalized } {}^{18}\text{F-FDG Uptake} = \frac{\text{count rate irradiated lung per mL}}{\text{count rate non-irradiated lung per mL}} \quad (2)$$

A hierarchical linear regression model was applied to estimate the regression line for each individual case and to estimate the variation in these lines across subjects. The resulting slope is the PMRR value for each case.

Pneumonitis was scored retrospectively using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 (CTCAE v3)³⁷. Three clinicians each scored pneumonitis using all clinic and hospital notes beginning before radiation (as a baseline) to 1 year after completing radiation. The consensus toxicity score was reported. Clinically symptomatic pneumonitis was defined as grade 2 or higher. Mean lung dose (MLD), the volume of lung irradiated to 5 Gy (V_5), 10 Gy (V_{10}), 20 Gy (V_{20}), and 30 Gy (V_{30}) were used as dosimetric parameters to estimate the volume of lung irradiated. These dosimetric parameters were included as endpoints because they are widely used to assess pneumonitis risk^{9, 38}.

Linear regression was used to determine the slope of the relationship of the post-treatment FDG uptake vs. the treatment plan dose. The associated r^2 and p value were used to assess adequacy of fit. A sensitivity analysis was performed using receiver operating characteristic (ROC) curves to determine the level of PMRR, MLD, V_5 , V_{10} , V_{20} , and V_{30} that can best correlate with symptomatic radiation pneumonitis. We built classifiers using a k-nearest neighbor scheme with $k=1-5$ and an 80/20 cross validation, where 80/20 are the data used to train/test the classifier. Simulations were run 1000 times to calculate the average error.

RESULTS

The 24 cases evaluated were lung cancer primaries. The patient characteristics are summarized in Table 1. The median prescription dose was 55.8 Gy (range 25 – 70 Gy). From the radiotherapy plans, the median lung volume receiving > 5 Gy was 47.5% (range 17.2–76.1%). The median lung volume receiving > 10 Gy was 35.1% (range 10.8–56.7%). The median lung volume receiving > 20 Gy (V_{20}) was 24.8% (range 4.0– 50.0%). The

median lung volume receiving > 30 Gy was 18.8% (range 3.4–39.7%). The median mean lung dose was 13.3 Gy (range 3.1–23.0 Gy).

The median time between radiotherapy completion and the restaging FDG-PET/CT imaging session was 59 days (range, 25–83 days). The mean SUV in the lung was calculated for each of the 24 cases; the median lung mean SUV was 1.2 (range, 0.61 to 1.61). No correlation was found between the mean lung SUV value and the time between radiotherapy completion and the PET/CT imaging session (restaging PET delay time).

The registration of the treatment planning CT with the PET/CT scan was performed, and correlative values derived using the radiation dose and FDG-PET were calculated. The median of the mean SUV from lung that received 0–5 Gy was 1.00 (range, 0.37–1.48), 5–10 Gy was 1.01 (range, 0.37–1.77), 10–20 Gy was 1.04 (0.42–1.53), and > 20 Gy was 1.29 (range, 0.41–8.01). For the 24 cases, the median of the maximal SUV within the lung irradiated to < 5 Gy was 1.7 (range, 1.36–8.01). The isodose distribution and FDG-PET images are shown in supplementary material. Normalized FDG uptake per dose from a representative case is shown in Figure 1 to illustrate the process in obtaining the normalized FDG uptake versus treatment planning dose. For all 24 cases, the normalized FDG uptake per dose was obtained.

No correlation was found between the slope of the normalized FDG uptake vs. dose and the restaging PET delay time. A histogram distribution of the PMRR values obtained is given in Figure 2 with symptomatic cases in the upper plot and asymptomatic cases in the lower plot. The response slope was varied in this study population over an order of magnitude.

All patients had a minimum r^2 value of 0.5 with mean 0.66 (range 0.51–0.91) and $p < 0.05$. In twenty two patients, a positive FDG uptake v. dose relationship was found. The three patients with negative slope had values of -0.001 , -0.002 , and -0.006 . All three cases had significant artifact in the lung fields near the diaphragm. Two of the cases had significant FDG avidity outside of the treatment field, possibly from infection.

Pneumonitis toxicity was assessed from medical records. The toxicity scores derived using the CTCv3 were: Grade 0 for 13, Grade 1 for 5, Grade 2 for 6, and Grade 3, 4 or 5 for none. Four patients, who had only radiographic findings within the radiation treatment field or minor clinical symptoms, were scored as grade 1 toxicity. Patients were stratified based on clinical score as symptomatic (2, 8 patients) or asymptomatic (0 or 1, 16 patients). The PMRR versus V_5 and V_{20} are shown in Figures 3 and 4. Only PMRR and V_5 give a significant area under the curve. We found that using a PMRR threshold of 0.017 yields an associated true positive rate of 0.67 and false positive rate of 0.15. The PMRR area under the ROC curve for is 0.85 ($p = 0.0087$). We also found that using V_5 threshold of 57.6 gives an associated true positive rate of 0.67 and false positive rate of 0.05. The V_5 area under the ROC curve is 0.81 ($p = 0.02$). The classification of symptomatic and asymptomatic patients is not equal to classification by chance alone³⁹. The error using PMRR to correlate with toxicity is 30% and for V_5 is 20%. Although PMRR has a slightly larger area under the curve than V_5 , the lower false positive rate of V_5 allows it to perform better as a classifier.

DISCUSSION

This is the first report to quantify the pneumonitis dose response to thoracic radiotherapy in lung cancer patients. We have demonstrated the PMRR in patients with lung cancer with free-breathing CT scans and post-treatment restaging (^{18}F -FDG PET) imaging. To eliminate residual tumor activity from the analysis a dose upper limit of the prescription dose minus 10 Gy effectively removed the residual gross tumor and PTV. As in patients with esophageal cancer, a linear relationship was found between the local radiation dose and the voxel-

averaged post-treatment FDG uptake. The slope of that relationship, which we call the PMRR, varied across the patients and was independent of the interval between radiotherapy completion and PET imaging (within 1–3 months) and of the percentage of volume of lung irradiated. MacManus et al. We propose this response slope is a measure of the underlying individual intensity of radiation pneumonitis and is a quantifiable surrogate for the radiation dose response. The PMRR, if validated in a larger study, may be used to evaluate candidate therapeutic strategies for pneumonitis. While MacManus et al. found that the visual scoring system showed significant correlation with radiation pneumonitis³¹, we have shown that the PMRR is an objective surrogate marker of radiation pneumonitis.

Respiratory gating with PET (4D PET/CT) may improve the accuracy of the PMRR calculation. 4D PET/CT has been demonstrated to reduce the "smearing effect" thereby increasing the signal to noise ratio and subsequently the SUV⁴⁰. 4D PET/CT results in lesion volumes closer to those assessed by CT and improved measurements of tracer uptake for lesions in the lungs⁴¹. 4D PET/CT aids image fusion for radiotherapy planning⁴². Similarly, the gating information will improve the registration of the planning CT to the post-treatment 4D PET/CT, which may improve the accuracy of the PMRR.

Dose and volume parameters assume equal susceptibility to pneumonitis among patients, but results from multiple studies have shown individual susceptibility varies greatly. Several dosimetric parameters have been studied alone and in combination including threshold values for percent volume of lung receiving certain doses^{9, 43}, MLD^{38, 44}, and models combining several parameters^{45, 46}. In a review of 99 patients treated for non-small-cell lung cancer using three-dimensional conformal radiotherapy, Graham *et al.*⁹ found a correlation between the total lung volume irradiated to V_{20} ($p < 0.001$) and the development of worse than Grade 2 pneumonitis. In that study, the fatal pneumonitis rate was 4%. They note outliers in their data, for example 1 patient with fatal pneumonitis had a V_{20} of only 22%, which is clinically considered a low risk value. Similarly, the V_{20} of the patients who developed worse than Grade 3 pneumonitis, overlapped the V_{20} of patients who did not experience any complications. Kwa *et al.*³⁸ evaluated 540 patients with breast or lung cancer who received thoracic radiotherapy using dose-volume analysis. Of these 540 patients, 73 patients developed Grade 2 pneumonitis or worse, with a significant difference ($p < 0.02$) between the pneumonitis rates in the lung cancer and breast cancer groups. In a study of children with refractory or relapsed Hodgkin's disease who received high-dose therapy and autologous hematopoietic cell transplantation, atopy was found to predict for diffuse lung injury syndrome⁴⁷. In that study, 44% of the patients had a history of allergic rhinitis and/or asthma. In a study of 122 pediatric patients receiving 15 Gy (Hodgkin's disease) to 70 Gy (sarcoma) for a range of thoracic malignancies, the 1-year cumulative incidence of symptomatic radiation pneumonitis was 8.2% with symptomatic cases found even in those receiving 15 Gy to the unilateral lung¹¹. Barriger et al⁴⁸ reviewed records of 167 patients with stage III non-small cell lung cancer receiving concurrent cisplatin and etoposide with modern 3D radiation techniques to 59.4 Gy. The only dosimetric parameter found to correlate with grade 2 pneumonitis was MLD > 18 Gy. Claude et al. studied 96 patients who received three-dimensional conformal radiotherapy for non-small cell lung cancer and found that dosimetric factors (MLD, V_{20} , V_{30}) and age (> or =60 years) were predictive of RP⁴⁹. Rodrigues et al. performed a systematic review of the predictive ability of various dose-volume histogram (DVH) parameters, MLD, and normal tissue complication probability in the incidence of RP. An association between DVH parameters and RP risk was demonstrated. However, the overall accuracy, sensitivity, specificity, and positive predictive value were generally poor to fair for all three classes of DVH metrics. Asakura et al. reported that DVH parameters were predictors of symptomatic RP in 37 esophageal cancer patients treated with radiotherapy with concomitant chemotherapy consisting of 5-fluorouracil and cisplatin⁵⁰. The addition of consolidation docetaxel also significantly

increased the risk of pneumonitis. This suggests an interplay between chemotherapy and the risk of pneumonitis, limiting the validity of standard dose-volume parameters for predicting radiation pneumonitis. Radiation-induced lung fibrosis volume is correlated with dose and has no threshold (⁵¹). MLD may be a useful parameter for comparing rival plans for reducing fibrosis volume (⁵¹).

This study focused on dosimetric and FDG-PET parameters. Clinical factors, such as co-morbidities and chemotherapy as described above, also appear to be relevant factors in assessing risk of radiation pneumonitis. Dehing-Oberije et al. used clinical factors such as performance status, smoking status, forced expiratory volume (FEV1), age with dosimetric parameters to predict pneumonitis⁵². They found that clinical factors were more important than dosimetric parameters in the multivariate model. Appelt and Vogelius published a model to quantify the effect of clinical parameters on radiation toxicity⁵³. The radiation pneumonitis model may be used to adjust for co-morbidities and other clinical factors in published dose-response relationship literature. Exhaled nitric oxide may be able to predict pneumonitis based on the change in nitric oxide at the end of radiation treatment⁵⁴.

The rate of pneumonitis in this study was 33% and in agreement with previously published series as reviewed by Rodrigues et al.⁵⁵, who reported a pneumonitis range of 13–37%. The relatively high rate of pneumonitis may be explained by the interpretation of the CTCv3 toxicity criteria and by the small number of cases in this series.

PMRR and V₅ correlated with symptomatic radiation pneumonitis, and V₅ performed better overall as a classifier with the associated low false positive rate. The large average error, which is a limitation of this study, may be due to the small sample size, biologic heterogeneity, and heterogeneity in time to follow-up PET is also large (25–85 days). Additional development of this method is under way including the prospective evaluation of a larger cohort.

In this study, the normal lung tissue response to irradiation was evaluated quantitatively using restaging FDG-PET imaging and radiation dose distribution in lung cancer patients. The data supported a linear relation between the radiation dose and the normalized FDG uptake in the lung. The slope of this relationship may be used as a surrogate marker of symptomatic radiation pneumonitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Radiation dose and FDG PET response

The FDG uptake in lung tissue, normalized to unirradiated lung, is shown versus the radiation dose (in Gy). The slope of this regression is the Pulmonary Metabolic Radiation Response (or PMRR).

Figure 2. Histogram distribution of [18F]2-fluoro-2-deoxyglucose (FDG) uptake response
Distribution of symptomatic cases (Grade 2 toxicity, upper plot) and PMRR (lower plot) shown in histogram plot for 24 cases. Slopes ranged from 0.000 to 0.049/Gy.

Figure 3. [18F]2-fluoro-2-deoxyglucose (FDG) response vs. V_5

Slope of linear regression for each of 24 cases plotted vs. percentage of lung volume that received 5 Gy (V_5). Using a PMRR threshold of 0.017 yields an associated true positive rate of 0.67 and false positive rate of 0.15. The PMRR area under the ROC curve for is 0.85 ($p = 0.0087$). Using V_5 threshold of 57.6 gives an associated true positive rate of 0.67 and false positive rate of 0.05. The V_5 area under the ROC curve is 0.81 ($p = 0.02$).

Figure 4. [18F]2-fluoro-2-deoxyglucose (FDG) response vs. V_{20}

Slope of linear regression for each of 24 cases plotted vs. percentage of lung volume that received 20 Gy (V_{20}). V_{20} did not yield a significant area under the curve.

Table 1**Patient Characteristics**

Characteristics	<i>n</i>
Age (y)	
Median	67 years
Range	58 – 79 years
Gender	
Male / Female	12 / 12
Stage	
I	2 (8)
II	4 (17)
III	15 (63)
IV	3 (13)
Location	
Upper Lobe	14 (58)
Lower Lobe	5 (21)
Main Stem Bronchus	1 (4)
Overlapping Boundaries	4 (17)
Histology	
Adenocarcinoma	15 (63)
Squamous Cell Carcinoma	9 (38)
Small Cell	2 (8)
Prescription dose (Gy)	
Median	55.8 Gy
Range	25 – 70 Gy
Time between completion of radiotherapy to PET imaging session	
Median	57 days
Range	25 to 83 days
Chemotherapy	
None	5 (54.5)
Induction prior to radiotherapy	1 (97.0)
Concurrent with radiotherapy	18

Abbreviations: Gy = Gray.

Percentages are presented in parenthesis.