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Radiation Pneumonitis: Correlation of Toxicity with the Pulmonary Metabolic Radiation Response

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Abstract

Purpose—To characterize the relationship between radiation pneumonitis (RP) clinical symptoms and pulmonary metabolic activity on post-treatment [¹⁸F]-fluorodeoxyglucose positron emission tomography (FDG PET).

Methods—We retrospectively studied 101 esophageal cancer patients who underwent restaging FDG PET/CT imaging between 3 and 12 weeks after completing thoracic radiotherapy. The Common Toxicity Criteria version 3 (CTC3) was used to score RP clinical symptoms. Linear regression was applied to the FDG PET/CT images to determine the normalized FDG uptake versus radiation dose. The pulmonary metabolic radiation response (PMRR) was quantified as this slope. Modeling was performed to determine the interaction of PMRR, mean lung dose (MLD), and percentage of lung receiving greater than 20 Gy (V20) with RP outcomes.

Results—Of the 101 patients, 25 had grade 0, 10 had grade 1, 60 had grade 2, 5 had grade 3, and 1 had grade 5 RP symptoms. Logistic regression demonstrated that increased values of both MLD and PMRR were associated with a higher probability of RP clinical symptoms ($P=0.032$ and $P=0.033$, respectively). Spearman's rank correlation found no association between the PMRR and dosimetric parameters (PTV, MLD, V5 through V30). Two-fold cross validation demonstrated the combination of MLD and PMRR was superior to either alone for assessing the development of

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Conflict of Interest Notification:

The authors declare that they have no commercial or financial interests related to this study to disclose.

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clinical symptoms of RP. The combined MLD (or V20) and PMRR had a higher sensitivity and accuracy (53.3 and 62.5, respectively) than either alone.

Conclusions—This study demonstrated a significant correlation between RP clinical symptoms and the PMRR measured by FDG PET/CT following thoracic radiotherapy.

Keywords

radiation pneumonitis; pulmonary injury; computed tomography; positron emission tomography

INTRODUCTION

Radiation pneumonitis (RP) is an inflammatory reaction within lung tissue in response to radiation injury and is the cause of treatment-related pulmonary complications in thoracic radiotherapy patients.¹ Because pulmonary inflammation appears as enhanced [¹⁸F]-fluorodeoxyglucose (¹⁸F-FDG) uptake on positron emission tomography (PET) imaging, ¹⁸F-FDG PET can provide a quantitative assessment of pneumonitis.² Previous investigators have noted radiation induced ¹⁸F-FDG PET inflammatory changes in normal lung tissue.^{3, 4} We found with statistical modeling a linear relationship between normalized ¹⁸F-FDG uptake and radiation dose in normal lung after thoracic radiotherapy.⁵ The slope of this linear relation, which we refer to as the pulmonary metabolic radiation response (PMRR), provides an objective, quantifiable measure of the inflammation response to radiation.

Many clinical studies of RP have assumed that patients were equally susceptible and that the dose and volume of lung irradiated determine the risk of RP. Other studies have correlated serum inflammatory biomarkers with RP symptoms.^{6–8} Whereas the volume of lung irradiated can be accurately determined from the radiation treatment plan, the individual inflammation response cannot be readily measured at the time of clinical symptoms. Because outliers in response to thoracic radiotherapy are often present, such as the case of fatal RP in Graham's data⁹ with a V20 (percentage of lung volume that received > 20 Gy) of only 22%, an objective measure of pulmonary radiation response is needed.

At The University of Texas M. D. Anderson Cancer Center (MDACC), esophageal cancer patients receive restaging ¹⁸F-FDG PET/CT 6 weeks after chemoradiotherapy to identify patients with interval metastases.¹⁰ In this retrospective study, we quantitatively evaluated the ¹⁸F-FDG uptake versus radiation dose in radiation-induced pulmonary inflammation and correlated those findings with symptoms of RP in patients with esophageal cancer who received thoracic radiotherapy.

PATIENTS AND METHODS

Patient Population and Radiotherapy Treatment

Subjects were 101 patients (Table 1) treated in the Department of Radiation Oncology at MDACC for esophageal cancer between November 1, 2003 and November 30, 2006. Patients who had CT treatment planning and follow-up PET-CT imaging between 24 and 84 days after completion of radiotherapy at MDACC were selected. Two-thirds of the PET/CT images were acquired with breath-hold CT images used for attenuation correction, the others used an average CT.¹¹ Patient identifiers were removed in accordance with an institutional review board approved retrospective study protocol (RCR 03-0800) in strict compliance with the Health Insurance Portability and Accountability Act of 1996 regulations.

Each patient underwent treatment planning in which CT images of the entire thorax were obtained at < 3-mm slice spacing. Approximately one-thirds of the treatment planning CT

images were acquired with average 4D CT and the others with free-breathing CT images. Treatment plans were generated using the Pinnacle-3 version 7.6c treatment planning system (Philips Medical Systems, Andover, MA), half of the patients had intensity modulated plans the others did not. The dose volume histogram (DVH) distributions between the 3D-CRT and IMRT treated patients were similar. All radiation dose calculations were performed with lung heterogeneity corrections.¹²

PET and Dose Registration

Restaging FDG PET/CT imaging was performed using on average 17.0 mCi (range 11.1–19.7 mCi) of ¹⁸F-FDG and imaging was initiated following an uptake period on average of 86.4 min (range 57.3–144.0 min). For the purposes of this analysis the treatment plans and restaging FDG PET/CT images were imported into the Pinnacle treatment planning system and spatially registered by using the Syntegra image fusion software version 1.2b (Philips Medical Systems) for each patient.

Image Analysis: Lung Segmentation and ¹⁸F-FDG Uptake

The PET/CT images were registered with the treatment planning CT and the lungs segmented as described previously.⁵ The ¹⁸F-FDG SUVs (standard uptake value) were calculated from the PET attenuation corrected emission images using the equation:

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

Normalized FDG uptake was calculated by using the non-irradiated (< 3 Gy) lung tissue estimate as an internal control and the following equation⁵:

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

Least-squares linear regression was applied to the resulting values to obtain the PMRR value (slope of the regression) for each case.

Clinical Toxicity Scoring

The patients' medical records were retrospectively reviewed. Information extracted included demographics, medical history, esophageal cancer disease characteristics¹³, follow-up radiographic images, and treatment-related factors. All radiographic images were reviewed by a thoracic diagnostic imaging expert. Clinical symptom of RP were scored according to the NIH Common Toxicity Criteria for Adverse Events version 3 (CTCAE v3.0).¹⁴ The score given to each patient was based on the maximum toxicity observed during this follow up period. All scores were reviewed by 3 of the co-authors and a consensus score was utilized. Since thoracic surgical intervention would interfere with the interpretation of clinical symptoms, symptoms were scored from the date that radiation was completed until the patient underwent thoracic surgical intervention or for a follow up period of one year.

Statistical Analysis

Variables were compared based on toxicity outcome (grade 2 or higher vs. grade 0–1) using two-sample t-tests assuming unequal variance. A test of the Spearman's rank correlation was used to assess the correlation between PMRR and dosimetry parameters (MLD, mean lung dose; PTV, planning target volume; V5 – V30, percentage of lung volume that received > 5

– 30 Gy). All tests were two-sided and P-values of 0.05 or less were considered statistically significant.

A logistic regression model was used to predict toxicity outcome based on MLD only, V20 only, PMRR only, both MLD and V20, both MLD and PMRR, and both V20 and PMRR. The significance of each combination of variables was assessed using a likelihood ratio test based on the deviance statistic. Two-fold cross validation was used to assess the predictive performance of the best model as follows. The data were partitioned into two sets (51 and 50), a logistic model was fit to one of the sets, and then probabilities of experiencing toxicity on the remaining samples were predicted based on this model. This two-fold cross validation was repeated 10,000 times. Sensitivity and specificity values were estimated from this experiment.

RESULTS

Patient characteristics

The characteristics of the 101 patients selected for this study are summarized in Table 1. The mean lung dose, averaged over all patients, was 12.5 Gy (range 3.4–20.9 Gy), V5 was 55.6% (range 10.9–95.0%), V10 38.0% (range 8.1–76.9%), V20 22.2% (range 4.7–40.5%) and V30 13.8% (range 2.1–29.5%). The average mean lung SUV was 0.76 (range 0.36 – 1.53) and the average maximum lung SUV was 4.96 (range 1.84 – 18.2).

CTCAE v 3.0 clinical RP scores were as follows: Grade 0, 25 patients; grade 1, 10 patients; grade 2, 60 patients; grade 3, 5 patients; grade 4, 0 patients; and grade 5, 1 patients. Patients were stratified based on clinical score as symptomatic (2, 66 patients) or asymptomatic (0 or 1, 35 patients). For patients who received surgery RP symptom onset was on average 1 day prior to [¹⁸F]-FDG PET imaging, for the others 5 days after. None of the patients who received surgery had grade > 2 toxicity. Each dosimetric parameter (MLD, V5, V10, V20, and V30) was higher in the symptomatic group.

Pulmonary SUV and Normalized FDG uptake

The treatment plan radiation dose distribution and [¹⁸F]-FDG PET image were registered for each case (Figure 1a-c). The average SUV values within the lung tissue that received between 0 and 5 Gy (SUV5) were compared between patients with versus without clinical symptoms of RP (0.66 versus 0.64, respectively). The distribution of PMRR values is shown in Figure 1d. There were no differences found in the PMRR distribution between patient groups using differing CT techniques for attenuation correction or dose calculation, or from radiation delivery technique. The maximum pulmonary SUV was found to be significantly greater in the symptomatic group (P=0.040). The PMRR was independent of the interval between completion of radiotherapy and the PET/CT imaging and independent of the [¹⁸F]-FDG uptake time on the day of the PET/CT.

Correlation of dosimetry and PMRR with clinical pneumonitis

Two-sampled t-test demonstrated that symptomatic patients had higher PMRR values than asymptomatic patients (p=0.0073). Consistent with previous reports^{9, 15, 16}, two-sampled t-test found symptomatic patients had higher MLD (P=0.0012), V5 (P=0.013), V10 (P=0.0010), V20 (P=0.0028), and V30 (P=0.0033) than asymptomatic patients. A test of Spearman's rank correlation was used to evaluate the associations between PMRR and PTV, MLD, and V5–V30. None of these tests showed statistically significant associations at the 5% level.

Next, we modeled the probability of developing clinical symptoms of RP using logistic regression on physical dosimetric parameters (MLD or V20) alone or in combination with the PMRR. These results are illustrated in Figures 2a & 2b. Two-fold cross validation was used to assess the performance of the MLD, V20, PMRR, MLD+V20, MLD+PMRR, and V20+PMRR models (Table 2). Because of the high correlation of the MLD and V20 variables, combining the MLD+V20 did not improve the model performance. Combining the MLD or V20 with the PMRR significantly improved ($P=0.008$ and 0.018 , respectively) the model performance. The combination of both MLD and PMRR yielded the best results with increased positive predictive values, negative predictive values, and accuracy relative to either factor alone.

DISCUSSION

In this study we demonstrate a correlation between [^{18}F]-FDG PET/CT response, and the clinical symptoms of RP after thoracic radiation. Studies using dosimetric parameters, e.g. V20 and MLD, to assess the risk of pulmonary complications and set guidelines for radiotherapy planning have had poor predictive power for RP symptoms.^{9, 17, 18} Measurement of the biological response is needed to help interpret the range in RP response for the same physical dosimetric parameters. Additionally, an objective measure of RP response will also provide a more accurate assessment of lung toxicity versus the present approach based on patient reporting.¹⁹ In this study, the PMRR correlated with the development of symptomatic RP after thoracic radiotherapy and the combination of the V20 or MLD with the PMRR provided a better model than either alone. Based on our findings, we hypothesize that the PMRR derived from post-treatment [^{18}F]-FDG PET/CT imaging can be used as an imaging biomarker of RP response.

CONCLUSION

In this study we found a significant correlation between RP clinical symptoms and the pulmonary metabolic response measured by [^{18}F]-FDG PET/CT following thoracic radiotherapy.

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Figure 1.

a) Coronal section through the radiotherapy treatment planning CT and isodose distribution. **b)** Corresponding section through restaging non-contrast CT, obtained during FDG PET/CT imaging. **c)** FDG PET image superimposed on coronal CT. **d)** Histogram plot of the FDG uptake versus radiotherapy dose regression slopes for each of the 101 cases.

Figure 2.

Toxicity analysis based on pulmonary metabolic radiation response (PMRR) and mean lung dose (MLD). **a)** Plot of toxicity outcome by PMRR and MLD. The lines delineate regions for which there is an 80% probability of grade 2 or higher toxicity. **b)** Plot of toxicity outcome by PMRR and V20. The lines delineate regions for which there is an 80% probability of grade 2 or higher toxicity.

Table 1

Patient Characteristics.

Characteristics	N (%)
Age	
Median	66 y
Range	41 – 84 y
Sex	
Male / Female	86 / 15
Disease Stage	
I	2 (2.0)
IIa	32 (31.7)
IIb	5 (5.0)
III	50 (49.5)
IV	11 (10.9)
Recurrent	1 (1.0)
Tumor Location	
Middle	12 (11.9)
Distal/GE junction	89 (88.1)
PTV	
Median	739.1 mL
Range	187.9 – 2055.9 mL
Prescription dose	
Median	50.4 Gy
Range	41.4 – 63 Gy
Time between radiotherapy and PET	
Median	41 days
Range	23 to 78 days
Chemotherapy	
Induction before radiotherapy	56 (55.4)
Concurrent with radiotherapy	98 (97.0)
Radiation Planning	
3-D Conformal	53 (52.5)
Intensity Modulated	48 (47.5)
Smoking History	
Yes	80 (79.2)
No	21 (20.8)
Histology	

Characteristics	N (%)
Adenocarcinoma	85 (84.2)
Squamous Cell Carcinoma	15 (14.9)
Small Cell Carcinoma	1 (1.0)
Median Follow Up Time	
Patients undergoing surgery (n=54)	58 days
Patients not undergoing surgery (n=47)	277 days

Abbreviations: GE = Gastroesophageal, PTV = planning target volume

Table 2

Predicted vs. True Toxicity for Models Based on Mean Lung Dose (MLD), Percentage Volume of Lung that Received > 20 Gy (V20), Pulmonary Metabolic Radiation Response (PMRR), or Combinations (MLD+V20, MLD+PMRR, or V20+PMRR). The P-values comparing the MLD versus MLD +PMRR models (P=0.008) and the V20 versus V20+PMRR models (P=0.018) were significant.

Model	Predicted Toxicity Status	True Toxicity Status *		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
		Yes	No					
MLD Only	Positive	255774	69494	38.8	80.1	78.6	41.0	53.1
	Negative	404226	280506					
V20 Only	Positive	247062	69859	37.4	80.0	78.0	40.4	52.2
	Negative	412938	280141					
PMRR Only	Positive	252587	69752	38.3	80.1	78.4	40.8	52.8
	Negative	407413	280248					
V20 + MLD	Positive	243196	69478	36.9	80.2	77.8	40.2	51.9
	Negative	416804	280522					
PMRR + MLD	Positive	351748	70155	53.3	80.0	83.4	47.6	62.5
	Negative	308252	279845					
PMRR + V20	Positive	326996	70164	49.5	80.0	82.3	45.7	60.1
	Negative	333004	279836					

Abbreviations: MLD, mean lung dose; PPV, positive predictive value; NPV, negative predictive value; PMRR, pulmonary metabolic radiation response.

* Cross-tabulation was based on 10,000 two-fold cross-validation runs. The specificities of all six models were set to be approximately 80%. The threshold of predicted probability of MLD only, V20 only, PMRR only, V20+MLD, MLD+PMRR, and V20+PMRR models were 73%, 71.5%, 68.4%, 73.9%, 72.5%, and 72.5%, respectively.