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Original Research Article

Association of lung fluorodeoxyglucose uptake with radiation pneumonitis after concurrent chemoradiation for non-small cell lung cancer

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ABSTRACT

Background: Increased uptake of fluorodeoxyglucose (FDG) by lung tissue could reflect inflammatory changes related to radiation pneumonitis (RP). In this secondary analysis of a clinical trial, we examined potential associations between posttreatment lung FDG uptake and RP severity in patients with non-small cell lung cancer (NSCLC) for up to 12 months after concurrent chemoradiation (CRT).
Methods: Subjects were 152 patients with NSCLC who had received concurrent CRT as part of the prospective trial NCT00915005. The following lung FDG variables were evaluated after CRT: maximum, mean, and peak standardized uptake values (SUVmax, SUVmean, SUVpeak) and global lung glycolysis (GLG; lung SUVmean × lung volume). RP severity was scored with the Common Terminology Criteria for Adverse Events v3.0.
Results: Significant associations were noted between PET findings and RP severity at 1–6 months (all $P < 0.05$), but not at 7–12 months after therapy (all $P > 0.05$). Lung FDG uptake at 1–3 months after treatment predicted later development of grade ≥2 RP (all $P < 0.05$), with cutoff values as follows: 4.54 for SUVmax, 3.69 for SUVpeak, 0.78 for SUVmean, and 2295 for GLG.
Conclusions: Lung FDG uptake correlated significantly with RP severity during the first 6 months after CRT. The cutoff values seem clinically meaningful for identifying patients at risk of developing RP after such therapy.

Introduction

Radiation pneumonitis (RP) is a common and potentially fatal complication among patients with locally advanced non-small cell lung cancer (NSCLC) treated with radiation therapy. On a cellular level, the acute phase of RP is characterized by the movement of inflammatory mononuclear cells from the vascular compartment to the alveolar space [1]. The ability to detect RP early by using advanced imaging modalities could provide significant clinical benefits to affected patients by allowing supportive care to be implemented promptly.

However, the clinical diagnosis of RP can be challenging. On images of irradiated lungs, RP can manifest as consolidation, ground glass opacities, or both. For patients with preexisting lung disease, the uncertainty in diagnosing RP is even greater, with studies reporting rates of diagnostic uncertainty ranging from 28% to 48% [2,3]. Computed tomography (CT) has low sensitivity and suboptimal specificity for detecting early tissue injury and

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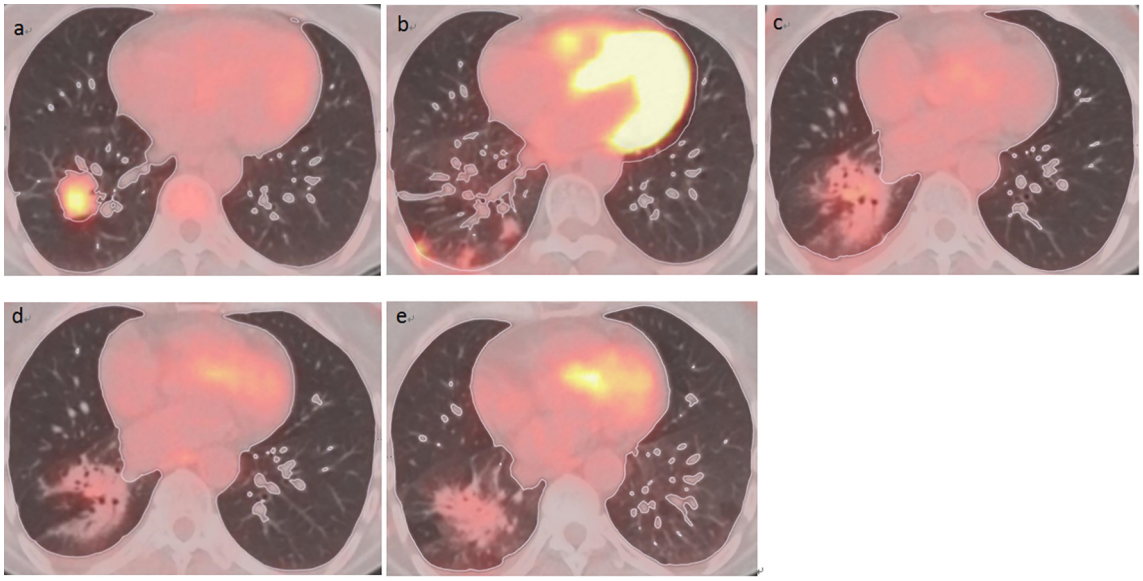

Fig. 1. PET/CT fusion scans from a patient showing inflammatory infiltration of the lungs, with interstitial infiltrates, ground glass opacities, homogeneous consolidation, and patchy consolidation. (A) Scan obtained before treatment; the bright yellow area inside the white outline is the primary lung tumor. (B) Scan obtained 2 months after treatment; the bright yellow area inside the white outline represents interstitial infiltrates. Scans obtained at 4 months (C), 7 months (D), and 10 months after treatment (E) illustrate the course of interstitial infiltration over time.

inflammation in the lung parenchyma because of its inability to distinguish RP imaging findings from those of other pulmonary disease processes [4]. Thus, the ability of molecular imaging to detect the inflammatory process associated with RP before the development of any visible structural manifestation makes it a potentially effective method for studying RP. RP manifests on 2-fluoro-2-deoxyglucose positron emission tomography (FDG PET) as increased FDG uptake, and such increases allow quantitative assessment of pneumonitis [5,6]. Thus, lung parenchymal FDG uptake on PET/CT could be a useful biomarker to quantify and predict lung inflammation after thoracic radiation [7,8]. However, no study has yet explored the longitudinal and cross-sectional relationships between molecular imaging and radiation-induced RP. In the current study, we obtained serial FDG PET scans during the first 12 months after treatment for patients with NSCLC participating in a prospective clinical protocol, and we correlated these findings with RP grade assessed by clinicians. We further aimed to identify the potential value of post-treatment FDG PET for assessing and predicting the severity of lung RP after thoracic radiation.

Materials and methods

Patients

The study was secondary analysis of randomized patient groups in a prospective clinical trial (NCT00915005) conducted from June 2009 through April 2014 at The University of Texas M.D. Anderson Cancer Center in Houston, Texas, USA. Eligibility criteria for patients included having pathologic confirmation of NSCLC, being at least 18 years old, having unresectable disease, and being scheduled to receive curative-intent concurrent chemoradiation therapy (CRT) with either carboplatin and paclitaxel, or etoposide and cisplatin or pemetrexed for patients with lung adenocarcinoma. This study was approved by the appropriate institutional review board, and all participants gave written informed consent to participate.

FDG PET image analysis

FDG PET scans were obtained from patients before treatment and at 1–3 months, 4–6 months, 7–9 months, and 10–12 months after treatment. All patients had fasted for a minimum of 6 h and had a blood glucose level of 80–120 mg/dL (4.4–6.6 mmol/L) before intravenous administration of ^{18}F-FDG (555–740 MBq [15–20 mCi]). Data were acquired 60 min after radiotracer injection, with 3 min per bed in 2D acquisition mode, from the orbit to the mid-thigh, with a GE Discovery ST PET/CT scanner. No CT contrast was injected for the CT component of the PET/CT scan. PET/CT images were processed and evaluated by a clinical investigator and an experienced nuclear medicine physician using Mirada XD3 software (Mirada Medical, Denver, CO, USA). The region of interest was the volume of both lungs with the following corrections. First, the volume was restricted to areas on the CT scan with a radiodensity of −400 Hounsfield units; then both lungs were outlined manually on the post-treatment PET/CT fusion scans, excluding the gross tumor volume (GTV) and central airway, and parenchymal changes thought to be related to treatment (e.g., ground glass opacities, interstitial infiltrates, homogeneous or patchy consolidation, and reticulation) were marked (Fig. 1). PET spillover artifacts attributable to heart, tumor, and liver activity were manually contoured and carefully excluded from the segmented lung volume [9]. The FDG uptake variables for the region of interest (volume of both lungs, excluding GTV) were generated automatically with the XD3 software, including maximum standardized uptake value [SUVmax], SUVmean, SUVpeak, and global lung glycolysis (GLG). SUVpeak was defined as the average SUV within a 1-cm^3 sphere centered in the lung region having the highest uptake [10]. GLG was defined as the SUVmean for both lungs (excluding the GTV) multiplied by the volume of both lungs (also excluding GTV) [4].

Clinician-rated toxicity

RP was systematically recorded and scored during the trial according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3 (CTCAE v3) [11].The score

Table 1
Patient characteristics.

Characteristic	No. of patients	%
Age, years		
Median (range): 66 (33–85)		
Sex		
Male	81	53
Female	71	47
Race		
White	134	88
Other	18	12
Disease stage		
II	11	7.0
III	124	82
IV	7	4.5
Recurrence	10	6.5
Tumor histology		
Adenocarcinoma	83	55
SCC	48	32
Other	21	13
Zubrod performance score		
0	1	0.8
1	140	92
2	11	7.2
Induction chemotherapy		
No	100	66
Yes	52	34
Adjuvant chemotherapy		
No	122	80
Yes	30	20
Modality		
IMRT	91	60
PSPT	61	40
Total tumor dose, Gy		
Median (range): 74 (62–74)		
Highest-grade toxicity after treatment*		
0	40	26.3
1	47	30.9
2	58	38.2
3	7	4.6
4	0	0
RP		
Grade 1		
1–3 Months after treatment	50	33
4–6 Months after treatment	53	35
7–9 Months after treatment	35	23
10–12 Months after treatment	33	22
Grade 2		
1–3 Months after treatment	35	23
4–6 Months after treatment	43	28
7–9 Months after treatment	27	18
10–12 Months after treatment	21	14
Grade 3		
1–3 Months after treatment	5	3.3
4–6 Months after treatment	3	2.0
7–9 Months after treatment	3	2.0
10–12 Months after treatment	1	0.6
Symptomatic RP#		
1–3 Months after treatment	41	27
4–6 Months after treatment	47	31
7–9 Months after treatment	30	20
10–12 Months after treatment	22	14
GTV, median (range), cm^3	152	70 (4.8–686)
Total tumor dose, median (range), Gy	152	70 (60–87)
Mean lung dose, Gy	152	17.25 (4.2–23.7)

Abbreviations: SCC, squamous cell carcinoma; GTV, gross tumor volume; SUVmean, mean standardized uptake value; CTCAE, Common Terminology Criteria for Adverse Events; PSPT, passively scattered proton therapy; IMRT, intensity-modulated photon radiation therapy.

* Toxicity was assessed with the Common Terminology Criteria for Adverse Events V 3.0.

Symptoms considered to indicate RP included coughing and shortness of breath (which would also be characterized as CTCAE RP grade 2).

(grade) was determined on the basis of both lung radiographic findings and RP symptoms (obtained from clinic notes made by the treating clinicians and from other consultations). Grade 1 is associated with no symptoms; grade 2, with symptoms that do not interfere with activities of daily living; grade 3, with symptoms that do interfere with activities of daily living; grade 4, with symptoms that are life-threatening, and grade 5, with death.

Statistical analysis

Patient characteristics were evaluated with descriptive statistics. Cross-sectional correlations between the post-treatment PET variables and CTCAE RP grade were assessed with Spearman correlation coefficients. Mixed effect models were used to examine the longitudinal relationships between lung SUVmean and CTCAE RP score over the four specified time periods (1–3 months, 4–6 months, 7–9 months, and 10–12 months after treatment); ordinal logistic regression was used to calculate the cumulative probability of association of SUV variables across various levels of CTCAE RP grade. The predictive value of post-treatment PET findings with regard to CTCAE RP (grade $\geq$ 2 vs. 0–1) was analyzed with binary logistic models. To simplify the application of these values in clinical practice, we used receiver operating characteristic (ROC) curve regression analysis to identify cutoff values that were the most sensitive for identifying RP grades 2–4 at after therapy (Suppl Fig. S1). The best cutoff value was determined using the criteria of minimal distance to (0/1) for candidate predictors such as lung SUVmax, SUVpeak, SUVmean, and GLG after treatment. Statistical analyses were done with SAS version 9.4.

Results

Patient, tumor, and treatment characteristics are shown in Table 1. All 152 patients completed the protocol-dictated treatment regimen (concurrent CRT). Most patients had stage III disease and good performance status. Twenty-six patients (17%) had four PET/CT scans, 50 (33%) had 3 scans, 50 (33%) had 3 scans, and 26 (17%) had one scan. Between 14% and 31% had RP symptoms during any measurement period. No patient had grade 4 or 5 RP. Values of SUVmax, SUVpeak, SUVmean, and GLG at each measurement point are shown in Supplementary Table S1.

Cross-sectional correlation between RP grade and PET variables

Spearman correlation analysis showed that SUVmax, SUVmean, SUVpeak all correlated with RP grade at the 1–3 months and 4–6 months measurement periods (all $P < 0.05$), but not at the 7–9 months or 10–12 months periods (all $P > 0.05$). GLG correlated with RP grade at the 1–3 months period but not at the 4–6 months, 7–9 months, and 10–12 months periods (all $P \geq 0.05$) (Table 2).

Longitudinal correlations between RP grade and PET variables

In a mixed-effect longitudinal model, patients with grade 2 or 3 RP had significantly higher SUVmax, SUVmean, SUVpeak, and GLG values than those with grade 0 or 1 RP at 1–3 months and 4–6 months after treatment (all $P < 0.001$), but not at the 7–9 months and 10–12 months period ($P > 0.05$) (Fig. 2).

PET variables and RP severity after treatment

Like the mixed-effect longitudinal results reported above, an ordinal logistic regression model also showed that higher lung SUVmax, SUVpeak, and SUVmean values were associated with more severe RP (grade 2–3 by CTCAE v3) at 1–3 months and 4–

Table 2
Associations between FDG PET variables and the development of radiation pneumonitis at various times after treatment.

	SUVmax			SUVpeak			SUVmean			GLG		
	Estimate	*OR (95% CI)*	*P*	Estimate	*OR (95% CI)*	*P*	Estimate	*OR (95% CI)*	*P*	Estimate	*OR (95% CI)*	*P*
1–3 mo after treatment	0.89	2.45 (1.87–3.19)	0.01	0.95	2.60 (1.93–3.50)	0.01	4.3	7.07 (1.38–16.38)	0.01	0.001	1.001 (1.001–1.002)	0.01
4–6 mo after treatment	0.44	1.55 (1.23–1.97)	0.01	0.50	1.66 (1.26–2.20)	0.01	4.4	7.96 (1.03–20.18)	0.01	0.001	1.000 (1.000–1.001)	0.19
7–9 mo after treatment	0.07	1.08 (0.76–1.53)	0.67	0.13	1.15 (0.74–1.79)	0.55	0.76	2.13 (0.07–64.78)	0.66	0.001	1.000 (0.999–1.002)	0.45
10–12 mo after treatment	−0.03	0.97 (0.75–1.26)	0.81	−0.03	0.96 (0.68–1.36)	0.83	0.18	1.20 (0.05–28.24)	0.91	−0.001	0.999 (0.998–1.000)	0.06

Abbreviations: SUV, standardized uptake value; GLG, global lung glycolysis; mo, month; OR, odds ratio; CI, confidence interval.

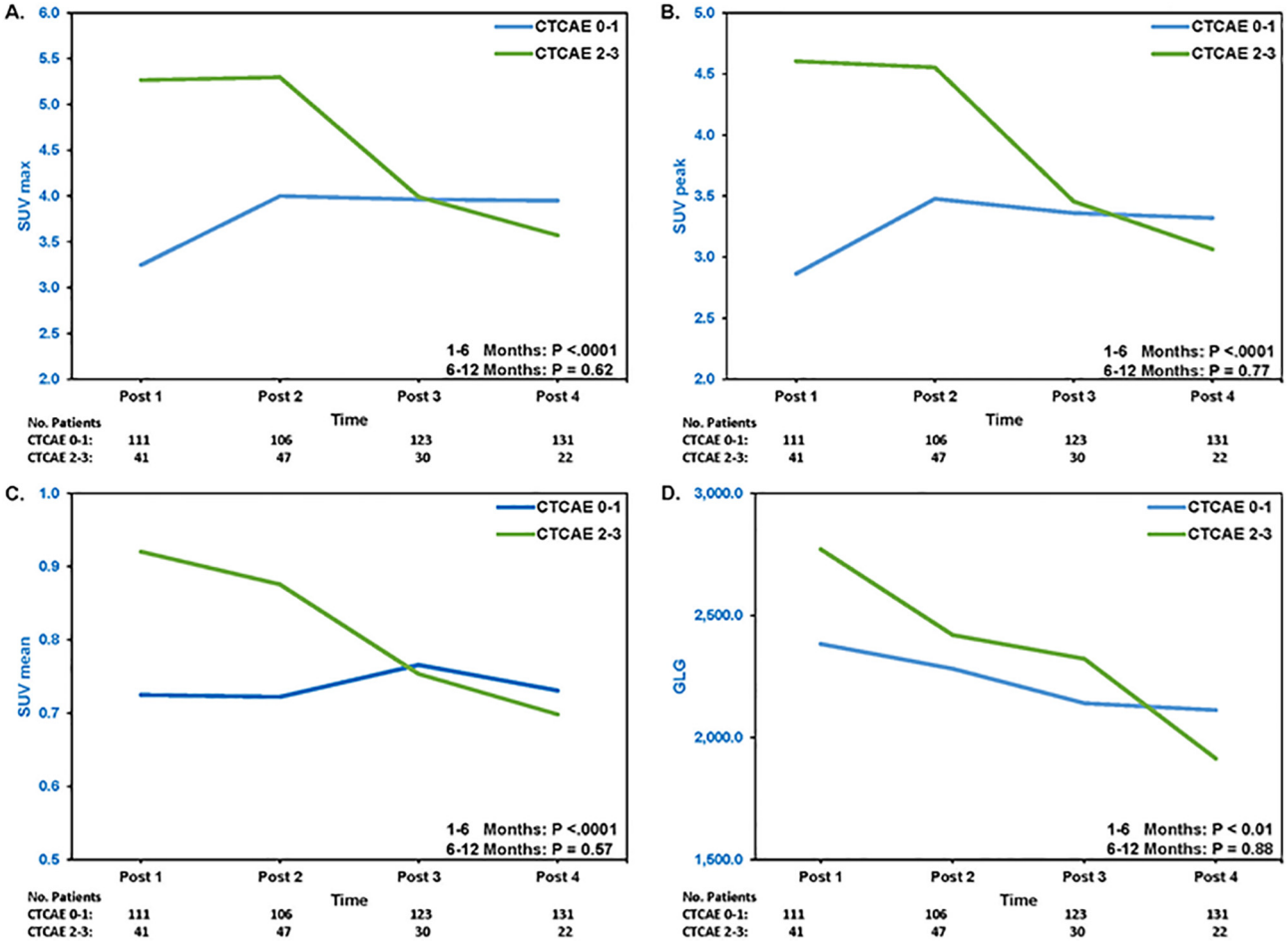

Fig. 2. Longitudinal correlations between SUV variables and radiation pneumonitis (RP). All four variables studied [(A) SUVmax, (B) SUVpeak, (C) SUVmean, and (D) global lung glycolysis {GLG}] showed significant correlations with RP of grade 0–1 and 2–3 during the first 6 months after therapy, but not thereafter. All four of these variables were higher in patients with CTCAE RP grade ≥2 than in patients with CTCAE RP 0–1 during the first 6 months after treatment, but not thereafter. Abbreviations: SUV, standardized uptake value; GLG, global lung glycolysis; CTCAE, Common Terminology Criteria for Adverse Events version 3; post 1, 1–3 months after treatment; post 2, 4–6 months after treatment; post 3, 7–9 months after treatment; post 4, 10–12 months after treatment.

6 months after treatment (all $P < 0.01$), but not afterwards (all $P > 0.05$). Higher lung GLG was associated with more severe RP at 1–3 months after treatment ($P < 0.01$), but not afterwards (all $P > 0.05$) (Table 3). The cumulative probabilities of SUV variables after treatment for RP severity (by CTCAE grade) are shown in Fig. 3.

Predictive value of lung PET variables at 1–3 or 4–6 months for subsequent development of RP grade ≥2

In a binary logistic model, lung FDG uptake variables at 1–3 months after treatment predicted CTCAE RP grade ≥2 at 4–6 months after treatment (all $P < 0.05$), but not afterwards (all $P > 0.05$). In contrast, lung FDG uptake variables at 4–6 months could not predict CTCAE RP grade ≥2 at 7–9 months or 10–12 months after treatment (Table 3). The identified predictive cut-off values of lung FDG uptake in 1–3 months for RP grade ≥2 at 4–6 months after treatment were 0.54 for SUVmax; 3.69 for SUV-peak; 0.78 for SUVmean; and 2295 for GLG (Supplementary Table S2).

Discussion

In this study, we observed significant associations between lung FDG uptake after CRT for NSCLC and the incidence and severity of subsequent RP, graded according to the CTCAE v3. We further

Table 3
Predictive value of FDG uptake variables at 1–3 or 4–6 months for subsequent development of grade ≥2 radiation pneumonitis.

Predictive variables	Time point for RP (grade ≥ 2 vs. 0–1)	Odds ratio (95% CI)	*P* Value
SUVmax at 1–3 mo	4–6 mo	1.31 (1.05–1.63)	0.015
	7–9 mo	—	0.457
	10–12 mo	—	0.055
SUVmean at 1–3 mo	4–6 mo	3.18 (1.52–6.65)	0.003
	7–9 mo	—	0.237
	10–12 mo	—	0.051
SUVpeak at 1–3 mo	4–6 mo	1.33 (1.04–1.70)	0.022
	7–9 mo	—	0.386
	10–12 mo	—	0.059
GLG at 1–3 mo	4–6 mo	1.35 (1.03–1.80)	0.043
	7–9 mo	—	0.684
	10–12 mo	—	0.836
SUVmax at 4–6 mo	7–9 mo	—	0.157
	10–12 mo	—	0.874
SUVmean at 4–6 mo	7–9 mo	—	0.209
	10–12 mo	—	0.926
SUVpeak at 4–6 mo	7–9 mo	—	0.171
	10–12 mo	—	0.929
GLG at 4–6 mo.	7–9 mo	—	0.176
	10–12 mo	—	0.121

Abbreviations: RP, radiation pneumonitis; SUV, standardized uptake value; GLG, global lung glycolysis.

found that higher lung FDG uptake variables during the first 1–3 months after treatment predicted the subsequent development of grade ≥2 RP. We also defined optimal cut-off values for the FDG uptake variables that corresponded to the risk of CTCAE grade 2–4 RP.

Our results confirmed that the intensity of FDG uptake on PET can be used to objectively grade established pneumonitis and perhaps to identify patients at higher risk of developing high-grade pneumonitis [12,13]. In another study of 101 patients with esophageal cancer [14], the authors found that higher mean lung doses were associated with greater risk of pneumonitis, and another variable, "pulmonary metabolic radiation response," was also associated with increased risk of pneumonitis. Our data demonstrated that lung SUVmax, SUVpeak, and SUVmean, i.e., the intensity of FDG uptake in pulmonary tissue after CRT, correlated with the incidence and severity of RP at 1–6 months after treatment, which is consistent with previous reports [12,13,15]. Although GLG did not correlate with RP at 4–6 months after treatment in our cross-sectional analysis, it did correlate with RP at 1–6 months after treatment in our longitudinal analysis.

In another study of 20 patients with stage III NSCLC who had undergone FDG PET/CT imaging before and after thoracic irradiation [4], the authors suggested that lung SUVmean and GLG after treatment were potentially useful biomarkers for quantifying lung inflammation. A potential drawback of using SUVmax as a biomarker is that the reported values may reflect the presence of only one or a few "hot" pixels [16]. By contrast, SUVpeak measurements (a circular volume of a fixed diameter [e.g., 1 cm] in the hottest area) are more reproducible, because they reflect the mean value of a larger number of pixels that are directly involved in and surrounding the "hottest" (highest-uptake) area. Thus SUVmean may be similar to SUVmax in terms of representing the area of highest metabolism, but it avoids the statistical fluctuations of SUVmax by incorporating larger numbers of pixels within the hottest tumor area [17].

The greatest strength of our study is our analysis of serial FDG PET scans obtained from the beginning of treatment until 12 months after treatment and our ability to correlate FDG uptake variables with RP severity (graded by CTCAE v3). Our longitudinal analysis indicated that SUVmax, SUVpeak, SUVmean, and GLG all showed similar trends from the completion of treatment to 12 months later (Fig. 2). Patients with CTCAE RP grade 2–3 experienced detrimental symptoms and had higher values of all FDG PET variables within the first 6 months after treatment relative to those with grade 0–1 RP, but this association was not observed past the sixth month after treatment (Fig. 2).

Our results are consistent with clinical findings on the development of RP, which in its most severe forms is characterized on imaging by an acute exudative phase and a chronic fibrosis phase [18,19]. The former usually occurs within the first 6 months after treatment and the latter afterward [20]. Radiation fibrosis, which occurs >6 months after radiotherapy, may cause less FDG uptake than the acute/exudative inflammation during the first few months. Thus FDG PET may be more valuable for predicting RP within the first 6 months after treatment rather than afterward.

Further, the association of FDG uptake variables with RP grade from our logistic regression models (Table 3) suggests that the SUVmax, SUVpeak, SUVmean, and GLG values for a specific patient soon after treatment could reflect the likelihood of that patient subsequently developing clinically significant RP. To the best of our knowledge, no studies have evaluated using FDG PET *after* treatment to predict the subsequent development of RP. Several other studies have attempted to identify predictors of RP from images obtained *before* treatment; in one such study, a retrospective analysis of 100 patients who had FDG PET/CT images available before treatment [9], pretreatment pulmonary FDG uptake, quantified by SUV95, could predict clinician-rated RP. However, the SUVmean, SUVmax, SUVpeak, and GLG as reported here are easier to measure than SUV95, and using the proposed cut-off values (taken from median data) of SUVmax ≥4.54, SUVpeak ≥3.69, SUVmean ≥0.78, and GLG ≥2295 after treatment could be useful for identifying patients who may be at higher risk of subsequent development of severe lung toxicity and thus may require more intensive management of RP or perhaps prophylaxis.

This study did have some limitations. First, although FDG-PET scans to assess and predict the development of RP were a secondary endpoint in the clinical trial, and the scans were obtained prospectively according to the protocol for that trial, there were some missing data in some of the time points. Second, FDG uptake can be affected by several kinds of factors including injection time, body weight, the decision to order imaging based on RP-related symptoms, and available scanning time. Third, not every patient was evaluated at each period, and so the numbers of patients in each time interval varied. However, 83% patients in this study had at least 2 FDG PET scans, and 50% patients had 3 or more FDG PET scans. For the patients with 4 FDG PET scans, we obtained both cross-sectional and longitudinal correlations between CTCAE grade and PET variables and got the same results. Our power analyses indicated that having power of 80% to detect an effect size of 0.78 $[(\mu 2 - \mu 1)/\sigma]$ at 4 time points, as shown in the SUVmean analysis, with correlation of the repeated measures of 0.487, our study needed only 16 patients for each group, and therefore our sample was large enough for these longitudinal analyses. Finally, although our patients were participating in a prospective randomized trial and scans were obtained prospectively, this analysis was retrospective and subject to all of the limitation of post hoc analyses.

In conclusion, we have demonstrated in this study that the uptake of FDG by normal lung tissue during the first 3 months after completion of CRT correlated with the severity of RP during the first 6 months after treatment. We found that higher lung FDG uptake variables in the early intervals after treatment predicted higher-grade subsequent RP. Our cutoff values for FDG uptake after treatment (4.54 for SUVmax, 3.69 for SUVpeak, 0.78 for SUVmean, and 2295 for GLG) may be clinically meaningful for identifying patients at risk of developing radiation-related pneumonitis, one of the most important factors limiting radiation doses to thoracic tumors.

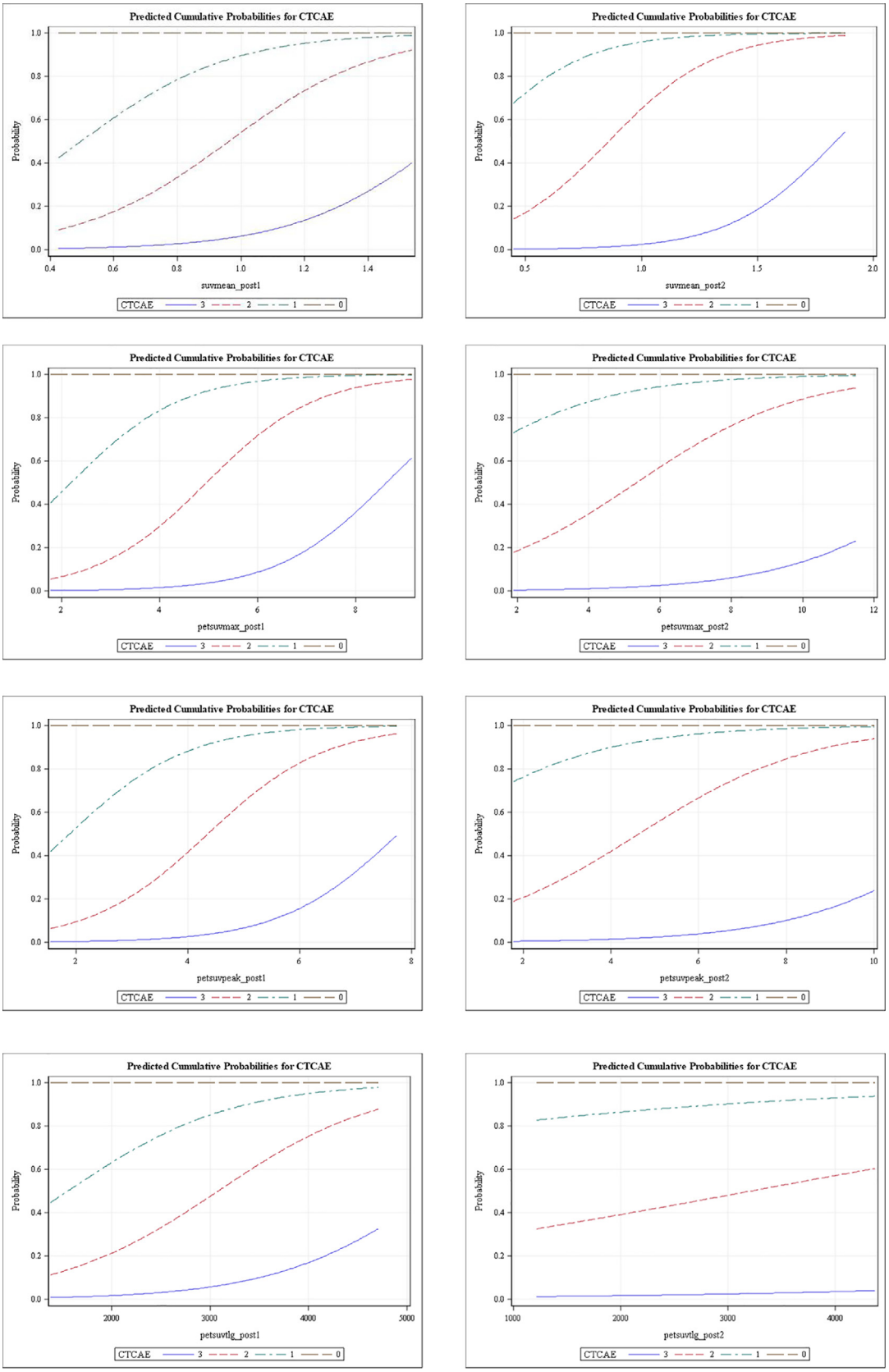

Fig. 3. Cumulative probabilities of developing grade 0, 1, 2, or 3 radiation pneumonitis (RP) according to FDG uptake variables on PET. Panels A and B, SUVmean; panels C and D, SUVmax; panels E and F, SUVpeak; panels G and H, global lung glycolysis. Abbreviations: SUV, standardized uptake value; post1, 1–3 months after treatment; post2, 4–6 months after treatment.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctro.2017.04.001.

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