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Patient-Reported Lung Symptoms as an Early Signal of Impending Radiation Pneumonitis in Patients with Non-Small Cell Lung Cancer Treated with Chemoradiation: An Observational Study

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Abstract

Purpose—Clinician ratings of concurrent chemoradiation (CRT)-induced radiation pneumonitis (RP) in patients with non-small cell lung cancer (NSCLC) are based on both imaging and patient-reported lung symptoms. We compared the value of patient-reported outcomes versus normal-lung uptake of ¹⁸F-fluoro-2-deoxyglucose in positron emission computed tomography (FDG PET/CT) during the last week of treatment, for indicating the development of grade 2 RP within 4 months of CRT completion.

Methods—132 patients with NSCLC reported RP-related symptoms (coughing, shortness of breath) repeatedly using the validated MD Anderson Symptom Inventory lung cancer module. Of these patients, 68 had FDG PET/CT scans that were analyzed for normal-lung mean standardized FDG uptake values (SUV_{mean}) before, during, and up to 4 months after CRT. Clinicians rated RP

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using CTCAE version 3. Logistic regression models examined potential predictors for developing CTCAE RP 2.

Results—For the entire sample, patient-rated RP-related symptoms during the last week of CRT correlated with clinically meaningful CTCAE RP 2 post-CRT (OR=2.74, 95% CI 1.25-5.99, $P=0.012$), controlled for sex, age, mean lung radiation dose, comorbidity, and baseline symptoms. Moderate/severe patient-rated RP-related symptom score (≥ 4 on a 0–10 scale, $P=0.001$) and normal-lung FDG uptake ($SUV_{mean} > 0.78$, $P=0.002$) in last week of CRT were equally strong predictors of post-CRT CTCAE RP 2 (C -index=0.78, 0.77).

Conclusions—During the last week of CRT, routine assessment of moderate to severe RP-related symptoms provides a simple way to identify patients with NSCLC who may be at risk for developing significant post-CRT RP, especially when PET/CT images of normal-lung FDG uptake are not available.

Keywords

radiation pneumonitis; lung FDG PET/CT; MD Anderson Symptom Inventory (MDASI); patient reported outcomes; concurrent chemoradiation (CRT)

INTRODUCTION

Radiation pneumonitis (RP) is a severe and potentially fatal complication of radiation therapy for patients with locally advanced non-small cell lung cancer (NSCLC). RP is an inflammatory reaction of the lung tissue that is characterized clinically by worsening dyspnea and/or coughing.

RP is diagnosed from a combination of radiological imaging changes and clinical symptoms. On radiological images, RP commonly presents as patchy infiltration in the alveolar spaces [1] that manifests as ground-glass opacities, consolidation, or both, usually within the irradiated lung. Computed tomography alone is not sufficiently sensitive or specific for detecting early tissue injury and inflammation in the lung parenchyma [2]. A more effective method for visualizing the inflammatory process is ^{18}F -fluoro-2-deoxyglucose (FDG) positron emission computed tomography (PET/CT). Pulmonary inflammation manifests on FDG PET/CT as enhanced FDG uptake by the lung parenchyma, which enables quantitative assessment of RP [3; 4]. Increased FDG uptake is linked with several inflammatory processes [5-7], and high and diffuse FDG uptake after the completion of radiation therapy has been reported among patients who developed RP [2; 8]. We recently showed that a mean normal-lung standard uptake value (SUV_{mean}) > 0.78 1–3 months after therapy predicted later development of clinically meaningful RP [9].

RP is typically documented by clinicians who rate the severity of treatment-related toxicities according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Most clinical studies consider CTCAE grade 3–5 RP to be a significant clinical outcome (even though RP at this level is increasingly rare, thanks to advanced radiotherapy techniques) [10; 11]; in contrast, CTCAE grade 2 RP-related symptomatic effects have not been well studied. Alternatively, patient-reported outcomes (PROs) are increasingly used to document patient symptom burden, functional ability, and quality of life

[12]. The MD Anderson Symptom Inventory (MDASI) [13] is a brief yet comprehensive PRO-based multisymptom questionnaire with demonstrated sensitivity and utility for capturing symptom burden in patients with NSCLC during the acute phase of concurrent chemoradiation therapy (CRT) [14-16]. Even so, prospective PRO-based studies that quantify the development of RP-related symptoms (eg, dyspnea, coughing) during CRT and the value of PROs for signaling the impending development of CTCAE RP 2 in patients with NSCLC post-CRT are lacking.

Having the ability to identify individuals at high risk for developing moderate-to-severe RP is vital [17; 18], given that 10%-20% of this patient population can be expected to develop this condition, along with related, dose-limiting symptomatic effects. Severe RP is fatal for approximately 50% of those who develop it. Although the utility of baseline PET/CT as a way to examine FDG uptake as a biomarker for quantifying and predicting lung inflammation and RP after thoracic radiotherapy has been explored [19; 20], this approach is costly, is typically only prescribed for patients who truly need it, and is limited by the availability of PET/CT scanners in community practices and by lack of skill in reading FDG PET/CT results. Further, whether the symptom burden represented by both clinician-rated RP and relevant patient-reported symptoms reflects FDG PET/CT imaging results is unknown.

Using data from a prospective randomized clinical trial that examined treatment toxicities in patients with stage II-IV NSCLC undergoing two types of CRT [21], we investigated whether patient-reported moderate to severe RP-related symptoms in the last week of CRT could serve as an early signal of impending clinically meaningful lung injury, in concordance with FDG PET/CT results. Given that RP typically develops 4–12 weeks after the end of therapy [22], we hypothesized that subjective PRO ratings of RP-related symptoms assessed during the last week of CRT and objective RP-related FDG PET/CT imaging changes would have similar value for indicating the subsequent development of CTCAE RP 2 within 4 months of treatment completion. Compared with FDG PET/CT results, patient-reported RP-specific symptom ratings collected as part of routine care could be a more cost-effective, widely accessible way to inform clinicians about patients who might be at high risk for developing RP, so that timely interventions to limit its extent or prevent it entirely can be initiated.

MATERIALS AND METHODS

Our study was a secondary analysis of a subset of data from a randomized trial. Detailed methods are described elsewhere [21].

Patients

We evaluated patients with NSCLC who were recruited in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas from June 2009 through April 2014 and who had participated in the PRO component of a randomized clinical trial (clinicaltrials.gov #NCT00915005). Eligible patients were 18 years old, had unresectable NSCLC, and were scheduled to receive curative-intent CRT with carboplatin and paclitaxel. Because we found no differences in RP severity by treatment type

(intensity-modulated radiation therapy vs passively scattered proton therapy), we did not use randomization code to stratify the sample by radiotherapy type [21].

The study was approved by the MD Anderson Institutional Review Board. Informed consent was obtained from all individual participants included in the study.

FDG PET/CT Image Analysis

FDG PET/CT scans were obtained from a subset of patients before, during, and at the end of CRT (after the delivery of 40–50 Gy), and for 4 months post-CRT. All patients fasted for a minimum of 6 hours to achieve a blood glucose level of 80–120 mg/dL (4.4–6.6 mmol/L) before intravenous administration of FDG (555–740 MBq [15–20 mCi]). Data were acquired with a GE Discovery ST PET/CT scanner 60 minutes after radiotracer injection, with 3 minutes per bed in 2D acquisition mode, from orbit to mid-thigh.

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), which automatically generated normal-lung SUV_{mean} values [19].

Patient-Reported Outcomes

Patients rated symptoms on a 0–10 scale via the MDASI lung cancer module (MDASI-LC) [7], which was administered before CRT commenced, weekly during CRT, weekly for 2 months post-CRT, and then every other week until 4 months post-CRT. Patients responded to the questionnaires either on paper or with a computerized, telephone-based interactive voice system. We analyzed two composite MDASI-LC symptom-burden scores: RP-related symptoms (component score of shortness of breath and coughing) and systemic symptoms (component score of fatigue, disturbed sleep, and lack of appetite, the three most-severe symptoms identified in previous studies of this patient population [15]). Any score ≥ 4 was considered moderate to severe [23–25]. The PRO assessment made 0–7 days before completion of CRT was used as the end-of-therapy timepoint.

Clinician-Rated RP

RP was scored using CTCAE version 3. Each patient had 1–2 CTCAE grades during the 1–4 months after RT. The highest score assigned within the post-CRT study period was used in the analysis. Each adverse event was rated from 1–5: grade 1, asymptomatic, radiographic findings only; grade 2, symptomatic, not interfering with activities of daily living; grade 3, symptomatic, interfering with activities of daily living, O_2 indicated; grade 4, life-threatening, ventilatory support indicated; Grade 5, dead [18]. All CTCAE scores were based on radiographic imaging or reports, clinic notes from treating clinicians, and other consultations. Cases were reviewed by physicians and nurses until all discrepancies were resolved by unanimous agreement.

Statistical Analysis

This is a secondary analysis of data collected under the original randomized controlled trial. We included all patients who provided PRO data during the last week of CRT. Patient characteristics were evaluated with descriptive statistics. Loess curves present the

trajectories of the mean severity of systemic and RP-related symptoms over time during and after CRT. Mixed-effect models were used to compare changes in PRO scores over time, from before CRT to 4 months after CRT, and between patients with CTCAE RP 2 vs 1. Random intercepts were included, and weeks from randomization were treated as continuous time variables in all mixed-effect models. Mixed-effects modeling accounts for correlations between repeated observations in the same subject, unequally spaced or missing observations, and expression of linear correlations while controlling for confounding variables [26].

Among the subgroup of patients who contributed both PROs and imaging data at end of CRT, the association between PRO and FDG PET/CT (normal-lung SUV_{mean}) variables and posttreatment CTCAE RP grade (2 vs 1) were estimated using multiple logistic regression models. We assessed the *C*-index to compare the performance of four models: basic model (age, sex, comorbidities, mean lung dose, baseline RP-related PRO score), SUV_{mean} model (basic model + SUV_{mean}), RP-symptom model (basic model + RP-related symptoms at end of CRT), and combined model (basic model + SUV_{mean} + RP-related symptoms at end of CRT). The *C*-index is used to assess the discriminatory ability of standard logistic models; $C=0.5$ indicates random predictions and $C=1.0$ indicates a perfectly discriminating model [27]. This method has been used to compare the accuracy of PROs in predicting clinical outcomes [28]. Models were compared by log-likelihood ratio test to examine whether adding RP-related symptoms significantly improved the goodness-of-fit.

All patients who contributed PROs at end of therapy were included in the logistic regression analyses to generate the value of PROs as early signals of the impending development of post-CRT CTACE RP 2.

SAS version 9.3 was used for all statistical analyses. Statistical significance was set at $P<0.05$, and all tests were 2-tailed.

RESULTS

Patient characteristics are shown in Table 1. Of 152 patients who completed the treatment regimen in the trial, 132 provided PRO data during the last week of CRT and were retained for analysis; of these, 68 also provided FDG PET/CT imaging scans. Most patients had good performance status (0-1) and stage III disease; none died during the study. Forty-five percent developed CTCAE RP 2. All patients received carboplatin and paclitaxel chemotherapy.

Patient-Reported Symptoms and FDG PET/CT Profiles Over Time

Patient-reported systemic symptoms (mean of MDASI-LC fatigue, disturbed sleep, and lack of appetite) increased during therapy (est=0.22, 95%CI 0.17-0.27; $P<0.0001$) but decreased post-CRT (est=-0.07, 95%CI -0.09-0.05; $P=0.0006$) (Figure 1A). We observed no group-by-time interaction for systemic symptoms between patients who developed CTCAE RP 2 vs those who did not ($P=0.148$). Conversely, RP-related symptoms (mean of MDASI-LC shortness of breath and coughing) increased gradually from the start of CRT to 4 months post-CRT (est=0.03, 95%CI 0.02-0.05; $P<0.0001$) (Figure 1A). Longitudinally, RP-related symptoms were significantly higher for patients with CTCAE RP 2 vs 1 (est=0.945,

$P<0.001$) (Figure1B). By the last week of CRT, 33.8% of patients reported moderate to severe RP symptoms. Post-CRT, 67% of patients had moderate to severe RP symptoms with grade 2–4 RP.

The longitudinal increase in SUV_{mean} was significantly associated with the increase in patient-reported RP symptoms (est=1.62, 95% CI 0.87-2.35; $P=0.015$) but not with change in systemic symptoms over time.

There was no significant difference in mean RP-related symptom scores between patients with vs without SUV_{mean} data by end of therapy (3.0 vs 3.1; $P=0.810$).

Patient-Reported RP-Related Symptoms as an Early Signal of RP Risk

In a logistic regression analysis of all 132 patients with MDASI-LC data during last week of therapy, controlled for sex, age, comorbidities, mean lung dose, and baseline patient-rated RP symptoms, patients reporting RP-related symptom severity at 4 had 2.7 times the risk for developing CTCAE RP 2, compared with those reporting RP-related symptom severity at <4 at the end of therapy (OR=2.74, 95% CI 1.25-5.99, $P=0.012$).

Patient-Reported RP-Related Symptoms and Normal-Lung SUV_{mean} as Early Signals of RP Risk

For the 68 patients with both PRO and imaging data, controlled for sex, age, mean lung dose, and baseline patient-rated RP symptoms, RP-related symptoms during the last week of therapy were significantly associated with subsequent development of CTCAE RP 2 post-CRT ($P=0.001$), as was normal-lung SUV_{mean} at end of therapy ($P=0.002$). Goodness-of-fit was significantly improved when patient-reported RP-related symptoms in the last week of therapy were added into the basic model ($P=0.0003$) or added into the model with SUV_{mean} at end of therapy ($P=0.0009$).

The C -indexes for these presented similar levels of predictive value (0.78, 95% CI 0.65-0.89 for the RP-symptom model versus 0.77, 95% CI 0.66-0.90 for the SUV_{mean} model), although the combined model with both end-of-therapy RP-related PROs and SUV_{mean} presented the strongest C -index (0.85, 95% CI 0.75-0.95) (Table 2). An agreement contrast analysis showed that the C -indices for the basic model and the SUV_{mean} model did not differ significantly from each other ($P=0.932$).

DISCUSSION

In this study of 132 patients with stage II-IV NSCLC up to 4 months after CRT, a patient-reported RP-related symptom score 4 on a 0–10 scale during the last week of therapy correlated with subsequent development of CTCAE RP 2 during the 4 months post-CRT. Further, the subjective PRO-based model agreed with the objective measure (SUV_{mean} post-CRT) regarding the chance for developing CTCAE RP 2. These results suggest that a patient-reported RP-related symptom score may itself signal the imminent development of moderate to severe RP post-CRT, independent of other types of measures. Even so, if an institution's routine clinical practice includes PET/CT scans at the end of CRT, combining PET/CT with PRO assessments would be ideal for identifying high-risk patients.

Our findings suggest that pulmonary symptoms worsen as radiation dose accumulates, whereas PROs increase gradually from the start of CRT to 4 months post-CRT (Figure 1A). Benefitting from a longitudinal, quantitative study design, we demonstrate for the first time that patients with CTCAE RP 2 experience significant worsening of RP-related (but not systemic) symptoms (Figure 1B), compared with patients with CTCAE RP 1. PRO-based RP-related symptom profiles were consistent with normal lung SUV_{mean} results and CTCAE grades [9].

PET/CT imaging of the baseline intensity of FDG uptake can be used to identify patients at higher risk for developing high-grade RP [19; 29–31]. Our results confirmed not only this observation, but also the value of the intensity of FDG uptake in pulmonary tissue near completion of treatment for indicating the subsequent development of post-CRT CTCAE RP 2. Our recent study [9] defined an FDG uptake cutpoint that might aid in applying this knowledge in patient care: a lung SUV_{mean} of 0.78 by end of CRT presents a sensitive threshold for predicting later CTCAE RP 2.

Even easier, PROs, such as those obtained from the MDASI-LC, are becoming increasingly appreciated in research and clinical practice. PRO-based symptom instruments are sensitive to early response to CRT and more reflective of treatment-induced toxicity [32; 33]. The current study supports the utility of a toxicity-specific PRO component score (mean of coughing and shortness of breath) for capturing lung-inflammation processes involved in the development of even lower-grade RP (1, which we found in 32% of patients) [7; 12; 34].

Admittedly, only 7 patients (5.3%) in our study experienced CTCAE grade 3 RP, probably because we use advanced radiation delivery techniques to minimize the radiation exposure to normal lung. However, 39% of patients had grade 2 RP, representing a group that should be targeted for further care. By the end of therapy, the ability of RP-related symptoms, but not systemic symptoms, to signal which patients were likely to develop post-CRT CTCAE RP 2 paralleled that of the objective FDG PET/CT results and clinician-rated RP toxicity scores, suggesting that PROs are sensitive to treatment-related effects. Model-fit testing demonstrated that both PRO and SUV_{mean} models had significant value for signaling RP-related clinical outcomes. *C*-index statistics showed that predictive accuracy increased 18% by adding RP-related symptoms and 17% by adding SUV_{mean} , suggesting that these two markers are equally strong predictors.

We used a previously defined score of 4 on the 0–10 scale to indicate clinically meaningful RP-related symptoms at the end of treatment and to signal the impending development of clinically significant RP (CTCAE RP 2) post-CRT. In a busy oncology practice, predefined PRO-based cutpoints could be more user-friendly than FDG PET/CT results for identifying patients who are at high risk for developing RP and who may need more intensive and individualized follow-up for RP management.

Our study had several limitations. Because this symptom study was a secondary analysis, no sample size was calculated during the study design. Instead, we included every patient who provided PRO data during the last week of chemoradiation therapy. Further, only patients with a clinical indication for imaging examination, in the treating physician's opinion,

underwent FDG PET/CT scanning at the end of therapy. Thus, only a subset of patients (68/132) were included in the modeling comparing the value for both PROs and SUV_{mean} as signals of the impending development of CTCAE RP 2. However, we used all 132 patients and each patient's worst post-CRT CTCAE RP score to generate the OR (95%CI) for the final PRO model. Further, we note that FDG uptake may be affected by several factors, including injection time and body weight, and that different PET/CT scanners can produce different results for the same patient.

In summary, we fully defined the value of patient-reported RP-related symptom burden (dyspnea/coughing) at end of CRT for NSCLC for signaling the subsequent development of clinically significant RP post-CRT. Both the subjective RP-related symptoms and the objective FDG PET/CT outcomes had similar value for predicting post-CRT RP. Given that imaging can be costly and is generally done only when clinically indicated, especially in community settings, assessing RP-related symptoms via the PRO-based MDASI-LC at the end of therapy could be a simple, inexpensive, yet clinically meaningful method for identifying patients who may need individualized symptom control post-CRT.

Knowing when a patient is at risk for RP would promote optimization of treatment and supportive-care strategies, not only to ensure cancer control, but also to minimize the effects of treatment on daily functioning. Given the recent encouraging report showing that routine PRO assessment in oncology care significantly prolonged survival [35], further research into whether the use of PROs in routine patient care can reduce grade 2 RP and RP-related mortality is warranted.

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Fig. 1.

Time trajectories of patient-reported RP-related symptom ratings (MDASI-LC), clinician-reported RP grades (CTCAE), and FDG PET/CT results (normal-lung SUV_{mean})

(a) MDASI-LC symptom component scores for RP-related symptoms (mean of shortness of breath and coughing) and systemic symptoms (fatigue, disturbed sleep, lack of appetite). (b) MDASI-LC RP-related symptoms by post-CRT CTCAE RP grade (1 vs 2).

Abbreviations: CRT, concurrent chemoradiation therapy; CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3; FDG PET/CT, ^{18}F -fluoro-2-deoxyglucosepositron emission computed tomography; MDASI-LC, MD Anderson Symptom Inventory lung cancer module; RP, radiation pneumonitis; SUV, standard uptake value of normal lung tissue on positron emission tomography.

Table 1Patient characteristics (*N*=132)

Characteristic	<i>n</i>	%
Age, years		
Median (range): 65 (33–84)		
Sex		
Male	71	53.8
Female	61	46.2
Race		
White	117	88.6
Other	15	11.4
Disease stage		
I/II	24	18.2
III	102	77.2
IV	4	3.0
Zubrod performance score at baseline		
0	1	0.7
1	140	92.1
2–3	11	7.2
4	0	0
Charlson Comorbidity Index		
0	31	46
1	17	25
2	13	19
3–4	7	10
Highest CTCAE RP grade post-CRT ^a		
0	31	23.5
1	42	31.8
2	52	39.4
3	7	5.3
4	0	0
	<i>n</i>	Median (range)
Gross tumor volume, cm ³	132	69.8 (1.9–686.6)
Total tumor dose, Gy	132	70 (60–87)
Mean lung dose, Gy	132	17.25 (4.2–23.7)
	<i>n</i>	Mean (SD)
SUV _{mean}		
Before CRT	149	0.67 (0.17)
During CRT	74	0.64 (0.18)

Characteristic	<i>n</i>	%
After CRT	131	0.80 (0.24)
RP-related symptoms ^b		
Before CRT	145	2.19 (1.81)
During CRT	132	3.03 (2.25)
After CRT	86	3.53 (2.43)
Systemic symptoms ^c		
Before CRT	145	1.86 (1.82)
During CRT	132	3.76 (2.28)
After CRT	86	2.94 (2.09)

^aHighest grade assessed by CTCAE during the 4 months after treatment.

^bMean of the MDASI-LC items shortness of breath and coughing.

^cMean of the MDASI-LC items fatigue, disturbed sleep, and lack of appetite.

Abbreviations: CRT, concurrent chemoradiation; CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3; MDASI-LC, MD Anderson Symptom Inventory lung cancer module; RP, radiation pneumonitis; SD, standard deviation; SUV_{mean}, mean standard uptake value for normal lung tissue on positron emission tomography.

Table 2

Predictive value of end-of-CRT patient-reported RP-related symptoms and normal-lung SUV_{mean} for development of post-CRT CTCAE RP 2^a (*N*=68)

	Log-likelihood ratio test		Predictive accuracy	
	-2 log likelihood	<i>P</i>	<i>C</i> -index (95%CI)	Improved by adding the predictor
Basic model (age, sex, comorbidities, and mean lung dose)	84.07	Ref	0.66 (0.52-0.80)	
Model with SUV _{mean} only	72.20	0.0006	0.77 (0.66-0.90)	17%
Model with RP-related symptoms only	70.93	0.0003	0.78 (0.65-0.89)	18%
Model with both SUV _{mean} and RP-related symptoms	61.19	<0.0001	0.85 (0.75-0.95)	29%

^a All models included sex, age, comorbidities, mean lung dose, and baseline patient-rated RP symptoms. Abbreviations: CI, confidence interval; CRT, concurrent chemoradiation; CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3; RP, radiation pneumonitis; SUV_{mean}, mean standardized uptake value for normal lung tissue on positron emission tomography.