ORIGINAL ARTICLE

Predicting Radiation Esophagitis Using ^{18}F-FDG PET During Chemoradiotherapy for Locally Advanced Non–Small Cell Lung Cancer

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Received 31 July 2015; revised 9 October 2015; accepted 10 October 2015

ABSTRACT

Introduction: Treatment of locally advanced non–small cell lung cancer with chemoradiotherapy (CRT) is limited by development of toxicity in normal tissue, including radiation esophagitis (RE). Increasingly, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is being used for adaptive planning. Our aim was to assess changes in esophageal FDG uptake during CRT and relate the changes to the onset and severity of RE.

Methods: This prospective study in patients with stage II–III non–small cell lung cancer involved serial four-dimensional computed tomography and PET scans during CRT (60–74Gy). RE was recorded weekly using the Common Terminology Criteria for Adverse Events (v4.0), and imaging was performed at weeks 0, 2, 4, and 7. Changes in the esophagus's peak standard uptake value (SUV_{peak}) were analyzed for each time point and correlated with grade of RE using the Wilcoxon rank-sum test. The volume of esophagus receiving 50 Gy (V50) and volume of esophagus receiving 60 Gy (V60) were correlated with the development of RE, and the C-statistic (area under the curve [AUC]) was calculated to measure predictivity of grade 3 RE.

Results: RE developed in 20 of 27 patients (74%), with grade 3 reached in 6 (22%). A significant percentage increase in SUV_{peak} in the patients with RE was noted at week 4 ($p = 0.01$) and week 7 ($p = 0.03$). For grade 3 RE, a significant percentage increase in SUV_{peak} was noted at week 2 ($p = 0.01$) and week 7 ($p = 0.03$) compared with that for less than grade 3 RE. Median V50 (46.3%) and V60 (33.4%) were significantly higher in patients with RE ($p = 0.04$). The AUC measurements suggested that the percentage change in SUV_{peak} at week 2 (AUC = 0.69) and V50 (AUC = 0.67) and V60 (AUC = 0.66) were similarly predictive of grade 3 RE.

Conclusions: Serial FDG-PET images during CRT show significant increases in SUV_{peak} for patients in whom RE develops. The changes at week 2 may predict those at risk for the development of grade 3 RE and may be informative for adaptive planning and early intervention.

Keywords: Non–small cell lung cancer; Chemoradiotherapy; Esophagitis; 18-FDG PET; Toxicity

Introduction

Dose escalation and adaptive radiation therapy have been proposed for use in managing locally advanced non–small cell lung cancer (NSCLC). Unfortunately, such

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Disclosure: This research was supported in part by Canadian Cancer Society (Ontario Division) Lung Cancer Research Grant #020348. The authors declare no other conflict of interest.

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ISSN: 1556-0864

http://dx.doi.org/10.1016/j.jtho.2015.10.006

efforts have been hindered by development of increased toxicity in normal tissue, particularly radiation esophagitis (RE).[1,2] Still, the current standard chemoradiotherapy (CRT) regimens yield poor outcomes, with the 5-year overall survival rate at 15%.[1]

Grade 3 RE will develop in approximately 18% of patients undergoing CRT[1,3]; it is associated with severe morbidity and can necessitate supportive feeding and hospital admissions and can also potentially prolong treatment times and negatively affect overall survival.[4] Several dosimetric and volumetric factors have been suggested to be predictive of RE, including mean esophageal dose,[5] esophagus length, and volume of esophagus receiving greater than 50 Gy (V50)[6] or 60 Gy (V60), as is shown in the meta-analysis by Palma et al.[3]

^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) imaging is established in staging lung cancers and has been shown to correlate with outcomes after CRT.[4,7–9] Using FDG-PET to plan radiotherapy improves accuracy of contouring[10,11] and can aid in adaptive planning to boost regions of high or residual uptake.[12–14] The optimal timing of dose escalation is to be determined[12,13]; however, meeting normal tissue constraints to avoid damage remains a limiting factor.

There are few studies reporting FDG-PET changes in relation to development of RE. Nijkamp et al. showed PET changes within 3 months after CRT in patients in whom RE developed,[15] whereas Yuan et al. showed that PET standard uptake value (SUV) increased significantly after 45 Gy of radiotherapy, particularly in patients with stage III lung cancer who were receiving concurrent chemotherapy, and they hypothesized that this increase could be predictive of RE.[7]

The primary objective of this study was to assess FDG avidity within the esophagus at set intervals during a course of CRT and relate the observed changes in uptake to onset of any grade of RE and onset of grade 3 toxicity. The secondary objective was to relate physical dose parameters to the observed FDG-PET changes and assess which would be most predictive of grade 3 toxicity.

Methods

This was a prospective single-institution, single-arm cohort study of FDG-PET imaging during CRT for patients with locally advanced NSCLC. The patients enrolled had inoperable histologically confirmed NSCLC but were deemed suitable for concurrent platinum-based chemotherapy with radical radiotherapy. Patients received 60 Gy to 74 Gy (2 Gy per fraction). All study patients underwent four-dimensional (4D) FDG-PET/computed tomography (CT) scans for radiotherapy planning at week 0; for response monitoring at weeks 2, 4, and 7 during CRT; and subsequently at a 3-month follow-up. Patients were evaluated weekly during treatment, and RE was recorded using the Common Terminology Criteria for Adverse Events (v4.0).

All 4D PET/CT scans were performed in the treatment position on a dedicated PET-CT simulator (Discovery ST, GE Healthcare, Milwaukee, WI). Patients were fasted and had regular blood glucose monitoring before receiving the injection of FDG (5 MBq/kg) for the PET scan. All PET/CT scans for the given week were inherently coregistered, and both exhale and inhale scans were transferred into our clinical treatment planning system (Pinnacle[3], version 9.0, Philips Radiation Oncology Systems, Milpitas, CA) for contouring, image registration, and plan generation. The 4D images from subsequent weeks were coregistered to the planning scans on the basis of the exhale 4D CT scans and a rigid registration based on bony anatomy and the carina. Quality of the registration was assessed by a physicist and a physician before contouring.

The gross tumor volume (GTV) was contoured on the planning 4D CT data set, copied onto the data sets containing registered PET-CT data, and modified according to FDG uptake. Clinical target volume expansions of 5 mm were created on both inhale and exhale images and combined to form the internal target volume (ITV), and an additional 5 mm expansion was added to ITV to form the planning target volume.[16] Organs at risk were contoured on the exhale 4D CT data set according to our standard protocol for planning lung treatment.

The esophagus was contoured from cricoid to gastroesophageal junction on the basis of CT images and then transferred to the coregistered PET data set. Figure 1 illustrates an example case of a coregistered PET with dosimetric information showing the change in PET uptake seen in GTV on week 2 and the changes within the esophagus by week 7. Previous studies suggested FDG-PET changes from RE are seen mainly at the level of the tumor,[7] which correlates with the areas receiving higher radiation doses. To evaluate the FDG-PET changes caused by RE, we segmented the esophagus into two regions, one receiving more than 5 Gy (ESO-A) and the other serving as a background region receiving less than 5 Gy (ESO-B). This segmentation allowed us to use the esophagus as its own control and compare changes in FDG-PET uptake that were due to radiation delivery.

Many patients had tumor or nodal disease adjacent to the esophagus, for which FDG-PET uptake was expected to decrease with treatment. We therefore analyzed ESO-A after excluding the region within 5 mm of the ITV to reduce confounding FDG-PET changes related to tumor response, as shown in Figure 2.

Peak SUV (SUV_{peak}), defined by the 95th percentile, was used for evaluation because it was considered more reproducible and less influenced by outlying values than

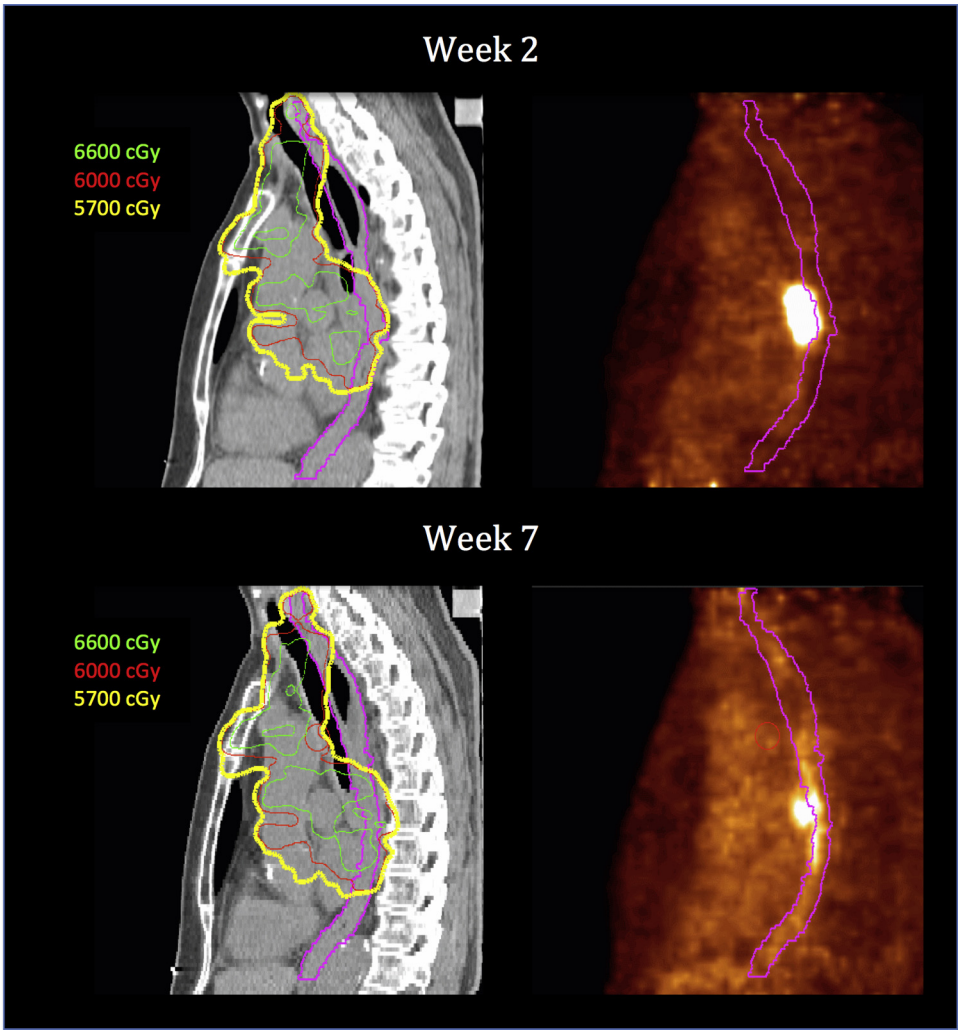

Figure 1. Computed tomography with dose distribution (*green*, *red*, *and yellow isodose curves*) and corresponding positron emission tomography images demonstrating changes within the esophagus (contour) from week 2 to week 7 of chemoradiation.

is SUV_{max}.[17] The SUV_{peak} for each region was determined on the exhale 4D PET scan. We evaluated the percentage increase in SUV_{peak} in ESO-A compared with that in the background (ESO-B) by using the following equation:

$$\%\ increase = 100 \times \frac{[SUV_{peak}(ESO-A) - SUV_{peak}(ESO-B)]}{SUV_{peak}(ESO-B)} \quad (1)$$

Statistical Considerations

The analysis was carried out with SAS software (v9.3, SAS Institute, Cary, NC). Descriptive statistics were used to summarize the demographics and disease characteristics. Fisher's exact test and Wilcoxon Mann-Whitney test were performed to test their association with the development of any RE (grade >0) and specifically grade 3. The Wilcoxon Mann-Whitney test was also used to test association of PET and volumetric (primary and nodal GTV) and dosimetric parameters, such as the percentage increase in SUV_{peak}, V50, and V60, with development of any grade of RE and grade 3 RE. Furthermore, the C-statistic (area under the curve [AUC]) was calculated for these parameters to demonstrate their predictivity of development of any grade of RE (grade >1) and particularly grade 3.

Ethical Considerations

The study protocol was approved by the local research ethics board and independent ethics committee. It was conducted in accordance with the ethical principles from the Declaration of Helsinki and was consistent with the guidelines of the International Conference on Harmonization Good Clinical Practice and applicable regulatory requirements.

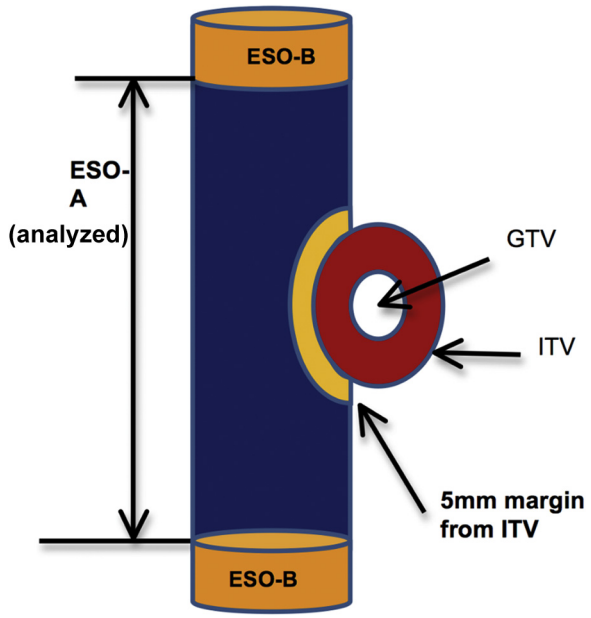

Figure 2. Esophagus segmentation for evaluation.

Table 1. Patient Demographics and Characteristics

Variable	Value (N = 27)
Median age (range), y	63 years (36-79)
ECOG performance status, n (%)	
0	15 (56%)
1	12 (44%)
Sex, n (%)	
Female	7 (26%)
Male	20 (74%)
Histologic diagnosis, n (%)	
NSCLC NOS	4 (14.8%)
Adenocarcinoma	18 (66.7%)
Squamous	5 (18.5%)
Tumor (T) stage, n (%)	
T1	8 (29.6%)
T2	6 (22.2%)
T3	8 (29.6%)
T4	3 (11.1%)
Tx	2 (7.4%)
Nodal (N) stage, n (%)	
N1	2 (7.4%)
N2	18 (66.7%)
N3	7 (25.9%)
Disease stage, n (%)	
2A	2 (7.4%)
3A	14 (51.9%)
3B	11 (40.7%)
Gross tumor volume (cc)	
Primary, median (range)	69.3 (0-351.4)
Nodal, median (range)	25.9 (4.6-152.0)

ECOG, Eastern Cooperative Oncology Group; NSCLC NOS, non-small cell lung cancer not otherwise specified.

Results

A total of 27 patients on the study protocol were treated with CRT. Their demographic characteristics are shown in Table 1. All patients completed radiotherapy, with 25 patients (93%) receiving 60 to 66 Gy and two patients receiving 70 to 74 Gy in 2-Gy fractions. The two patients receiving 70 to 74 Gy had T2N2 disease and were considered to benefit from a higher dose while meeting the normal tissue constraints. Concurrent chemotherapy regimens included carboplatin/cisplatin (days 1, 8, 29, and 36) with etoposide (days 1–5 and 29–33) for 19 patients, cisplatin with pemetrexed (days 1, 22, and 43) for four patients, and carboplatin with paclitaxel (weekly) for four patients. Analysis of the development of RE in relation to concurrent chemotherapy regimen was not possible because of the small number of patients.

Of the 27 patients, 24 (89%) completed all concurrent chemotherapy cycles at the full dose. The remaining three patients missed one cycle on account of pancytopenia, grade 3 RE, and intercurrent infection. Although 22 patients were due to receive adjuvant chemotherapy 3 to 4 weeks after CRT, only 16 patients completed all planned cycles. As RE developed in all patients during CRT, with only one patient peaking with grade 3 RE during adjuvant chemotherapy, all patients receiving adjuvant chemotherapy were included in the analysis.

The maximum esophageal dose was 67.8 Gy (95% confidence interval: 63.2–72.4). RE developed in 20 patients (74%), and 14 of them reached maximum grade 2 toxicity at a median time of 3 weeks (range 1–5 weeks). Six patients (22%) had grade 3 toxicity that occurred at a median of 6 weeks (range 5–17.5 weeks). No grade 4 or 5 toxicity was noted in the study group. The time trend for development of RE during chemoradiation and timing of concurrent chemotherapy are shown in Figure 3. Of the six patients with grade 3 toxicity, two peaked after completion of radiotherapy (at week 10 and week 17.5); grade 3 toxicity developed during adjuvant chemotherapy in only one of these patients.

As shown in Table 2, there were no differences between patients with or without RE in terms of Eastern Cooperative Oncology Group performance score, age, sex, or histologic diagnosis. Stage of cancer was significant ($p = 0.04$) for development of esophagitis inasmuch as no toxicity developed in either of the two patients with stage II cancer. Tumor (T) and nodal (N) stage were not significantly associated with development of RE of any grade or grade 3. With regard to primary GTV or nodal GTV volumes, we did not note any significant differences between patients in whom any RE or grade 3 RE in particular developed (as shown in Table 3).

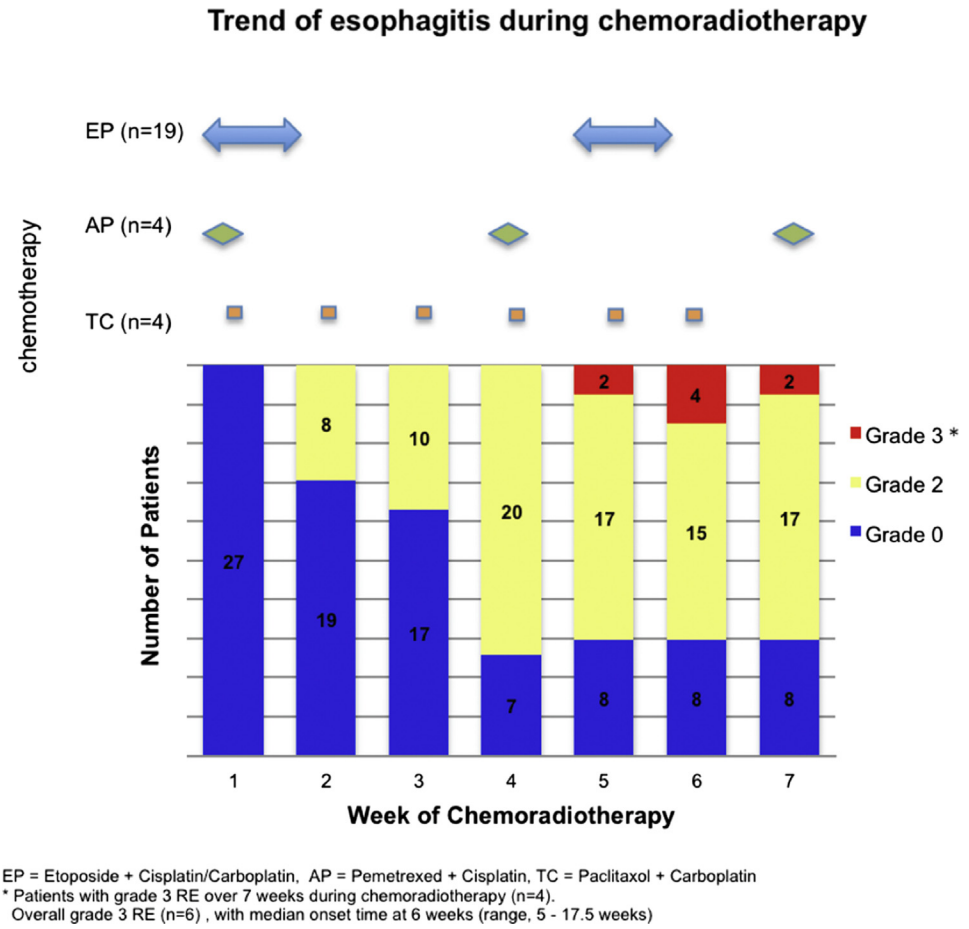

Figure 3. Development of esophagitis during chemoradiation and timing of concurrent chemotherapy.

The percentage increase in SUV_{peak} in ESO-A relative to ESO-B in patients in whom RE developed compared with that in patients with no RE was significant at week 4 ($p = 0.01$) and week 7 ($p = 0.03$), as is also shown in Table 3. Those with grade 3 RE also had a significant percentage increase in SUV_{peak} (ESO-A) at week 2 ($p = 0.01$) and week 7 ($p = 0.03$) compared with those having lower than grade 3 toxicity (see Table 3).

Tumor dose and maximum esophageal dose showed no significant difference in patients in whom any RE or grade 3 toxicity developed. Patients with RE had a mean V50 of 43.3% (± 11.4) and V60 of 30.9% (± 14.2). Both these values were significantly higher ($p = 0.04$) than in patients with no RE; however, neither V50 nor V60 was significant for predicting the development of grade 3 toxicity.

We calculated the C-statistic for V50 and V60 and the percentage increase in SUV_{peak} at week 2 for predicting grade 3 RE and found that the percentage increase in SUV_{peak} (week 2) (AUC 0.69) was similar to V50 (AUC 0.67) and V60 (AUC 0.66) from the standpoint of being predictive for the development of RE.

Discussion

This study is the first to look at evolving FDG-PET changes at multiple time points during the course of CRT in relation to the development of RE. The incidence and timing of development of RE that we noted in our study population were similar to those previously reported in patients undergoing CRT.[5,15,18,19] We did not find any correlation between age, histologic findings, performance status, or sex and development of RE. We noted a significant difference in number of patients with grade 3 RE compared with the number of patients with grade 2, which has been noted in other studies[7] and would be in keeping with higher doses delivered close to the esophagus because of mediastinal disease. We did not find any significant differences between T stage and N stage from the standpoint of relationship to development of RE, and there were no significant differences based on the tumor or nodal GTV. This fact may be explained by the location of the primary or nodal disease in relation to the esophagus, particularly if they were predominantly right sided.

Our data show an increase in SUV_{peak} during treatment in patients in whom RE develops compared with in

Table 2. Patient Demographics and Correlation with Esophagitis of Any Grade and Grade 3

	Esophagitis (Grade > 0)	No Esophagitis		Grade <3 RE	Grade 3 RE	
Variable	N = 20	N = 7	*p* Value	N = 21	N = 6[a]	p Value
Median age (range)	64 (36-79)	54 (37-71)	0.32	63 (37-79)	65 (36-78)	0.58
ECOG performance status, n (%)						
0	11 (55%)	4 (57%)	1.00	13 (62%)	2 (33.3%)	0.36
1	9 (45%)	3 (43%)		8 (38%)	4 (66.7%)	
Sex, n (%)						
Female	5 (25 %)	2 (29%)	1.00	5 (24%)	2 (33.3%)	0.63
Male	15 (75%)	5 (71%)		16 (76%)	4 (66.7%)	
Histologic diagnosis, n (%)						
NSCLC NOS	1 (5.0%)	3 (42.9%)	0.06	3 (14.3%)	1 (16.7%)	0.53
Adenocarcinoma	15 (75.0%)	3 (42.9%)		15 (71.4%)	3 (50.0%)	
Squamous	4 (20.0%)	1 (14.3%)		3 (14.3%)	2 (33.3%)	
Stage, n (%)						
2A	0 (0.0%)	2 (28.6%)	0.04	2 (9.5%)	0 (0.0%)	0.48
3A	10 (50.0%)	4 (57.1%)		12 (57.1%)	2 (33.3%)	
3B	10 (50.0%)	1 (14.3%)		7 (33.3%)	4 (66.7%)	
Tumor (T) stage, n (%)						
T1	7 (35.0%)	1 (14.3%)	0.56	7 (33.3%)	1 (16.7%)	0.91
T2	4 (20.0%)	2 (28.6%)		4 (19.0%)	2 (33.3%)	
T3	5 (25.0%)	3 (42.9%)		6 (28.6%)	2 (33.3%)	
T4	3 (15.0%)	0 (0.0%)		2 (9.5%)	1 (16.7%)	
Tx	1 (5.0%)	1 (14.3%)		2 (9.5%)	0 (0.0%)	
Nodal (N) stage, n (%)						
N1	0 (0.0%)	2 (28.6%)	0.08	2 (9.5%)	0 (0.0%)	1.00
N2	14 (70.0%)	4 (57.1%)		14 (66.7%)	4 (66.7%)	
N3	6 (30.0%)	1 (14.3%)		5 (23.8%)	2 (33.3%)	

[a]Total patients with grade 3 RE, median time of onset 6 weeks (range 5-17.5 wk).
RE, radiation esophagatis; ECOG, Eastern Cooperative Oncology Group; NSCLC NOS, non-small cell lung cancer not otherwise specified.

those without toxicity. Yuan et al.[7] had reported significant FDG-PET changes after delivery of 45 Gy, and similarly, other studies have also reported changes in SUV uptake related to the development of RE at single time points during or after radiotherapy.[15] Comparatively, our study demonstrated a trend toward progressively increasing SUV_{peak} from baseline during treatment, with the increase reaching significance by week 4 and week 7 and correlating with delivery of 40 Gy versus between 66 and 70 Gy. Clinically, in most patients the onset of RE was noted during week 2 and 3 of treatment, which may limit the application of these reported PET changes in practice.

Our study is also the first to report on FDG-PET changes specific to grade 3 toxicity, as is also shown in Table 3. The increase in SUV_{peak} for patients who had grade 3 RE compared with in those with lower than grade 3 RE was significant at week 2 and again at week 7, whereas the peak in clinical presentation occurred at week 6. These results suggest the existence of an early significant increase in SUV_{peak} at week 2 in patients in whom grade 3 toxicity develops. Identifying patients at risk for the development of RE ahead of clinical presentation could allow for earlier intervention to reduce morbidity. To date, however, there has been a lack of data indicating whether earlier management of RE would alter the clinical course of RE and morbidity.[11] Previous studies using interventions such as sucralfate[20] and amifostine[21] have not shown significance in preventing or reducing the incidence of RE, and medical management continues to be supportive. This may be due to the fact that the previous studies were performed on all patients and, unlike our study, did not have a predictive tool to identify patients at higher risk for the development of RE.

The trend toward increasing SUVs in patients with any grade of RE was not seen in patients with grade 3 toxicity. In the case of patients with grade 3 RE, SUVs at week 4 were not significantly increased; however, they did peak significantly by week 7. A review of the individual PET data from the six patients with grade 3 toxicity shows that in some patients, the FDG-PET SUV decreased or had a smaller increase between week 2 and 4; however, it peaked in all of them by week 7. Clinically, grade 2 toxicity had developed in all these patients by week 2 and they were given supportive treatment in the form of analgesia, anti-reflux medications, sucralfate, anti-inflammatory solutions, or combinations thereof.

Table 3. Comparison of Volumetric, Dosimetric, and PET Parameters with Any Grade and Grade 3 Radiation Esophagitis

	Esophagitis (Grade >0)	No Esophagitis		Grade <3 RE	Grade 3 RE	
Variable	N = 20	N = 7	*p* Value	N = 21	N = 6[a]	*p* Value
Primary GTV (cc), mean ± SD	87.4 ± 93.4	62.8 ± 39.4	0.76	61.4 ± 60.8	149.7 ± 116.4	0.06
Primary GTV (cc), median (range)	69.4 (0.0-351.5)	69.2 (6.9-106.6)		65.6 (0.0-236.2)	143.8 (12.3-351.5)	
Node GTV (cc), mean ± SD	40.1 ± 37.2	41.6 ± 39.3	0.98	37.4 ± 37.9	51.4 ± 34.6	0.23
Node GTV (cc), median (range)	25.2 (4.6-152.1)	27.2 (5.5-106.5)		23.8 (4.6-152.1)	43.2 (19.7-114.6)	
Tumor dose (Gy), mean ± SD	64.8 ± 3.8	65.1 ± 2.3	0.76	64.5 ± 3.0	66.3 ± 4.5	0.38
Max. esophagus dose (Gy), mean ± SD	68.8 ± 4.3	65.1 ± 4.8	0.11	67.0 ± 3.9	70.5 ± 6.3	0.37
Mean V50 ± SD (%)	43.3 ± 11.4	28.2 ± 18.3	0.04	38.2 ± 15.9	43.5 ± 9.6	0.54
Mean V60 ± SD (%)	30.9 ± 14.2	16.5 ± 15.3	0.04	26.0 ± 15.6	31.0 ± 16.2	0.62
Increase in SUV_{peak}, %						
Week 0, mean ± SD	8.1 ± 18.6	−1.9 ± 11.8	0.11	2.7 ± 15.1	15.2 ± 22.8	0.21
Week 2, mean ± SD	10.9 ± 14.6	5.8 ± 11.1	0.46	7.0 ± 14.4	18.5 ± 5.0	0.01
Week 4, mean ± SD	23.5 ± 39.5	−3.7 ± 11.2	0.01	15.8 ± 39.6	18.7 ± 23.8	0.54
Week 7, mean ± SD	45.5 ± 43.5	8.0 ± 14.7	0.03	26.6 ± 35.2	68.0 ± 48.4	0.03

[a]Total patients with grade 3 RE, median time of onset 6 weeks (range 5-17.5 weeks).
RE, radiation esophagatis; GTV, gross tumor volume; Max., maximum; SD, standard deviation; V50, volume of esophagus receiving 50 Gy; V60, volume of esophagus receiving 60 Gy; SUV_{peak}, peak standard uptake value.

It is possible that the difference in trend seen at week 4 in patients with grade 3 toxicity may be due to these interventions for RE having the effect of leading to a reduction in SUV uptake at week 4.

Comparatively, the patients with lower than grade 3 RE included asymptomatic patients and patients with grade 2 disease, who had symptoms ranging from mild and requiring no intervention to severe painful dysphagia affecting intake. Use of supportive treatments in this group was variable and irregular, which may explain why the trend in SUVs did not fluctuate. These findings suggest that interventions to alleviate the symptoms and severity of RE may be associated with a decrease in FDG-PET uptake. PET changes correlating with tumor response have been described, but no formal studies correlating change in SUV with treatment of RE have been performed.

Our data relate to RE due to CRT for lung cancer. It is well documented that RE is a common toxicity resulting from lung radiotherapy and that the severity increases with use of concurrent chemotherapy.[1,3] Studies examining PET changes resulting from RE have included mainly patients undergoing CRT and have identified the factors of radiotherapy dose and volume in relation to RE. However PET changes are noted in benign esophageal conditions, including gastric reflux and *Candida* infection,[22,23] and they have been described in patients with reflux esophagitis secondary to chemotherapy.[24] In chemotherapy-induced reflux esophagitis, PET uptake was noted to gradually increase during and following completion of chemotherapy. In our study the region of high SUV uptake was in the region of high dose and tumor volume and therefore is felt to be related to the combined effect of CRT, rather than chemotherapy related reflux esophagitis or *Candida* infection. Although patients received adjuvant chemotherapy, we thought it less likely to be contributing to RE because the onset of the toxicity occurred during CRT and in all patients except one, it peaked before commencement of adjuvant chemotherapy.

The application of dosimetric parameters in our study group showed that both V50 and V60 did correlate with development of RE, as was suggested by previous studies.[3,6] However, neither V50 nor V60 was significantly different in patients with grade 3 versus less than grade 3 toxicity—a finding that differs from those of the meta-analysis by Palma et al. The C-statistic suggests that using the percentage increase in SUV_{peak} at week 2 may be as predictive of grade 3 RE as are V50 and V60; however, our study has the limitations of small numbers of patients and grade 3 toxicity events.

In this study, we excluded a region of esophagus within the planning target volume to reduce the confounding FDG-PET changes related to tumor response. This approach may have excluded the region of esophagus receiving the highest dose, thus resulting in an underestimation of our values for SUV_{peak}. Even with this potential underestimation, however, we still demonstrated significant changes in SUV with respect to development of RE.

Our patient population was small but less heterogeneous that those of other studies examining RE and FDG-PET uptake. We included patients who were known to be at higher risk for the development of RE (predominantly grade 3 disease) and all of whom were receiving CRT in a dose of 2 Gy per fraction. The data collected are unique

in providing progressive FDG-PET changes related to development of RE in a population that may benefit from adaptive planning to improve outcomes. On the basis of our group's previous work on adaptive planning using FDG-PET, it was noted that dose escalation is feasible in more patients earlier in the course of radiotherapy (in week 0 or 2) rather than later (in week 4).[25] This study supports consideration of performing FDG-PET in week 2 to gain additional information regarding esophageal toxicity, which could influence decisions related to dose escalation. On the basis of the findings of both studies, we are currently undertaking a prospective study using PET in week 0 for dose escalation, and our protocol includes the option of performing a PET scan in week 2 to explore prevention of RE.

Conclusions

Our study highlights the complexity of using FDG-PET to evaluate RE and predict its course. In moving toward adaptive planning and dose escalation to improve outcomes, our findings suggest that evaluating patients with 4D PET at week 2 of CRT could be advantageous in highlighting those at risk for the development of grade 3 RE, a significant toxicity. Such evaluation may also provide an opportunity to consider earlier aggressive intervention in at-risk patients and investigate whether such intervention would alter the course of toxicity. Further prospective research on using FDG-PET as a tool for improving the therapeutic ratio of CRT in locally advanced NSCLC is warranted.

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