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

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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.

Introduction

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

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