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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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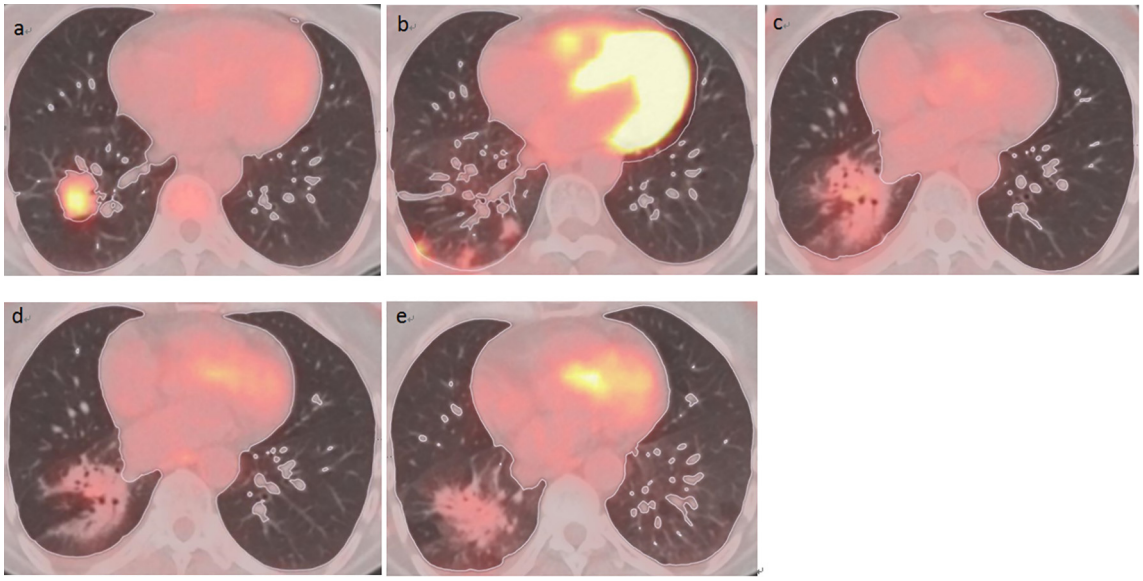

Fig. 1. PET/CT fusion scans from a patient showing inflammatory infiltration of the lungs, with interstitial infiltrates, ground glass opacities, homogeneous consolidation, and patchy consolidation. (A) Scan obtained before treatment; the bright yellow area inside the white outline is the primary lung 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