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Prediction of Radiation Esophagitis in Non–Small Cell Lung Cancer Using Clinical Factors, Dosimetric Parameters, and Pretreatment Cytokine Levels[1,2]

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Abstract

Radiation esophagitis (RE) is a common adverse event associated with radiotherapy for non–small cell lung cancer (NSCLC). While plasma cytokine levels have been correlated with other forms of radiation-induced toxicity, their association with RE has been less well studied. We analyzed data from 126 patients treated on 4 prospective clinical trials. Logistic regression models based on combinations of dosimetric factors [maximum dose to 2 cubic cm (D2cc) and generalized equivalent uniform dose (gEUD)], clinical variables, and pretreatment plasma levels of 30 cytokines were developed. Cross-validated estimates of area under the receiver operating characteristic curve (AUC) and log likelihood were used to assess prediction accuracy. Dose-only models predicted grade 3 RE with AUC values of 0.750 (D2cc) and 0.727 (gEUD). Combining clinical factors with D2cc increased the AUC to 0.779. Incorporating pretreatment cytokine measurements, modeled as direct associations with RE and as potential interactions with the dose-esophagitis association, produced AUC values of 0.758 and 0.773, respectively. D2cc and gEUD correlated with grade 3 RE with odds ratios (ORs) of 1.094/Gy and 1.096/Gy, respectively. Female gender was associated with a higher risk of RE, with ORs of 1.09 and 1.112 in the D2cc and gEUD models, respectively. Older age was associated with decreased risk of RE, with ORs of 0.992/year and 0.991/year in the D2cc and gEUD models, respectively. Combining clinical with dosimetric factors but not pretreatment cytokine levels yielded improved prediction of grade 3 RE compared to prediction by dose alone. Such multifactorial modeling may prove useful in directing radiation treatment planning.

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Introduction

Locally advanced non–small cell lung cancer (NSCLC) is often treated with concurrent chemotherapy and radiation [1,2]. Radiation esophagitis (RE) is a common complication of this treatment, with the incidence of grade 3 or greater symptoms having been reported to be as high as 25% in prospective trials [3]. Grade 3 esophagitis, per Common Terminology Criteria for Adverse Events, indicates severe symptoms requiring intervention such as tube feeding or parenteral

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nutrition [4]. Acute RE usually develops between 2 and 4 weeks of treatment and, in addition to affecting quality of life, can necessitate treatment break, which is associated with inferior outcomes [5–7]. With improved understanding of the clinical, dosimetric, and biologic risk factors for RE, it may be possible to identify patients for whom stricter esophageal dose constraints, prophylactic nutritional optimization, or other action may be beneficial for reducing toxicity and increasing chances for completing treatment.

Clinical factors associated with RE include concurrent chemotherapy, gender, age, body mass index, pretreatment dysphagia, and nodal stage [8–10]. Dose-escalated, twice-daily, and hyopfractionated radiotherapy courses increase risk [2,9,11–13]. Improved esophageal sparing with intensity-modulated radiotherapy (IMRT) has shown promise for reducing rates of grade 3+ RE compared to 3D-conformal (3DCRT), although this has not been consistent in all studies [14–22]. A multitude of dosimetric factors predictive of RE have been described, including mean esophageal dose, maximum esophageal dose, and various doses to esophageal surface area, length, and volumes (including total, infield, and relative volumes) [8–10,14,23–39]. More advanced approaches, including normal tissue complication probability modeling and anatomic correction, have shown unclear benefit [27,38,40]. More recently, a multi-institutional study evaluating multiple dose-volume metrics identified the maximum dose to 2 cubic cm (D2cc) and generalized equivalent uniform dose (gEUD) as superior parameters [41].

Cytokines represent a large, heterogeneous group of proteins involved in regulating inflammatory and fibrotic responses to injury [42]. Multiple cytokines have been linked with reflux-associated and eosinophilic esophagitis [43–45]. Single nucleotide polymorphisms (SNPs) in several cytokines and cytokine receptors have been associated with an increased risk of RE [46–48]. In mouse models, esophageal radiation has been found to induce transcription of multiple inflammatory cytokines [49,50].

While plasma cytokine levels have been extensively investigated as potential biomarkers for radiation-induced lung toxicity (RILT) (reviewed in [51]), their potential role in RE has been less well studied. In predicting RILT, differences in both pretreatment and radiation-induced plasma cytokine levels have been shown to correlate with risk [51–53]. However, as RE, compared to radiation pneumonitis and pulmonary fibrosis, often develops relatively early in radiation course, biomarkers evaluable prior to initiation of radiotherapy would be of greatest utility for RE, as they could direct intervention prior to the onset of toxicity. We hypothesized that variations in pretreatment plasma cytokine levels may correlate with increased or decreased risk of RE. We investigated combining pretreatment plasma cytokine data with dosimetric and clinical factors in an effort to improve prediction of RE in patients undergoing definitive radiotherapy for NSCLC. Dosimetric factors of D2cc and gEUD were selected due to recently published favorable results using these parameters [41].

Materials and Methods

Study Population

This work analyzed data from 4 prospective Institutional Review Board–approved lung-cancer studies: 1) a phase 1/2 study of radiation dose escalation with concurrent chemotherapy, 2-3) two consecutive studies using functional imaging and biomarkers to assess patient outcome, and 4) a study using midtreatment positron emission tomography (PET) to guide individualized dose escalation. Included in this analysis were patients with stage I to III NSCLC treated with standard fractionation, i.e., not stereotactic body radiotherapy. All clinical data were prospectively collected. Smoking status was missing for 10 patients, which was handled via single imputation.

Treatment Regimen

All patients were treated with definitive radiotherapy with or without sequential or concurrent chemotherapy. In cases of sequential treatment, chemotherapy was administered following radiotherapy. In most cases, radiation was delivered using 3DCRT as previously described [54], whereas IMRT was used for a minority of patients. Gross tumor volume included the primary tumor and any involved hilar or mediastinal lymph nodes, as determined by tissue diagnosis and/or PET–computed tomography (CT). Uninvolved lymph node regions were not included in the clinical target volume. The esophagus was contoured per Radiation Therapy Oncology Group guidelines on each patient's CT simulation scan. Tissue inhomogeneity corrections were applied for all plans.

As dose and fractionation varied among patients, we standardized values to biologic effective dose (BED), which normalizes doses of various fractionations by supposing a hypothetical condition of an infinite number of fractions. Tumor and esophageal BEDs were calculated using the linear-quadratic formula using an alpha/beta ratio of 10 Gy. Patients were evaluated weekly during radiotherapy and at regular intervals following completion of treatment. Radiation-induced esophageal toxicity was graded by physicians during on-treatment and follow-up visits per Common Terminology Criteria for Adverse Events v3.0 [4].

Cytokine Analysis

Plasma concentrations of 30 cytokines were measured: epidermal growth factor, eotaxin, fractalkine, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interferon α, interleukin (IL)1α, IL1β, IL2, IL4, IL5, IL6, IL7, IL8, IL10, IL12 subunit 40 (IL12p40), IL12 p35 and p40 heterodimer (IL12p70), IL13, IL15, IL17, IL1 receptor antagonist, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, macrophage inflammatory protein 1β, soluble CD40 ligand, TGFα, TGFβ1, TNFα, and vascular endothelial growth factor. This panel was selected to represent a diverse collection of cytokines implicated in many inflammatory processes including RILT and esophagitis of various etiologies. Cytokine measurements were performed in platelet-poor plasma samples within 2 weeks prior to the start of RT. Plasma samples were collected and prepared as previously described [55]. Briefly, blood samples were collected in the presence of the anticoagulant K_2EDTA (dikalium salt of ethylenediaminetetraacetic acid) and placed on ice immediately after collection. Samples were centrifuged within 2 hours of collection, after which the upper one-third of the supernatants was collected and stored at −80°C. Prior to cytokine measurements, samples were recentifuged in order to generate platelet-poor samples for analysis. TGFβ1 levels were measured using enzyme-linked immunosorbent assay as previously described [53], while the other 29 cytokines were measured using luminex multiplex assay (xMAP plasma assay; Luminx, St. Charles, MO). All sample tests were run in duplicate. Some cytokine measurements fell below a lower limit of detection. We used an *ad hoc* methodology to detect and account for these censored measurements, which is described in the Supplement.