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Esophagitis in patients with NSCLC

A model combining age, equivalent uniform dose and IL-8 may predict radiation esophagitis in patients with non-small cell lung cancer

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ABSTRACT

Background and purpose: To study whether cytokine markers may improve predictive accuracy of radiation esophagitis (RE) in non-small cell lung cancer (NSCLC) patients.
Materials and methods: A total of 129 patients with stage I–III NSCLC treated with radiotherapy (RT) from prospective studies were included. Thirty inflammatory cytokines were measured in platelet-poor plasma samples. Logistic regression was performed to evaluate the risk factors of RE. Stepwise Akaike information criterion (AIC) and likelihood ratio test were used to assess model predictions.
Results: Forty-nine of 129 patients (38.0%) developed grade ≥2 RE. Univariate analysis showed that age, stage, concurrent chemotherapy, and eight dosimetric parameters were significantly associated with grade ≥2 RE ($p < 0.05$). IL-4, IL-5, IL-8, IL-13, IL-15, IL-1α, TGFα and eotaxin were also associated with grade ≥2 RE ($p < 0.1$). Age, esophagus generalized equivalent uniform dose (EUD), and baseline IL-8 were independently associated grade ≥2 RE. The combination of these three factors had significantly higher predictive power than any single factor alone. Addition of IL-8 to toxicity model significantly improves RE predictive accuracy ($p = 0.019$).
Conclusions: Combining baseline level of IL-8, age and esophagus EUD may predict RE more accurately. Refinement of this model with larger sample sizes and validation from multicenter database are warranted.
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Radiation esophagitis (RE) is a common acute toxicity for non-small cell lung cancer (NSCLC) patients treated with radiation therapy (RT). It occurs during RT and often persists for several weeks after completion of RT. Grade ≥2 RE developed in about 50% of patients [1], which is clinically significant and may compromise the treatment result due to medical intervention or sometimes a treatment break. Identification of predictive factors for RE facilitates safe delivery of optimal prescribed dose to an individual patient. A meta-analysis published in 2013 [1] showed that V60 of esophagus provides the best predictive ability for RE among all clinical and dosimetric factors, although clinical stage, nodal stage, performance status, type of chemotherapy, RT schedule (total number of fractions, dose per fraction) are statistically predictive of RE.

Risk of RE in each individual patient is often not explained by these clinical factors. In clinical practice, patients with similar clinical factors and dose volume distributions to the esophagus commonly have different risks of RE. Additional biomarkers reflecting inherent radiosensitivity of esophagus might improve the predictive potential, including single nucleotide polymorphisms (SNPs) in the TGFβ1 gene [2–4], certain serum miRNA [5], or certain genetic parameters [6]. Currently, no reliable biomarker has been found that can be used in clinic as early predictors of RE.

Our hypothesis is (1) baseline levels of inflammatory cytokines, or their dynamic changes during RT, correlate with the risk of RE; and (2) the addition of inflammatory cytokines to other dosimetric and clinical factors improves the prediction of RE.

Methods

The study population included 129 patients with newly diagnosed stage I–III NSCLC, consecutively enrolled in 3 prospective Institutional Review Board-approved NSCLC studies conducted at

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the University of Michigan Cancer Center and the Veterans Affairs Medical Center, Ann Arbor, MI: (1) a phase 1/2 study of RT dose escalation (limited to a lung normal tissue complication probability [NTCP] value of <15%) with concurrent chemotherapy and 2 consecutive studies using (2) functional imaging and (3) biomarkers to assess outcome (ClinicalTrials.gov: NCT01190527, NCT00603057).

All patients received definitive radiotherapy. Radiotherapy was delivered using three-dimensional conformal technique. A median total dose of 70 Gy (range, 44–85.5 Gy) was administered in 2.0–2.9 Gy daily fractions over 4–7 weeks using 6 or 6/16 MV photons. The prescribed dose covered 95% planning target volume (PTV). In patients treated under dose escalated protocols, the effective volume of esophagus irradiated (Veff) computed with a normalization dose biologically equivalent to 72 Gy in 2 Gy fractions was limited to less than 1/3 of the esophagus.

On planning CT, the esophagus was defined to include the esophageal wall and lumen which was contoured from cricoid to gastroesophageal junction for dosimetric computation. Dose–volume histograms (DVH) for the esophagus were then calculated after conversion of doses to their 2 Gy equivalents (EQD2) using the linear quadratic model with alpha/beta of 10. The following dosimetric parameters of esophagus were retrieved or converted from the DVH: The total volume of esophagus (Vtotal); the maximum dose (Dmax); the mean dose (Dmean); the relative volume of esophagus receiving >60 Gy (rV60); the absolute volume of esophagus which received >60 Gy (aV60), and >70 Gy (aV70); generalized equivalent uniform dose (EUD) and NTCP. Lyman model parameters (TD50 = 68 Gy, $n = 1/a = 0.06$, $m = 0.11$) were used to compute EUD and NTCP [7].

All patients were evaluated prospectively weekly during RT, with follow-up evaluations at 1 month after completion of RT, every 3 months for 1 year, every 6 months at second year and yearly afterward. At each follow-up, patients underwent a history review and physical examination as well as a chest CT scan. Treatment-related toxicity including RE was evaluated and graded at the time of visit by the treating physician according to Common Terminology Criteria for Adverse Events version 3.0. The maximum esophagitis grade was recorded for each patient. The incidence of RE was calculated as the number of patients with RE divided by the total number of patients. The primary endpoint in this study was grade $\geq$2 RE, including dysphagia and odynophagia.

Serial blood samples were collected with K2EDTA (dikalium salt of ethylenediaminetetraacetic acid) anticoagulant within two weeks prior to RT (pre) and at 2 weeks (2w) and 4 weeks (4w) during RT. Blood samples were placed in ice immediately after collection, centrifuged within 6 h of collection at 3000 g for 30 min (4 °C), and supernatants were collected and stored at −80 °C until use.

Thirty cytokines related to inflammatory process and with available commercial kits were selected for this study. Measurements of cytokines were performed in these platelet-poor plasma samples. Commercial Human Cytokine/Chemokine Magnetic Bead Panel kits (MILLIPLEX® MAP, Cat. # HCYTMAG-60K-PX29 (premixed); Millipore, Billerica, MA) were used to measure the levels of 29 cytokines, including EGF, Eotaxin, Fractalkine, G-CSF, GM-CSF, IFNγ, IL-10, IL-12P40, IL-12P70, IL-13, IL-15, IL-17, IL-1RA, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IP-10, MCP-1, MIP-1α, MIP-1β, sCD40L, TGF-α, TNFα, VEGF. TGF-β1 level was measured by molecule-specific enzyme-linked immunosorbent assay (Human TGFβ1 DuoSet kit, R&D Systems Inc., Minneapolis, MN). All sample tests were run in duplicate, according to the manufacturer's instructions.

Univariate logistic regression was performed with Grade 2 or more RE as a dependent variable to determine potential predictors of RE, including clinical factors, dosimetric parameters, and cytokine levels (pre, 2w, 4w) and ratios at 2 and 4 weeks to baseline (2w/pre and 4w/pre). All cytokine levels were log-transformed for use in the logistic regression models because of their skewed distribution. All significant factors were considered for a multivariate model based upon their significance in univariate regression. Factors were selected using a forward stepwise selection procedure based upon the Akaike information criterion (AIC) as well as the likelihood ratio test (LRT). Because of the high degree of correlation between dosimetric measures, one dosimetric variable was selected by evaluating both the *p*-value and AIC for univariate models with dosimetric factors. The combined model was also compared with univariate models comparing AUC of each model's Receiver operating characteristic (ROC) curve from the data. Cutoff points were created for age, EUD, and baseline cytokine like IL-8 based on maximum values of the sum of sensitivity and specificity. All *p*-values were from two-sided test.

Results

Table 1 shows the baseline clinical characteristics. The median age of the 129 patients was 66 years (range, 40–92 years) with ECOG performance status 0–2. All patients received definitive RT with or without concurrent chemotherapy. Carboplatin and paclitaxel were used as concurrent chemotherapy regimen in 88% of patients.

Forty out of 129 patients (31.0%) developed grade 1 RE, 33 patients (25.6%) grade 2, 15 patients (11.6%) grade 3, and one patient (0.8%) grade 4. There were no esophagitis-related deaths. Altogether, 49 patients (38.0%) had grade $\geq$2 RE. The median time from the start of RT to the development of grade $\geq$2 RE was 4.0 weeks (range; 1–20 weeks). It was 3.0 weeks (range; 1–18 weeks) for grade 2 RE and 4.5 weeks (range; 2–20 weeks) for grade 3–4 RE.

Age, gender, smoking history, stage, RT dose and concurrent chemotherapy were evaluated for the association with RE, with age and RT dose as continuous variables. Younger age (OR: 0.94, 95% CI: 0.91–0.98; $p = 0.003$), stage III disease (OR: 4.70, 95% CI: 1.00–21.70; $p = 0.048$), use of concurrent chemotherapy (OR:

Table 1
Baseline patient and treatment related characteristics.

Variables	*N* (%)
Gender	
Male	100 (77.5)
Female	29 (22.5)
Smoking history	
Never or former smoker	59 (45.8)
Current smoker or recently quit	63 (48.8)
Unknown	7 (5.4)
Histology	
Adenocarcinoma	25 (19.4)
Squamous carcinoma	47 (36.4)
Poorly differentiated	42 (32.6)
NOS	15 (11.6)
Stage	
I–II	15 (11.6)
III	112 (86.8)
Unknown	2 (1.6)
Concurrent chemotherapy	
Yes	88 (68.2)
No	31 (24.0)
Unknown	10 (7.8)
Radiation dose (Gy)	
44–59	6 (4.6)
60–69	56 (43.4)
70–79	46 (35.7)
80–85.5	21 (16.3)

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