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Predictors of Pneumonitis after Lung Cancer Radiotherapy

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Purpose/Objective(s): Multiple factors influence the risk of developing pneumonitis after radiotherapy for lung cancer, but few resources exist to guide clinicians in predicting risk in an individual patient using modern techniques. We analyzed toxicity data from a state-wide consortium to develop an integrated pneumonitis risk model.

Materials/Methods: All patients received radiation therapy for stage II-III NSCLC between April 2012 and July 2019. Data were prospectively collected from 24 academic and community clinics participating in a state-wide quality consortium. Pneumonitis within 6 months of treatment was graded by local practitioners (no centralized review). Weighted, univariate regression models were used to describe the risk of pneumonitis toxicity as a function of dosimetric and clinical covariates. Pneumonitis was modeled as either $G \geq 2$ versus $G \leq 1$ or as $G \geq 3$ versus $G \leq 2$. We used a stepwise modeling procedure to build a multivariable model. AUC values were calculated for each model to quantify the ability of each covariate to discriminate between patients who did or did not experience toxicity.

Results: Our analysis included 1302 patients, equally divided between male and female, with a median age of 67 years. Median comorbidity count was 1 and over 48% of patients had $\geq$ 2 comorbidities. 68% of patients had an ECOG performance status of 0-1. The overall rate of pneumonitis in the 6 months following RT was 16% (215 cases). 6% (92 cases) were G2+ and 1% (13 cases) were G3+. Adjusting for incomplete follow-up, estimated rates for G2+ and G3+ were 32% and 2%, respectively. In univariate analyses, V5, V10, V20, V30, and Mean Lung Dose (MLD) were positively associated with G2+ pneumonitis risk (OR 1.34, 1.34, 1.79, 1.48 per 10% increase, and 1.11 per 1 Gy increase respectively), while current smoking status was associated with lower odds of pneumonitis (OR 0.311). G2+ pneumonitis risk of $> = 22\%$ was independently predicted by MLD of $> = 20$ Gy, V20 of $> = 35\%$, and V5 of $> = 75\%$ which correspond to commonly-used planning constraints. In multivariate analyses, the lung V5 metric remained a significant predictor of G2+ pneumonitis even when controlling for MLD, despite being closely correlated (coefficient 0.743). For G3+ pneumonitis, MLD (OR 1.25 per Gy) and V20 (OR 2.59 per 10% increase) were statistically significant predictors. Number of comorbidities was an independent predictor of G3+, but not G2+ pneumonitis (OR 1.61 per comorbidity).

Conclusion: We present a large, prospectively-collected dataset evaluating pneumonitis risk after definitive radiation therapy for lung cancer. We incorporate comorbidity burden, smoking status, and dosimetric parameters in an integrated risk model. Low-grade pneumonitis is associated with MLD, V5, and V20, and negatively associated with smoking. High-grade pneumonitis is positively associated with MLD, V20, and comorbidity burden. These data may guide clinicians in assessing pneumonitis risk in individual patients.

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A Potential Biomarker — Vitronectin Predicting for Grade ≥2 Radiation Pneumonitis in Lung Cancer Patients Receiving Thoracic Radiotherapy

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Purpose/Objective(s): Our previous findings have identified vitronectin (VN) as a potential biomarker for radiation pneumonitis (RP) through proteomics and molecular mechanism studies. In the present study, we further explore associations between plasma level and single nucleotide polymorphism (SNP) analysis of VN and the risk of developing grade $\geq$2 RP in lung cancer patients receiving radiotherapy.

Materials/Methods: We identified a cohort of 173 patients with lung cancer received radiotherapy. Blood samples were collected from all study subjects within one week before radiation. VN reference SNP rs704 and rs2227721 were genotyped in these patients. Plasma VN concentrations were detected by enzyme-linked immunosorbent assay (ELISA)before irradiation. Clinical variables and genotypes associated with risk of grade $\geq$2 RP were analyzed by univariate and multivariate Cox regression. Kaplan-Meier curves were applied to estimate the cumulative RP probability, and receiver operating characteristic (ROC) curve was used to identify cutoff values. T-test and one-way ANOVA were conducted to evaluate the expression of plasma levels.

Results: A total of 63 (36.4%) patients developed grade $\geq$2 RP and 19(11.0%) patients suffered grade 3 RP. Tumor histology, use of chemotherapy, tumor status, nodal status, V20 and mean lung dose (MLD) were associated with grade $\geq$2 RP risk in univariate analysis ($P < 0.05$). On multivariate analysis, the VN rs704 GA/GG and rs2227721 AA/AC genotypes had a statistically significantly lower risk of grade $\geq$2 RP than rs704 AA and rs2227721 CC genotypes (adjusted hazard ratio [HR],0.479; 95% confidence interval [CI],0.269-0.850; $P = 0.012$; adjusted HR,0.467; 95% CI,0.247-0.883; $P = 0.019$, respectively). The baseline secretion level of VN in patients with grade $\geq$2 RP (143.8±71.3μg/mL)was significantly higher than that in grade$\leq$1 RP ones(66.1±28.9μg/mL) ($P<.0001$), and it was proportional to the severity of RP (grade 3 vs grade 2, $P<.0001$ & grade 2 vs grade 1, $P<.0001$).Moreover, we found significantly elevated VN plasma level in AA genotype of rs704 compared with GA/GG genotypes($P = 0.048$). In addition, combining the cutoff points of MLD and plasma level, RP risk groupings were as followed: high risk, MLD$\geq$11Gy and plasma level $\geq$90μg/mL(31of 44 patients,70.5%); intermediate risk, MLD$\geq$11Gy and level<90μg/mL or MLD<11Gy and level $\geq$90μg/mL(26 of 73 patients,35.6%); and low risk, MLD<11Gy and plasma level<90μg/mL(6 of 56 patients,10.7%) ($P<.0001$).

Conclusion: Patients with relatively high plasma levels of VN before radiotherapy were associated with the higher risk of RP, and