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Scientific Article

Using benchmarked lung radiation dose constraints to predict pneumonitis risk: Developing a nomogram for patients with mediastinal lymphoma

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Abstract

Purpose: We identified lung dosimetric constraints to assist in predicting the radiation pneumonitis (RP) risk in patients with mediastinal lymphoma and then identified the clinical prognostic factors that were associated with the achievement of key dosimetric constraints.

Methods and Materials: In 190 patients who received mediastinal intensity modulated radiation therapy, we used univariate χ^2 and multivariate logistic models to identify the predictors of RP and achievement of lung dose-volume histogram (DVH) constraints and build a predictive nomogram for RP.

Results: An increased risk of RP was strongly associated with mean lung dose (MLD) > 13.5 Gy (odds ratio [OR]: 8.13; 95% confidence interval [CI], 3.01-21.93; $P < .001$) and the percent of lung volume receiving ≥5 Gy (V5) > 55% (OR: 7.01; 95% CI, 2.94-16.72; $P < .001$). Therefore, patients had low RP risk (8%) if both MLD ≤13.5 and V5 ≤55 constraints were achieved, moderate risk (24%) if only MLD was achieved, and the highest risk (48%) if MLD was not achieved. Deep-inspiration breath-hold (DIBH) technique during treatment strongly prognosticated achieving MLD and V5 DVH constraints (OR,3.88; 95% CI, 1.84-8.19; $P < .001$). Specifically, 86% of patients who were treated with DIBH versus 63% without DIBH achieved DVH constraints ($P < .001$). This

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translated into a "number needed to treat" with DIBH of 4 patients to enable 1 additional patient to achieve both constraints. In comparison, the clinical characteristics were marginal prognosticators: DVH constraints were more likely achieved in nonbulky disease (OR: 3.01; 95% CI, 0.89-4.53; $P = .09$) and patients who had not previously received salvage chemotherapy (OR, 2.44; 95% CI, 0.98-6.11; $P = .06$). Nomogram-predicted risks of RP ranged from 4% to 60% on the basis of MLD and V5, total radiation dose, and use of salvage chemotherapy.

Conclusions: Achieving mean lung and V5 DVH constraints is critical to reduce RP risk in patients with lymphoma who receive mediastinal intensity modulated radiation therapy. The use of the DIBH technique is a promising risk-modifying treatment approach in patients with mediastinal lymphoma and especially in patients with a history of nonmodifiable risk factors for RP such as bulky disease and salvage chemotherapy.

Introduction

Avoiding irradiation of normal tissue is a fundamental component of high-quality radiation therapy, benchmarked through the use of dosimetric dose-volume histogram (DVH) constraints that were established to minimize toxicity.[1,2] For patients undergoing mediastinal radiation for lymphoma, the goal in using lung dosimetric constraints is to reduce the risk of radiation pneumonitis (RP), which is a relatively common and occasionally lethal side effect of thoracic irradiation. Patients with mediastinal lymphoma are at risk for RP with a risk of approximately 8% to 15% reported in prior studies.[3,4]

Several nonmodifiable disease factors appear to influence RP risk. Patients with bulky disease or relapsed/refractory lymphoma seem to be especially vulnerable to RP, probably from the exposure to several lines of cytotoxic chemotherapy and targeted agents with known risks of lung damage.[5,6] Yet, these dosimetric benchmarks can be difficult to achieve in patients with mediastinal lymphoma due to the often large thoracic radiation target volumes and corresponding volumes of normal lung that are exposed to falloff radiation doses.

The magnitude of risk reduction of RP that is associated with achieving lung dosimetric constraints has not been well quantified. Also unknown is whether the risk of RP for patients with nonmodifiable adverse intrinsic disease characteristics can be reduced by meeting dosimetric constraints. We sought to address these knowledge gaps by analyzing a large group of patients who had received intensity modulated radiation therapy (IMRT) for mediastinal lymphoma. To develop an approach to predict RP risk in these patients, we sought to identify the lung dosimetric constraints that are associated with RP. Second, we sought to identify modifiable and nonmodifiable clinical prognostic factors that are associated with the achievement of these dosimetric constraints to reduce the risk of RP. These findings supported the development of a nomogram for RP risk after radiation therapy for lymphoma that is located in the mediastinum.

Methods and materials

Study population and clinical covariates

We retrospectively reviewed the records of 190 consecutive adult patients who received mediastinal IMRT for Hodgkin or non-Hodgkin lymphoma at our institution between 2009 and 2014. We abstracted patient characteristics including clinical covariates (ie, sociodemographic characteristics, comorbidity, histology, Ann Arbor disease stage, and bulky disease [defined as a conglomerate nodal mass of >10 cm on axial computed tomography imaging]) and treatment characteristics (ie, radiation dosimetric variables, use of a motion-management technique called deep-inspiration breath-hold [DIBH], and chemotherapy). Lung dosimetric information was obtained from the electronic radiation treatment plans.

Radiation treatment techniques and planning

All patients underwent computed tomography-based simulation and IMRT treatment planning. The details of the simulation, DIBH, and IMRT are found in the Supplementary Methods section M1.[7-9]

Radiation pneumonitis

Acute symptomatic RP was based on pulmonary symptoms up to 12 months from radiation treatment without evidence of other potential etiologies (eg, infectious pneumonia) and scored in accordance with the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria.[10] Grade 1 RP was defined as the development of mild dyspnea on exertion or dry cough, grade 2 RP as persistent cough that requires narcotic or antitussive agents as well as dyspnea on minimal exertion, and grade 3 as severe cough that is unresponsive to narcotic or antitussive agents, dyspnea at rest, or clinical or radiographic evidence of acute