Practical Radiation Oncology (2016) **xx**, xxx–xxx

practical radiation oncology
pro
www.practicalradonc.org

Original Article

Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease

Houda Bahig MD [a], Edith Filion MD [a], Toni Vu MD [a], Jean Chalaoui MD [b], Louise Lambert MD [a], David Roberge MD [a], Michel Gagnon MD [c], Bernard Fortin MD, MSc [d], Dominic Béliveau-Nadeau MSc [a], Dominique Mathieu MSc [a], Marie-Pierre Campeau MD [a,*]

[a]*Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada*
[b]*Department of Radiology, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada*
[c]*Department of Internal Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada*
[d]*Department of Radiation Oncology, Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada*

Received 10 October 2015; revised 18 January 2016; accepted 21 January 2016

Abstract

Purpose: To investigate the incidence and predictive factors of severe radiation pneumonitis (RP) after stereotactic ablative radiation therapy (SABR) in early-stage lung cancer patients with preexisting radiological interstitial lung disease (ILD).

Methods and materials: A retrospective analysis of patients with stage I lung cancer treated with SABR from 2009 to 2014 was conducted. Interstitial lung disease diagnosis and grading was based on pretreatment high-resolution computed tomography imaging. A central review of pretreatment computed tomography by a single experienced thoracic radiologist was conducted. Univariate and multivariate analyses were conducted to determine potential predictors of severe RP in patients with ILD.

Results: Among 504 patients treated with SABR in this period, 6% were identified as having preexisting ILD. There was a 4% rate of ≥ grade 3 RP in the entire cohort. Interstitial lung disease was associated with increased risk of ≥ grade 3 RP (32% in ILD+ vs 2% in ILD-, $P < .001$). Five patients (21%) with ILD developed grade 5 RP. Lower forced expiratory volume in 1 second and forced vital capacity, higher V5Gy and mean lung dose, presence of severe radiological ILD, and combined emphysema were significant predictors of ≥ grade 3 RP on univariate analysis; only forced expiratory volume in 1 second remained on multivariate analysis.

Conclusion: Interstitial lung disease is associated with an increased risk of severe RP after SABR. Chest imaging should be reviewed for ILD before SABR, and the risk of fatal RP should be carefully weighed against the benefits of SABR in this subgroup.

Conflicts of interest: None.

* Corresponding author. Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, 1560 Sherbrook East, Montréal, Quebec, H2L 4M1, Canada.

E-mail address: marie-pierre.campeau.chum@ssss.gouv.qc.ca (M.-P. Campeau).

http://dx.doi.org/10.1016/j.prro.2016.01.009

Introduction

Interstitial lung disease (ILD) encompasses a heterogeneous group of pulmonary entities with restrictive physiology and impaired gas exchange leading to irreversible fibrosis.[1] The presence of ILD is considered a contraindication to conventional radiation therapy because of high rates of radiation pneumonitis (RP). In a study by Makimoto involving patients treated with conventional radiation therapy, ILD was associated with 47% rate of clinical RP.[2] In another study by Samuki, ILD was found to be the most important predictive factor of grade ≥ 3 RP in patients treated with conformal radiation therapy for lung or thymus cancer.[3]

Stereotactic ablative radiation therapy (SABR) is recognized to carry minimal risks of toxicities, with $<5\%$ rate of grade ≥ 3 RP.[4–6] Previously reported lethal toxicities have included bronchial stenosis, hemoptysis, fistulae, and respiratory failure.[7,8] In a meta-analysis by Grutters, SABR-related mortality was below 1%, and nearly 80% of these deaths were related to RP.[9] Recently, the possibility of increased pulmonary toxicity in patients with ILD has been raised in small series.[10,11] Estimating the absolute risk of toxicity for patients with ILD requires a better understanding of the incidence of undiagnosed ILD in patients treated with SABR. The purpose of this study was thus to investigate the incidence and predictive factors of severe RP after SABR in patients with preexisting ILD.

Methods and Materials

Patients' characteristics

Patients in the IRB-approved retrospective analysis had early-stage non-small cell lung cancer (NSCLC) and were treated with SABR from 2009 to 2014 at the CHU Montreal. All patients had stage T1-2N0M0 tumors and were either ineligible for surgery or refused surgery. Baseline investigations included: complete blood count and biochemistries, a thoracic computed tomography (CT) scan, bronchoscopy, 18-fluoro-2-deoxy-d-glucose positron emission tomographic scan, pulmonary function tests, and, when available, histological confirmation of NSCLC. When pathological diagnosis could not be obtained, tumor progression on CT and increased 18-fluoro-2-deoxy-d-glucose positron emission tomographic uptake were used to establish diagnosis of malignancy. Decision to treat was made in a multidisciplinary tumor board. Pretreatment pulmonary function tests were centrally reviewed by a single respirologist.

Evaluation of pretreatment ILD

Interstitial lung disease diagnosis and grading was based on pretreatment high-resolution diagnostic CT imaging, (HRCT) using various devices. High-resolution CTs with no contrast were obtained in supine position and full inspiration, with spiral acquisition from the apex to lung bases. Data were reconstructed with a 2-mm section thickness using a high spatial frequency algorithm. All images were reviewed on a Picture Archiving and Communication System station in lung window (window width, 1500 HU; window level, -500 HU). In 3 patients, for whom pretreatment diagnostic HRCT imaging were not available, ILD diagnosis and grading was based on review of planning CT. All CT scans were centrally read or revised at our institution to determine presence or absence of interstitial lung changes. Features of ILD were reviewed and graded by a single experienced thoracic radiologist in a lung window. Interstitial lung disease images were graded as mild, moderate, or severe based radiological features and distribution of the disease. Mild ILD was defined as reticular or ground-glass opacities and traction bronchiectasis involving less than one-third of the volume of 1 lung. Moderate ILD was defined by the presence of early cystic changes, or a disease involving more than one-third of 1 lung but no more than 50% of the entire pulmonary volume (both lungs combined). Finally, severe ILD was defined by the presence of advanced cystic changes or disease involving more than 50% of the entire pulmonary volume. Computed tomography scans were evaluated for presence of concurrent radiological emphysema based on visual assessment of HRCT in lung window by the same expert thoracic radiologist. An emphysema diagnosis was made in the presence of decreased attenuation surrounded by a thin wall or without visible wall, resulting from parenchymal destruction, and/or presence of bullae corresponding to confluent areas of low attenuation measuring at least 1 cm and associated vascular rarefaction.[12]

Radiation therapy

Patients were treated with robotic near-real-time tumor tracking or using an internal target volume (ITV). CyberKnife (Accuray, Sunnyvale, CA) tumor tracking was performed using implanted fiducials or, when the tumor was sufficiently large and dense,[13] using direct soft tissue tumor tracking. Internal target volume–based SABR was performed using volumetric intensity modulated radiation therapy, helical tomotherapy, or robotic spine tracking platforms. All patients had a 3-mm slice thickness 4-dimensional supine planning CT with no contrast. For patients treated with arc therapy or tomotherapy, a double vacuum immobilization device was used. Internal target volume was based on the tumor motion seen on 4-dimensional CT. An additional planning tumor volume (PTV) margin of 3-5 mm was added to the gross tumor volume (tumor tracking cases) or ITV. Lung constraints were as per STARS (Randomized Study to Compare CyberKnife to Surgical Resection In Stage I Non-small Cell Lung Cancer) Lung Trial.[14] Dose constraints for other organs were as per Radiation Therapy Oncology Group (RTOG) 0236[15] and RTOG 0813.[16]