Original Study

Correlation of Dosimetric and Clinical Factors With the Development of Esophagitis and Radiation Pneumonitis in Patients With Limited-Stage Small-Cell Lung Carcinoma

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Abstract

Treatment of patients with limited-stage small-cell lung carcinoma with chemoradiotherapy can result in significant pulmonary and esophageal toxicity. In this study we explored clinical and dosimetric predictors of radiation pneumonitis and esophagitis. Mean lung dose and volume of lung receiving 20 Gy were significantly correlated with Grade ≥ 3 radiation pneumonitis; minimum dose to the hottest 45% of the esophagus and mean esophageal dose were significantly correlated with Grade ≥ 3 esophagitis.

Background: The purpose of the study was to correlate clinical and dosimetric factors with the development of esophagitis and radiation pneumonitis in patients with limited-stage small-cell lung carcinoma (LS SCLC). **Patients and Methods:** One hundred eighteen patients who received curative intent chemoradiotherapy for LS SCLC and had electronically archived radiation treatment plans were included. The medical charts were reviewed for clinical data. The treatment plan was reviewed for critical structure delineation and dose delivered. Treatment planning data were analyzed using Computational Environment for Radiotherapy Research (V3.3). Dosimetric parameters were correlated with the risk of toxicity using Spearman rank correlation. **Results:** Radiotherapy dose was 40 Gy in 15 fractions (fx) (n = 80) and 45 Gy in 30 fractions twice per day (n = 38). The 6-month cumulative incidence of Grade ≥ 2 radiation pneumonitis was 6.5% and 7.9% for the 40 Gy/15 fx and 45 Gy/30 fx groups, respectively ($P = .40$). The 3-month cumulative incidence of Grade 3 esophagitis was 7.5% and 13.2% for the 40 Gy/15 fx and 45 Gy/30 fx groups, respectively ($P = .31$). Grade ≥ 3 pneumonitis was correlated with volume of lung receiving 20 Gy (V_{20}) and mean lung dose. Grade ≥ 3 esophagitis was correlated with mean esophagus dose and minimum dose to the hottest 45% of the esophagus (D45). **Conclusion:** Mean lung dose and V_{20} were significant predictors of radiation pneumonitis in LS SCLC. Mean esophageal dose and D45 were significant predictors of esophagitis. These 2 treatment schedules have similar toxicity profiles.

Clinical Lung Cancer, Vol. 16, No. 3, 216-20
Keywords: Dosimetry, Esophagitis, Radiation pneumonitis, Small Cell Lung Cancer, Toxicity

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Submitted: Sep 3, 2014; Revised: Nov 24, 2014; Accepted: Nov 25, 2014; Epub: Dec 2, 2014

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Introduction

Limited-stage (LS) small-cell lung carcinoma (SCLC) is currently managed with early-cycle concurrent chemoradiotherapy followed by prophylactic cranial irradiation (PCI).[1] The optimal dose and fractionation for thoracic radiotherapy in LS SCLC remains controversial. In our institution, 2 dose/fractionation regimens have been used in routine clinical practice including a common Canadian hypofractionated fractionation (or 40 Gy in 15 fractions delivered in 2.67 Gy fractions once daily over 3 weeks[2]) and a hyperfractionated regimen (45 Gy in 30 fractions delivered in 1.5 Gy fractions twice daily [b.i.d.] over 3 weeks[1]).

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.clc.2014.11.008

Radiation pneumonitis and radiation esophagitis are frequent sources of morbidity and potential mortality in patients with LS SCLC.[3-6] Most dosimetric constraints used to evaluate radiotherapy plans are derived from patients with non–small-cell lung carcinoma (NSCLC), with radiation delivered in conventional 1.8 Gy or 2.0 Gy per day treatments. Mean lung dose (MLD) and the volume of lung receiving 20 Gy (V_{20}) are known predictors of radiation pneumonitis in these patients.[7] Reproducible and robust dosimetric estimators of esophagitis risk are not as well known, however, parameters such as the surface area, and length of esophagus in the radiation field, the mean esophageal dose, maximum dose, and V_{60} have been proposed in the literature.[8,9] Besides dosimetric factors, treatment factors (eg, sequential/concurrent chemotherapy schedules, targeting of upper/mid or lower lobe tumors) and patient factors (eg, age, smoking status) have also been correlated with radiation toxicity.[10]

Common predictors and dosimetric parameters of radiation pneumonitis and esophagitis in conventionally-treated NSCLC might not be applicable to patients with SCLC who are treated with different dose and fractionation regimens.

There currently exists limited data that support the use of dosimetric and clinical factors in estimating risk of radiation pneumonitis and esophagitis in LS SCLC. In 2006, Tsujino et al.[11] provided initial evidence that $V_{15,\ 20,\ 30}$ and normal tissue complication probability correlated with the development of radiation pneumonitis based on a study of 43 SCLC patients who received accelerated hyperfractionated radiotherapy (45 Gy/30 fractions b.i.d.) with concurrent chemotherapy. The purpose of our study was to assess dosimetric and clinical parameters in patients with LS SCLC who received either 45 Gy in 30 fractions delivered in 1.5-Gy fractions b.i.d. or 40 Gy in 15 fractions delivered in 2.67 Gy fractions once daily to determine predictors of toxicity for each fractionation regimen.

Patients and Methods

Patients

Between December 2004 and September 2012, 118 patients were treated with curative intent chemoradiotherapy for LS SCLC and had electronically archived radiation plans available for analysis. A portion of patients had multiple phase plans or midtreatment replans which precluded analysis without accurate deformable registration. The medical charts were reviewed retrospectively to determine demographic information, chemotherapy details, toxicity (graded per Common Terminology Criteria for Adverse Events version 3.0), and vital status. This study was conducted with research ethics board approval.

All patients were staged using computed tomography (CT) scans of the thorax, CT or ultrasound of the abdomen, a bone scan, and either a CT or magnetic resonance imaging scan of the brain. Eighteen (15%) patients also received positron emission tomography (PET)/CT staging.

Patients were CT simulated using a 4-dimensional (4D) planning scan. Radiotherapy was planned on either the helical planning scan or the exhale data set of the 4D CT scan. The staging PET/CT scan was fused to the planning CT scan when available. The gross tumor volume (GTV) for the tumor and involved lymph nodes was delineated on the exhale (GTVex) and inhale (GTVin) data sets. A 0.5-cm clinical target volume expansion was used around the GTVin and GTVex. These clinical target volumes were combined to form an internal target volume. Finally a 0.5-cm planning target volume expansion was used around the internal target volume. No elective nodal irradiation was used. Patients were treated with 3-D conformal radiotherapy. Patients received either daily cone beam CT or megvoltage portal images for position verification.

Treatment Characteristics

Radiotherapy was delivered using a 3-D conformal technique. All patients were CT simulated and planned using the Pinnacle treatment planning system with doses corrected for tissue heterogeneity. The institutional policy was for early radiotherapy delivered concurrently with platinum-based chemotherapy; however, due to patterns of referral or patient factors, not all patients were treated in this fashion and some patients received sequential rather than concurrent chemoradiotherapy. The thoracic radiotherapy dose was either 40 Gy in 15 fractions delivered in 2.67-Gy fractions once daily or 45 Gy in 30 fractions delivered in 1.5-Gy fractions b.i.d. Patients were routinely offered 45 Gy in 30 fractions starting in 2007, however, due to patient or oncologist preference, some patients continued to be treated with 40 Gy in 15 fractions. PCI was offered to eligible patients after completion of chemotherapy, typically at a dose of 25 Gy in 10 fractions.[12] Chemotherapy consisted mainly of etoposide and a platinum analogue.

Patients were monitored weekly during treatment for toxicity. After completion of treatment, patients were typically seen at

Table 1 Patient Characteristics

Variable	40 Gy in 15 Fractions (n = 80)	45 Gy in 30 Fractions (n = 38)	*P*
Sex			
Male	48 (60)	26 (68)	.42[a]
Female	32 (40)	12 (32)	
Median Age (Range)	67.3 (44.9-83.2)	65.5 (40.9-84.2)	.5[b]
Chemotherapy			
Sequential	18 (23)	3 (8)	.05[a]
Concurrent cycle 1-3	52 (65)	33 (87)	
Concurrent cycle 4-6	10 (12)	2 (5)	
Smoking Status			
Current	23 (29)	14 (37)	.40[a]
Former	57 (71)	24 (63)	
Toxicity Per CTCAE			
Radiation pneumonitis			
Grade 2	3 (4)	2 (5)	.56[a]
Grade 3	0	1 (3)	
Grade 5	2 (3)	1 (3)	
None	75 (94)	34 (90)	
Esophagitis			
Grade 2	38 (48)	9 (24)	.04[a]
Grade 3	6 (7)	5 (13)	
None	36 (45)	24 (63)	

Values are presented as n (%) except where otherwise specified.
Abbreviation: CTCAE = common terminology criteria for adverse events version 3.0.
[a]Fisher exact test.
[b]*t* test.