Radiation pneumonitis in non-small-cell lung cancer patients treated with helical tomotherapy

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Abstract

Objective: In this study, we investigated the incidence of radiation pneumonitis (RP) in non-small-cell lung cancer (NSCLC) patients undergoing helical tomotherapy (HT) and the clinical and dosimetric factors associated with it.

Materials and Methods: We analyzed data from the treatment protocols of 62 NSCLC patients. The median total radiation dose was 64 Gy (range 57.6–66 Gy) at 1.8–2.2 Gy/fraction. Thirty-four of these patients underwent HT alone and 28 underwent HT in combination with chemotherapy. Treatment-related pneumonitis was graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

Results: We found that RP grades 1, 2, 3 and 5 occurred in 29 (46.8%), 23 (37.1%), 8 (12.9%), and 2 (3.2%) patients, respectively. Using univariate analyses, we found that a grade ≥3 RP was associated with poor performance status (PS), age, planning target volume, mean lung dose, and relative V_5 through V_{25}, in increments of 5 Gy ($P < 0.005$). We determined that PS and V_5V_{15} were the most significant factors associated with grade ≥3 RP using multivariate analysis.

Conclusions: We found that poor PS and V_5–V_{15} were the risk factors associated with grade ≥3 RP in NSCLC patients treated with HT. Thus, for NSCLC patients treated with HT, the volume of total lung with low-dose region (V_5–V_{15}) should be carefully regulated and the use of HT should be restricted in patients with Eastern Cooperative Oncology Group ≥2.

Key words: Helical tomotherapy, non-small-cell lung cancer, radiation pneumonitis

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Introduction

Helical tomotherapy (HT) is a novel form of intensity-modulated radiotherapy (IMRT). It is delivered on a continuous helix and utilizes an integrated megavoltage computed tomography (CT) unit that allows for real-time verification of patient positioning.[1,2] Unlike conventional IMRT radiotherapy techniques which rely on limited static angles, HT delivers an optimized, homogenous signal dose to the tumor while reducing radiation exposure to organs at risk (OAR).[1-5] However, even at the lower radiation doses of HT there is concern about exposure of healthy tissues to radiation which might lead to lung toxicity.[3,5-9] For example, Wang *et al.*,[8,9] reported that V_5 of the total lung was the most important risk factor for the development of radiation pneumonitis (RP).

The understanding of the relationship between RP and the clinical and dosimetric parameters of HT in the treatment of thoracic cancer is limited.[1,3,4] In this retrospective study, we investigated the incidence of RP in 62 non-small-cell lung cancer (NSCLC) patients who underwent radiotherapy with HT in our institution. Here, we evaluate whether HT increases the risk of severe RP and the specific clinical and dosimetric factors that might contribute to this risk.

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Materials and Methods

Study population

Sixty-two patients with inoperable NSCLC staged according to the tumor, node, metastasis (TNM) staging system of the 7th edition of the American Joint Committee on cancer were studied retrospectively between May 2012 and March

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2014 at the Military General Hospital of Beijing PLA. The patients' characteristics are summarized in Table 1. All patients (stage I: 7 patients, stage II: 13 patient, stage III: 42 patient) had been newly diagnosed and confirmed using pathology testing. Performance status (PS) was scored according to the Eastern Cooperative Oncology Group (ECOG) scale. Median age was 66 years (range, 33–87 years).

Thirty-four patients received HT radiotherapy alone and 28 patients received concurrent chemoradiotherapy followed by consolidation chemotherapy. The concurrent chemotherapy regimen consisted of etoposide plus cisplatin (3 weeks/cycle for 2 cycles) during radiotherapy followed by gemcitabine or paclitaxel plus cisplatin/carboplatin (3 weeks/cycle for 3–4 cycles) after radiotherapy.

Helical tomotherapy technique

Dose-volume histograms (DVHs) were generated for the OAR. The HT plans were created using the Hi-Art Tomo Therapy 4.1.2.2 station (Tomo Therapy Inc., Madison, WI, USA). Treatment plans were delivered to the tomotherapy Hi-Art system (Tomo Therapy Inc.,). The tumor region was scanned every day using megavoltage CT imaging enabled for HT before treatment, and the patients were positioned using the integrated registration with the planning CT for both bony and soft tissue anatomy.

Patients were examined in a supine position with their arms above their heads and secured in an immobilization device using 4 dimensional CT simulation (Brilliance™ Big Bore CT; Philips, Cleveland, OH, USA) acquired during normal, quiet breathing with 5 mm slices. CT datasets with structures contoured in Pinnacle^3 (Version 9.2; Philips Medical Systems, Amsterdam, Netherlands) were transferred to the tomotherapy planning system using digital imaging and communication according to the established medicine RT protocol. The following parameters were used: The gross tumor volume (GTV) encompassed all detectable tumors and lymph nodes determined from CT. A four-dimensional-CT simulation was used for all patients, an internal target volume was obtained by summing the GTVs from all respiratory motion phases instead of GTV. Clinical tumor volume (CTV) including GTV with an additional 0.8 cm margin and the planning target volume (PTV) expanded from the CTV by 0.8–1 cm margins in all dimensions. The median prescribed radiation dose of PTV was 64 Gy (range 57.6–66 Gy) at 1.8–2.2 Gy/fraction. The target goals for PTV were that ≥95% of the PTV should receive 100% of the prescribed dose. Normal tissue constraints were prioritized in the following order for treatment planning purposes: Maximum spinal cord dose of 45 Gy, relative volume of total lung treated with a ≥20 Gy (V_{20}) <30%, V_{30} <20%, median lung dose (MLD) <18 Gy, relative volume of the esophagus receiving ≥55 Gy ≤30%, and the relative volume of the heart receiving ≥40 Gy ≤30%.

Dose-volume histogram parameters for lung

The total normal lung volume was defined as the total lung volume minus the primary GTV and the volume of the trachea and main bronchi. PTV, MLD, and the percent volume of the total lung receiving 5–50 Gy in increments of 5 Gy (V_5–V_{50}) were generated from the DVH.

Follow-up

Patients were examined 1-month after treatment and every 3 months thereafter. The median follow-up period was 10 months (range 6–20 months). The severity of RP was scored according to the Common Terminology Criteria for Adverse Events, version 3.0 as shown in Table 2.

Statistical analysis

The results of this study were analyzed using the statistical software package SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Values of $P \leq 0.05$ were considered statistically significant. The advent of grade ≥3 RP served as the primary endpoint and was defined as severe RP. Significance was established using the Chi-square or Fisher's exact test. Logistic analysis was used to investigate the relationship between RP and dosimetric parameters for lung DVH. The significant factors ($P \leq 0.05$) on univariate analysis were subjected to multivariate analysis using logistic regression.

Results

The median time for RP occurrence was 3.0 months (range: 1.2–6.2 months). RP developed in all patients as follows: Grade 1 (29 patients, 46.8%), grade 2 (23 patients, 37.1%), grade 3 (8 patients, 12.9%), and grade 5 (2 patients, 3.2%). For patients with grade ≥3 RP, symptoms were managed by administration of steroids, antibiotics, and oxygen via a face mask as medically necessary. The two patients that died of grade 5 RP did not receive chemotherapy. One patient aged 63 had ECOG 2, and the other aged 63 had ECOG 1.

Clinical factors associated with occurrence of grade ≥3 radiation pneumonitis

Clinical and treatment factors associated with cases of grade <3 RP and grade ≥3 RP are listed in Table 1. Using univariate analyses, the incidence of grade ≥3 RP was found to be significantly higher in both the ECOG 2 group and the age ≥70 years group. Other clinical factors (sex, smoking history, tumor stage, chemotherapy, and presence of chronic obstructive pulmonary diseases [COPD]) were not found to contribute to the occurrence of RP grade ≥3.

Table 1: Clinical factors associated with grade≥3 RP

Characteristics	*n* (%)		*P*
	Grade≥3 RP	Grade<3 RP	
Sex			
Male	7 (16.3)	36 (83.7)	0.356
Female	5 (26.3)	14 (73.7)	
Age, years			
<70	5 (10.9)	41 (89.1)	0.004
≥70	7 (43.8)	9 (56.3)	
ECOG			
0-1	6 (12.8)	41 (87.2)	0.020
2	6 (40.0)	9 (60.0)	
TNM stage			
I-II*	2 (10.0)	18 (90.0)	0.198
III	10 (23.8)	32 (76.2)	
Pathology			
Squamous cell	5 (13.9)	31 (86.1)	0.200
Adenocarcinoma	7 (26.9)	19 (73.1)	
Concurrent chemotherapy			
Yes	8 (28.6)	20 (71.4)	0.096
No	4 (11.8)	30 (88.2)	
COPD			
Yes	2 (15.4)	11 (84.6)	0.684
No	10 (20.4)	39 (79.6)	
Smoking history			
Yes	7 (18.4)	31 (81.6)	0.815
No	5 (20.8)	19 (79.2)	

COPD=Chronic obstructive pulmonary disease; ECOG=Eastern Cooperative Oncology Group; RP=Radiation pneumonitis; TNM=Tumor, node, metastasis

Table 2: Criteria for grading RP by the CTCAE v3.0

Grade	Pneumonitis
0	None
1	Asymptomatic; radiographic findings only
2	Symptomatic, not interfering with ADL
3	Symptomatic, interfering with ADL; O_2 indicated
4	Life-threatening; ventilatory support indicated
5	Death

ADL=Activities of daily living, CTCAE v3.0=Common Terminology Criteria for Adverse Events, version 3.0, RP=Radiation pneumonitis

Table 3: Dosimetry association with grade≥3 RP

Factor	Grade<3 (*n*=50), median (range)	Grade≥3 (*n*=14), median (range)	*P*
MLD, Gy	13 (10−19)	16 (10−17)	0.002
V_5	62 (43−97)	73 (62−85)	0.000
V_{10}	43 (25−75)	50 (40−60)	0.000
V_{15}	30 (17−43)	36 (30−52)	0.000
V_{20}	22 (11−29)	27 (17−29)	0.036
V_{25}	17 (8−22)	21 (12−23)	0.043
V_{30}	14 (6−19)	17 (9−18)	0.078
V_{35}	11 (5−17)	12 (7−15)	0.434
V_{40}	9 (3−15)	10 (6−13)	0.343
V_{45}	7 (3−13)	7 (5−10)	0.896
PTV, cm^3	355 (145−1256)	521 (229−1642)	0.003

V_5−V_{45}=The percentage of lung volume receiving 5−45 Gy; MLD=Mean lung dose; PTV=Planning target volume; RP=Radiation pneumonitis

Association of radiation pneumonitis grade ≥3 with dosimetric parameters for total lung

The MLD, V_5–$V_{45}$and PTV are listed in Table 3 for RP grade ≥3 and <3. Using univariate analyses, we found that the MLD, V_5–V_{25} and PTV contribute to the incidence of RP grade ≥3.

Multivariable factors associated with incidence of radiation pneumonitis grade ≥3

Using multivariate logistic regression analysis, we found that ECOG and V_5–V_{15} are significant independent risk factors for the development of grade ≥3 RP: ECOG (P = 0.040 [odd ratio (OR) 4.68, 95% confidence interval (CI) 1.07–20.3]), V_5 (P = 0.034 [OR 2.87, 95% CI 1.74–4.04]), V_{10} (P = 0.040 [OR 2.87, 95% CI 1.74-4.04]), and V_{15} (P = 0.030 [OR 8.0, 95% CI 1.41–102.3]).

Discussion

In this study, we found that the incidence of RP grade ≥3 RP was 16.2% after HT treatment for NSCLC patients, which was similar to the incidence reported for both three-dimensional conformal radiation therapy (3DCRT) and HT.[3,4,9-12] No cases of grade 4 RP were recorded and 2 patients died of grade 5 RP.

The need to reduce radiation dosage to the lung to lower the incidence of RP has been an ongoing challenge in practice. HT remains a preferable treatment option compared to 3DCRT and other IMRT techniques because its dosimetric parameters can be adjusted to the target volume to reduce the radiation exposure of healthy lung tissue. Bral *et al*.,[3] exploited this property of HT to increase the target dose to 67.2 Gy with concurrent chemotherapy the percentage of lung volume receiving 5–50 Gy and confirmed that HT was feasible and had an acceptable associated toxicity in lung cancer patients since there were very few cases of RP grade ≥3 (3%) and the incidence of late grade ≥3 RP was 21%. However, the damage to the total lung and the contralateral lung might be higher at the lower treatment dosages.[1,4]

In this study, we identified that the volume of lower dosimetric factors ($V_{5–15}$) is associated with an increased incidence of severe RP in NSCLC patients treated with HT. Gattaneo *et al*.,[1] found that, when compared to 3DCRT, HT spared a bigger lung volume from radiation at both the intermediate and high doses with a mean reduction of 3.6 Gy for MLD and 8% for V_{20}, while V_5 and V_{10} were unaffected. However, we found that the MLD is not a risk factor for grade ≥3 RP using multivariate analysis, possibly because MLD was lower than that in others reports.[1,4,6,9]

In one study, Wang *et al*.,[8,9] reported that delivery of a dose as low as 5 Gy to a large lung volume is not safe in

either lung or esophageal cancer cases. In our study, in patients with grade ≥3 RP, the lung volume appeared to be lower in $\geq V_{15}$, while V_5–V_{10} was higher than that reported in other studies.[1,3,4,6] The V_5 of the total lung was 62% (RP grade <3) and 73% (RP grade ≥3). Song *et al.*,[4] reported that the incidence of RP grade ≥3 was 18% with 10.8% of lung cancer patients dying of RP following HT treatment combined with chemotherapy. In this study, they identified that the total lung V_5 >60% is a risk factor for RP grade ≥3, a result that agrees with our study.

In our study, PS was the only significant predictive clinical factor for severe RP. The incidence of RP grade ≥3 was 12.8% among patients with ECOG 0–1, which was significantly lower than in patients with ECOG 2 (40.0%). When patients with poor PS were excluded from this analysis, the incidence of RP grade ≥3 was acceptably low in accordance with other reports.[4,8,9,10] Consequently, HT treatment should be avoided for patients with poor PS. Using univariate analyses, the risk of RP grade ≥3 was increased in patients with age ≥70 years. This result could not be replicated using multivariate analysis. Both Dang *et al*.,[12] and Parashar *et al*.,[13] showed that age was significantly associated with RP grade ≥2 or 3, and considered that elderly patients do indeed have a lower lung tolerance for radiation.

In univariate analyses, the volume of PTV contributes to the incidence of RP grade ≥3, a result that is not seen using multivariate analysis. Tumor stage was not found to be associated with RP grade ≥3 using both univariate and multivariate analysis. For the comparison of stages I, II and III, the volumes of PTVs were not correlated (not listed in results). We consider that the T and N stages influence the TNM stage, for instance stage III including T1-2N3, T3N1, and T4N0, and so on, so the volume of PTV of stages I-II is not always smaller than that of stage III.

A few studies reported a low risk of severe RP in patients not suffering from COPD. In contrast, other studies did not report any correlation between COPD and RP.[12,14,15] In this study, we did not observe a correlation of COPD and RP grade ≥3. This phenomenon may be explained by the following facts. First, there is a lower level of cellular oxygenation in the lung of patients with COPD, which might reduce their sensitivity to radiation. Second, COPD is graded using different scores so the patients that were administered radiotherapy had mild or moderate COPD excluding the severe cases. Different grades of COPD might have a different effect on lung toxicity in the subject undergoing the study in our institution. Third, patients with COPD likely suffered from emphysema which is anatomically equivalent to a lack of lung tissue. RP may result from the activation of a cytokine cascade by the radiation.[16] In patients with emphysema, normal lung tissue seldom exists around the tumor and results in a decrease in the activation of the cytokine cascade. Fourth, patients with COPD are often prescribed bronchodilators and steroids which may prevent radiation-induced lung toxicity. Therefore, the relationship between the incidence and severity of RP and COPD remains unclear.

In our study, we found that the administration of concurrent chemotherapy was not significantly associated with the incidence of severe RP. In contrast, Wang *et al*.,[9] and Dang *et al*.[12] reported a higher incidence of RP grade ≥3 in patients treated with concurrent chemotherapy. The concurrent regimen of etoposide plus cisplatin might not be as effective as other regimens.

Conclusions

In this study, we found that PS is the only clinical factor associated with the incidence of RP grade ≥3. For poor PS patients, the use of HT in NSCLC should be carefully regulated, since the dosimetric parameters of V_5–V_{15} are associated with the incidence of RP grade ≥3. In clinical practice, adjusting the dose-volume parameters to the patient's characteristics will help improve the regulation of the risk of developing RP. RP is a complicated process influenced by many clinical and dosage factors and even advanced technology did not eliminate these effects.

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