

Dosimetric and clinical predictors of radiation-induced lung toxicity in esophageal carcinoma

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ABSTRACT

Aims and background. Radiation-induced lung toxicity occurs frequently in patients with esophageal carcinoma. This study aims to evaluate the clinical and three-dimensional dosimetric parameters associated with lung toxicity after radiotherapy for esophageal carcinoma.

Methods and study design. The records of 56 patients treated for esophageal carcinoma were reviewed. The Radiation Therapy Oncology Group criteria for grading of lung toxicity were followed. Spearman's correlation test, the chi-square test and logistic regression analyses were used for statistical analysis.

Results. Ten of the 56 patients developed acute toxicity. The toxicity grades were grade 2 in 7 patients and grade 3 in 3 patients; none of the patients developed grade 4 or worse toxicity. One case of toxicity occurred during radiotherapy and 9 occurred 2 weeks to 3 months after radiotherapy. The median time was 2.0 months after radiotherapy. Fourteen patients developed late irradiated lung injury, 3 after 3.5 months, 7 after 9 months, and 4 after 14 months. Radiographic imaging demonstrated patchy consolidation (n = 5), atelectasis with parenchymal distortion (n = 6), and solid consolidation (n = 3). For acute toxicity, the irradiated esophageal volume, number of fields, and most dosimetric parameters were predictive. For late toxicity, chemotherapy combined with radiotherapy and other dosimetric parameters were predictive. No obvious association between the occurrence of acute and late injury was observed.

Conclusions. The percent of lung tissue receiving at least 25 Gy (V25), the number of fields, and the irradiated length of the esophagus can be used as predictors of the risk of acute toxicity. Lungs V30, as well as chemotherapy combined with radiotherapy, are predictive of late lung injury.

Introduction

Radiotherapy (RT) is indicated in patients with unresectable or medically inoperable esophageal carcinoma as a definitive or palliative treatment, with a 5-year survival benefit of 8.3% to 12%¹. Three-dimensional conformal radiotherapy (3D-CRT) has greatly improved the local control of esophageal carcinoma but not the long-term survival². Radiation-induced lung toxicity is a common dose-limiting toxic effect in patients receiving thoracic radiation therapy for esophageal carcinoma. In patients receiving definitive RT along with chemotherapy for stage III or IV unresectable esophageal carcinoma, this is particularly problematic because the doses are typically higher than those delivered in the preoperative or postoperative setting.

The clinical endpoints for radiation-induced lung injury have traditionally been divided into acute radiation pneumonitis (RP) and chronic lung fibrosis. Acute RP develops in 5% to 15% of patients a few weeks to months after radiation³. Additionally, the increasing use of concomitant chemotherapy appears to have increased the risk of acute and possibly late lung injury⁴. In recent years, acute and late irradiated lung injury has been more common in patients with unresectable esophageal cancer⁵.

Key words: esophageal cancer, three-dimensional conformal radiotherapy, radiation-induced lung toxicity.

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Three-dimensional treatment planning systems provide detailed information about the dose-volume distribution in the structures of interest. The risk of lung toxicity appears to be related to dose-volume parameters such as the irradiated lung volume; mean lung dose (MLD); percentage of the lung receiving at least 20 Gy (V20), 25 Gy (V25), or 30 Gy (V30); and total dose, although the precise nature of the relationships remains unclear⁶⁻⁹. Prediction of the risk of lung toxicity in esophageal carcinoma treated after RT with or without chemotherapy is important in clinical practice so that preventive measures can be adopted. Based on the experience of the Fourth Hospital of Hebei Medical University, a retrospective analysis was carried out to evaluate the clinical and dose-volume predictors of lung toxicity in patients with esophageal carcinoma treated with 3D-CRT.

Material and methods

Patient eligibility criteria for this study included (1) unresectable or medically inoperable middle and lower thoracic esophageal carcinoma treated by 3D-CRT as definitive or palliative treatment; (2) histologically or cytologically proven squamous cell carcinoma; and (3) Karnofsky performance status greater than or equal to 70.

Patient characteristics

Between January 2002 and June 2004, 56 consecutive patients at the Fourth Hospital of Hebei Medical University were eligible for the study. The study was approved by the institutional review board. The initial evaluation included a complete history, physical examination, chest radiograph, and chest computed tomography (CT). The patients' characteristics are shown in Table 1. There were 41 men and 15 women with a medi-

Table 1 - Univariate analysis of association between irradiated lung injury and clinical parameters

Patient characteristics	Number of patients	Acute radiation pneumonitis			Late radiation lung injury		
		Rate (%)	Chi-square value	P value	Rate (%)	Chi-square value	P value
Age (year)			0.770	0.380			0.877
≤64	29	24.1			24.1		
>64	27	14.8			25.9		
Chemotherapy combined with 3D-CRT			0.827	0.363		6.372	0.012
Yes	11	27.3			54.5		
No	45	15.6			17.8		
Comorbidities			0.438	0.508		1.867	0.172
Yes	16	12.5			37.5		
No	40	20.0			20.0		
Smoking history			0.901	0.342		0.096	0.757
Yes	26	23.1			26.9		
No	30	13.3			25.9		
Total lung volume (cm ³)			0.487	0.485		1.524	0.217
≤3300	28	14.3			17.9		
>3300	28	21.4			32.1		
Clinical stage			2.991	0.084		0.057	0.811
I + II	25	8.0			20.0		
III + IV	31	25.8			29.0		
Irradiated esophageal length (cm)			4.209	0.040		7.108	0.008
≤7.0	33	9.1			12.1		
>7.0	23	30.4			43.5		
CT infiltrated diameter (cm)			0.812	0.368		0.079	0.738
≤4.0	35	14.3			17.1		
>4.0	21	23.8			14.3		
Total dose (Gy)			3.881	0.049		2.885	0.089
≤64	27	7.4			14.8		
>64	29	27.6			34.5		
Number of fields			6.858	0.009		0.389	0.533
≤5	32	6.3			21.9		
>5	24	33.3			29.2		

3D-CRT, three-dimensional conformal radiotherapy; CT, computed tomography.

an age of 64 years (range, 31-81 years). Three patients had stage I disease, 22 patients stage II, 27 patients stage III, and 4 patients stage IV. Forty-four patients had carcinomas located in the middle thoracic esophagus and 12 in the lower thoracic esophagus. Lesion length by esophagogram was 2-16 cm, with a median of 6 cm. All patients were treated with curative intent. Of the 56 patients, 31 underwent whole-course 3D-CRT and 25 patients underwent early-course conventional radiotherapy plus late-course 3D-CRT. Concurrent chemotherapy ($n = 11$) and induced or consolidated chemotherapy ($n = 25$) were also part of the treatment. The chemotherapy consisted of cisplatin (20 mg/m^2 on days 1 to 5 of each cycle) plus 5-FU (750 mg/m^2 on days 1 to 5 of each cycle), ranging from 1 to 4 cycles. Among these 36 patients, 75% ($n = 27$) accepted 2 or more chemotherapy cycles and 25% ($n = 9$) only finished 1 cycle and refused further treatment because of their poor performance status. The other 20 patients only received radiotherapy to local esophageal lesions because of old age, poor performance status, or contraindications to chemotherapy.

Three-dimensional treatment planning, delivery and dose-volume parameters

Patients were placed in the treatment position during planning. CT scanning was performed using a CT simulator (SOMATOM Volume Zoom, Siemens Medical Systems). CT scans were obtained during quiet respiration and included the entire lung volume. The thickness of the individual sections of the scan was 3-5 mm. The CT scanning image data were directly transferred to the 3-dimensional planning system (Focus 4.1, Computerized Medical Systems, Inc).

In cases treated with 3D-CRT, targets were defined as follows in accordance with a report by the International Commission on Radiation Units and Measurements (ICRU)¹⁰: the gross tumor volume (GTV) encompassed all detectable tumors observed by esophagogram and esophagoscope and lymph nodes observed on CT scans with a short-axis diameter greater than 1 cm. The clinical target volume (CTV) included the GTV and extended a 5- to 8-mm margin around the circumference and a 20- to 25-mm margin in the long axis. The planning target volume (PTV) included the CTV plus a 5-mm margin. Target volumes and normal tissues (heart, spinal cord and lungs) were contoured on each section. Both lungs were treated as a single organ for radiation treatment planning and dose calculation. Dose distribution was computed without tissue heterogeneity correction. The prescribed dose was specified at the reference point (isocenter) of the PTV, as recommended by ICRU.

RT was delivered by means of 6-MV x-ray linear accelerators (ONCOR, Siemens Medical Systems). Of the 56 patients, 25 underwent early-course conventional radiotherapy plus late-course 3D-CRT, with no time interval between the 2 parts of radiotherapy. The dose frac-

tionation was 20-34 Gy in 10-17 fractions and 30-42 Gy in 15-21 fractions, respectively. The total dose was 50-76 Gy in 25-38 fractions over 6-7 weeks, with a median dose of 60 Gy. The radiation fields of the early-course conventional radiotherapy consisted of a pair of anterior-posterior and posterior-anterior opposite parallel fields in 17 cases, and 3 isocentric fields in 8 cases. The remaining 31 patients underwent whole-course 3D-CRT with a median dose of 64 Gy (range, 50-70 Gy) in 30 fractions (range, 25-35 fractions) over 6 weeks (range, 5-7 weeks).

The dose-volume parameters of early-course conventional radiotherapy cases were calculated at the point of the geometrical center of the GTV according to the dose-volume histograms (DVH) and dose distributions in each CT plane after the fields were corrected to the later 3D treatment planning. These parameters were analyzed as follows: MLD, percentage of lung receiving a dose of at least 5 to 40 Gy (V5-V40). Ninety to one hundred percent of the corresponding target volume (GTV, CTV, PTV) receiving doses were referred to as GTVD₉₀-GTVD₁₀₀, CTVD₉₀-CTVD₁₀₀, and PTVD₉₀-PTVD₁₀₀. The percentages of the corresponding target volumes (GTV, CTV, PTV) receiving a dose of 50 Gy were referred to as GTVV₅₀, CTVV₅₀ and PTVV₅₀.

Evaluation of irradiated lung toxicity and follow-up

After treatment, patients were followed up at 4-6 week intervals for the first year, and then every 3-4 months. Acute RP typically occurs 1-3 months after RT. Chronic lung fibrosis usually develops 3 months to several years after treatment. A diagnosis of irradiated lung injury was based on clinical and/or radiographic changes observed within the first 6 months after RT. Irradiated lung injury was scored according to the criteria of the Radiation Therapy Oncology Group (RTOG) for scoring of acute radiation morbidity in the lung. Because of the difficulty of accurately scoring lower grades of lung injury, only grade 2 and above were reported. The median follow-up for all patients was 21.0 months (range, 6.1-47 months).

Statistical analysis

It was expected that clinical parameters such as age (≤ 64 vs > 64 years), comorbidities, smoking history, and history of chemotherapy might affect the risk of development of lung injury after RT. Descriptive information is summarized as frequencies or percentages for categorical variables. Logistic regression analyses and the chi-square test were used to test the relationship between the different factors and lung injury. Correlations between dose-volume parameters were assessed with the Spearman correlation test. All statistical tests were performed with SPSS version 13.0. $P \leq 0.05$ was chosen as the level of statistical significance.

Results

Clinical parameters

Ten of the 56 patients (17.9%) developed acute RP, grade 2 (n = 7) or grade 3 (n = 3); no grade 4 or worse acute toxicity occurred. Toxicity occurred in one patient during RT, while it developed 2 weeks to 3 months after RT in the remaining 9 patients. The median time was 2.0 months after RT. The irradiated esophageal length (≤ 7.0 cm *vs* >7.0 cm), number of fields (≤ 5 *vs* >5) and total dose (≤ 64 Gy *vs* >64 Gy) were significantly associated with the occurrence of grade 2 or worse acute RP (Table 1).

Fourteen (25.0%) patients developed late irradiated lung injury 3.5 months (n = 3), 9 months (n = 7) and 14 months (n = 4) after RT. Irradiated esophageal length (≤ 7.0 cm *vs* >7.0 cm) and chemotherapy combined with RT were significantly associated with the development of late lung injury (Table 1).

Dosimetric parameters

The results of univariate analysis to investigate the association between dose-volume parameters and the occurrence of lung injury are summarized in Table 2 and Table 3. Many dosimetric and volumetric factors were significantly associated with acute RP of grade 2 or worse ($P < 0.05$). Among these parameters, the number of fields, V15, V20 and MLD were the most statistically significant factors ($P < 0.01$). V5-V40, and MLD were significantly associated with the occurrence of late lung injury ($P < 0.05$). Subsequently, the incidence of lung injury as a function of dose-volume parameters (V5-V40, as well as MLD) was calculated (Table 4). Data from the chi-square test showed that the incidence of lung injury was significantly lower in patients with V5 less than

Table 2 - Analysis of dose-volume parameters for predicting acute radiation pneumonitis

Parameter	Acute radiation pneumonitis			
	Yes (n = 10)	No (n = 46)	T value	P value
Irradiated esophageal length (cm)	8.4 ± 2.7	6.3 ± 2.4	2.523	0.015
Total dose (Gy)	6747 ± 486	6278 ± 585	2.449	0.018
Number of fields	6.7 ± 2.0	5.0 ± 1.5	3.165	0.003
Lung V5 (%)	71.5 ± 10.8	57.0 ± 17.2	2.658	0.010
Lung V10 (%)	54.6 ± 10.8	42.5 ± 14.6	2.558	0.013
Lung V15 (%)	42.3 ± 10.3	32.0 ± 11.5	2.711	0.009
Lung V20 (%)	33.6 ± 8.3	22.7 ± 9.3	3.529	0.001
Lung V25 (%)	23.6 ± 8.7	16.7 ± 8.2	2.506	0.015
MLD (cGy)	1587 ± 246	1234 ± 396	2.805	0.007
PTVD ₉₀ (cGy)	6195 ± 231	5963 ± 289	2.144	0.037
PTVV ₅₀ (%)	96 ± 9	88 ± 13	1.928	0.048

Lung V5-V25: percent of the lungs receiving at least 5 to 25 Gy; MLD, mean lung dose; PTVD₉₀, doses of 90% planning target volume; PTVV₅₀, percentage of planning target volume receiving a dose of 50 Gy.

Table 3 - Analysis of dose-volume parameters for predicting late radiation lung injury

Parameter	Late radiation lung injury			
	Yes (n = 14)	No (n = 42)	T value	P value
Irradiated esophageal length (cm)	8.8 ± 3.1	6.0 ± 2.0	3.870	0.000
Lung V5 (%)	69.3 ± 11.8	56.7 ± 17.5	2.508	0.015
Lung V10 (%)	54.2 ± 10.4	41.8 ± 14.7	2.934	0.005
Lung V15 (%)	43.1 ± 8.9	30.9 ± 11.3	3.668	0.001
Lung V20 (%)	32.6 ± 7.1	22.2 ± 9.6	3.736	0.000
Lung V25 (%)	24.8 ± 7.4	15.8 ± 7.9	3.747	0.000
Lung V30 (%)	17.14 ± 5.7	9.7 ± 5.3	4.397	0.000
Lung V35 (%)	11.4 ± 5.7	9.7 ± 5.3	3.750	0.000
Lung V40 (%)	7.9 ± 6.3	4.0 ± 3.0	3.086	0.003
MLD (cGy)	1614 ± 302	1200 ± 370	3.778	0.000

Lung V5-V40: percent of the lungs receiving at least 5 to 40 Gy; MLD, mean lung dose.

60%, V10 less than 50%, V15 less than 35%, V20 less than 25%, V25 less than 20%, and MLD less than 14 Gy ($P < 0.05$). Additionally, the incidence of late lung injury was also significantly lower in patients with V30 less than 15%, V35 less than 10%, and V40 less than 5% ($P < 0.05$). In multivariate analysis, V25, number of fields, and irradiated esophageal length were retained as single factors for acute RP (Table 5), and V30 and combined chemotherapy for late lung injury (Table 6). No obvious association between the presence of acute injury and the development of late injury was found ($P = 0.188$).

Discussion

The reported incidence of radiation-induced lung injury after RT ranges from 5% to 36%^{7,11-14}. It has been observed that radiation-induced lung injury occurs in esophageal carcinoma during RT and the incidence varies for different esophageal tumor sites. Theoretically, the radiation volume to the lungs in middle thoracic esophageal carcinomas might be more than that in upper thoracic carcinomas because of the shape characteristics of the lungs. Thus, it is desirable to predict the risk of development of radiation-induced lung injury.

There is no uniform toxicity reporting system and the toxicity scales vary according to different definitions. In our study, we adopted the radiation-induced lung toxicity scoring system recommended by the RTOG. The incidence of acute and late radiation-induced lung injury was 17.9% and 25.0%, respectively. Spearman's correlation test showed no significant association between the occurrences of the 2 types of lung injury. There were some exceptions due to different lung volume dose and pulmonary function, although patients with acute RP might possibly develop late lung injury.

Many dose-volume models for quantitative analyses of normal tissue effects have been designed since the

Table 4 - Observed rates of lung injury as a function of dose-volume parameters

Patient of lungs	n	Acute radiation pneumonitis			Late radiation lung injury		
		Rate (%)	Chi-square value	P value	Rate (%)	Chi-square value	P value
V5			3.881	0.049		5.364	0.021
≤60%	27	7.4			11.1		
>60%	29	27.6			37.9		
V10			4.209	0.040		4.156	0.041
≤50%	33	9.1			15.2		
>50%	23	30.4			39.1		
V15			4.926	0.026		4.029	0.045
≤35%	29	6.9			13.8		
>35%	27	29.6			37.0		
V20			4.926	0.026		4.029	0.045
≤25%	29	6.9			13.8		
>25%	27	29.6			37.0		
V25			8.461	0.004		8.086	0.004
≤20%	34	5.9			11.8		
>20%	22	36.4			45.5		
V30			2.222	0.136		14.894	0.000
≤15%	39	12.8			10.3		
>15%	17	29.4			58.8		
V35			2.739	0.098		11.667	0.001
≤10%	40	12.5			12.5		
>10%	16	31.3			56.3		
V40			0.901	0.342		4.691	0.030
≤5%	30	13.3			13.3		
>5%	26	23.1			38.5		
MLD (cGy)			4.383	0.036		9.524	0.002
≤1400	28	7.1			7.1		
>1400	28	28.6			42.9		

Lung V5-V25: percent of the lungs receiving at least 5 to 25 Gy; MLD, mean lung dose.

Table 5 - Multivariate logistic regression analysis of acute radiation pneumonitis

Variable	Coefficient	S _x value	Chi-square value	P value	RR
Lung V25	4.107	1.662	6.110	0.013	60.785
Number of fields	2.261	1.076	4.419	0.036	9.594
Irradiated esophageal length	5.511	2.249	6.005	0.014	247.459

Lung V25: percent of the lungs receiving at least 25 Gy; RR, relative risk.

Table 6 - Multivariate logistic regression analysis of late irradiated lung injury

Variable	Coefficient	S _x value	Chi-square value	P value	RR
Lung V30	2.153	1.141	3.563	0.045	8.614
Chemotherapy combined with 3D-CRT	3.761	1.687	4.970	0.026	10.023

Lung V30: percent of the lungs receiving at least 30 Gy; 3D-CRT, 3-dimensional conformal radiotherapy; RR, relative risk.

publication of the paper by Emami *et al.*¹⁵ in 1991. The DVH reduction model¹⁶ remains the most widely used, although it is not always considered an ideal representation of the 3D doses.

The DVH reduction model shows some limitations¹⁶. For example, it estimates the complication probability under uniform irradiation, which assumes all regions to be of equal functional importance and discards all organ-specific spatial information. Moreover, it is usually based on a single planning CT scan that does not ac-

count for anatomic variations during RT. Despite these caveats, this model is sufficiently flexible and predictive for clinical practice to allow representation of various dose-volume dependencies. A series of DVH-based studies^{8,17-22} have been published with the aim of predicting the risks of RP and thereby minimizing its occurrence. Although the published data on the association of DVH parameters and radiation-induced lung injury in patients with esophageal carcinoma receiving RT are not unified, most of this information has been de-

rived from studies of lung cancer patients. These studies^{13,23,24} have reported that DVH parameters, such as V5-V25, MLD, and mean biological lung dose are significantly associated with the occurrence of RP. Especially, studies^{7,21,22,28} suggested V20 or V30 as a single predictive factor for the risk of RP.

The findings of our study suggested that total dose, V20, V25, V30 and MLD were significantly predictive of the risk for at least grade 2 acute RP. Our data showed that the incidence of acute RP and late lung injury was significantly lower in patients with V25 <20% and V30 <15%, respectively. The statistical difference could not be analyzed between patients with comorbidities and those without because only a few patients (n = 6) completed the pulmonary function test before RT.

According to the traditional concept of radiation-induced lung toxicity, injury to critical target cells within the lungs and their consequent depletion leads to the sequence of early and late pulmonary injury. When the irradiated esophageal length increases, the area of radiation fields and the normal lung tissues included in the target volume correspondingly become larger, which will lead to acute radiation reactions or even lung injury. Likewise, the data from our study showed that the irradiated lesion length was a single factor for the risk of acute or late lung injury.

The size of radiation fields is determined in part by the volume of PTV. The PTV involved in PTVD₉₀ is larger than that in PTVD₉₅ and PTVD₁₀₀. Consequently, when PTVD₉₀ or PTVV₅₀ become larger, the dose or volume ratio of the irradiated lung increases correspondingly. Nutting and colleagues²⁵ suggested that 4 radiation fields in 3D-CRT increased the local target dose and significantly reduced the incidence of RP compared with 9 fields in intensity-modulated radiotherapy (IMRT). Our study showed that a lower dose to larger volumes was likely to produce a larger inflammatory response than a higher dose to a smaller volume. So it may be reasonable to design 3 or 4 beams for curative RT in esophageal carcinoma, especially for middle or lower thoracic lesions.

It has also been reported that chemotherapy, particularly when combined with thoracic RT, was associated with an increased risk of radiation-induced lung injury^{26,27}. Of 11 patients who received chemotherapy combined with RT in our study, 3 (27.3%) developed acute RP of grade 2 or higher and 6 (54.5%) developed late lung injury. So chemotherapy combined with RT, as a single factor, was significantly associated with the risk of late lung injury.

Given the pitfalls of describing radiation-induced lung toxicity and the DVH-based model, predicting the occurrence of lung toxicity is not an easy task. The quality of the predictions is related to the endpoint chosen and the model used to calculate the complication probability. Firstly, it must be kept in mind that our current findings are based on data from 56 esophageal cancer

patients, of whom only 10 developed acute RP and 14 developed late lung injury. Secondly, there was a lack of radiation field calibration in the 25 patients undergoing early-course conventional RT, which might increase the risk of lung injury caused by an additional isocentric dose to the corresponding radiation fields. Thirdly, 5 of the 14 patients with late lung injury had presented acute RP at an earlier stage. Although no evidence supported the late lung injury resulted from the acute RP occurring during RT, relating the late lung injury to the whole-course DVH might also be suboptimal.

Furthermore, we did not employ lung heterogeneity correction for dose calculations. There are several reasons for this omission. Firstly, there is no consensus about which algorithm should be used to correct heterogeneity, as most RTOG protocols for the treatment of thoracic tumors mandate treatment planning without inhomogeneity correction. Secondly, some studies^{29,30} reported that heterogeneity correction may result in isocenter doses greater than with uncorrected calculation. Dose planning for lung cancer has long been based on clinical experience and performed without correction for inhomogeneity, and there has been fear that heterogeneity correction may result in insufficiency of the radiation dose to the primary tumor.

In conclusion, our results suggest that 3 dose-volume parameters (V25, the number of fields, and irradiated esophagus length) may be used as predictors of the risk for acute RP and that V30, as well as combined chemotherapy with RT, may be predictive for late lung injury. Among these parameters, V25 and V30 are particularly useful and should be limited to less than 25% and 15%, respectively, to minimize the risk of radiation-induced lung injury following 3D-CRT for esophageal carcinoma.

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