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• *CLINICAL RESEARCH* •

Clinical and dosimetric factors of radiation-induced esophageal injury: Radiation-induced esophageal toxicity

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Abstract

AIM: To analyze the clinical and dosimetric predictive factors for radiation-induced esophageal injury in patients with non-small-cell lung cancer (NSCLC) during three-dimensional conformal radiotherapy (3D-CRT).

METHODS: We retrospectively analyzed 208 consecutive patients (146 men and 62 women) with NSCLC treated with 3D-CRT. The median age of the patients was 64 years (range 35-87 years). The clinical and treatment parameters including gender, age, performance status, sequential chemotherapy, concurrent chemotherapy, presence of carinal or subcarinal lymph nodes, pretreatment weight loss, mean dose to the entire esophagus, maximal point dose to the esophagus, and percentage of volume of esophagus receiving >55 Gy were studied. Clinical and dosimetric factors for radiation-induced acute and late grade 3-5 esophageal injury were analyzed according to Radiation Therapy Oncology Group (RTOG) criteria.

RESULTS: Twenty-five (12%) of the two hundred and eight patients developed acute or late grade 3-5 esophageal injury. Among them, nine patients had both acute and late grade 3-5 esophageal injury, two died of late esophageal perforation. Concurrent chemotherapy and maximal point dose to the esophagus $\geqslant$60 Gy were significantly associated with the risk of grade 3-5 esophageal injury. Fifty-four (26%) of the two hundred and eight patients received concurrent chemotherapy. Among them, 25 (46%) developed grade 3-5 esophageal injury (P = 0.0001<0.01). However, no grade 3-5 esophageal injury occurred in patients who received a maximal point dose to the esophagus <60 Gy (P = 0.0001<0.01).

CONCLUSION: Concurrent chemotherapy and the maximal esophageal point dose $\geqslant$60 Gy are significantly associated with the risk of grade 3-5 esophageal injury in patients with NSCLC treated with 3D-CRT.

Key words: 3D-CRT; Non-small-cell lung cancer; Chemotherapy; Esophagitis

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INTRODUCTION

Radiotherapy (RT) can achieve good results in the treatment of non-small-cell lung cancer (NSCLC). The key is how to monitor the dose to critical normal tissues such as the heart, normal lung, and esophagus. Several factors can minimize the dose of RT to the esophagus, including proximity of the esophagus to midline tumors or mediastinal adenopathy, proximity of the esophagus to higher priority organs such as spinal cord and heart and relative paucity of information on the clinical and dosimetric predictors of radiation-induced esophageal injury.

Clinicians familiar with RT planning are often forced to evaluate multiple plans that produce equivalent coverage of the target with variable sparing of critical structures. By our experience, the esophageal dose is not critically considered because the clinical and dosimetric variables predicting esophageal injury are not well characterized. The purpose of this investigation was to analyze the incidence of acute and late grade 3-5 esophageal injury in patients with NSCLC during three-dimensional conformal radiotherapy (3D-CRT) combined with or without chemotherapy (sequential or concurrent).

MATERIALS AND METHODS

Patients

From October 2000 to June 2002, 208 consecutive patients (146 men and 62 women, average 67 years of age) with inoperable NSCLC completed the treatment of high-dose RT. Patients were considered inoperable on the basis of mediastinal lymph node involvement (N2 or N3), bulky primary disease (T3 or T4), and/or advanced disease states. All patients had biopsy-proven NSCLC. Patient characteristics and pathologic subtypes are shown in Table 1. Patients with metastatic disease and those treated with palliative dose (<60 Gy) were not included in this study.

Initial evaluation

The initial evaluation was based on a complete history and physical examination, chest X-ray, CT of the chest through the liver and adrenal glands, and a bone scan. CT of the brain was obtained to evaluate any suspicious neurologic symptoms.

Treatment dose

All patients were treated with 1.8-2.0 Gy daily. The median dose to the isocenter was 70 Gy (range 60-72 Gy). Doses were reported without heterogenous corrections.

Chemotherapy

Ninety-eight (47%) patients received chemotherapy as a part of definitive treatment. Fifty-four patients received sequential chemotherapy (administered before initiation of RT). Fifty-four patients received concurrent chemotherapy (administered during RT). The chemotherapy records were available for 54 patients (Table 2), 43 of them were treated with concurrent cisplatin-based chemotherapy. None of the three patients treated with gemcitabine developed grade 3-5 esophageal injury. Two patients died (grade 5 esophageal injury) of perforation. No grade 3-5 esophageal injury was found in patients who received sequential chemotherapy of cisplatin and etoposide.

Evaluation during follow-up

During RT, patients were seen once a week or more as needed for evaluation and treatment of complaints. After completion of RT, patients were followed up at intervals of 2-3 mo for 2 years. Acute and late esophageal injuries were graded according to Radiation Therapy Oncology Group (RTOG) criteria (Table 3). The median follow-up period was 24 mo. The follow-up evaluations consisted of a history and physical examination.

Dosimetric analysis

Three-dimensional treatment was planned as previously described[1]. The esophagus was contoured from the thoracic inlet to the diaphragm. All patients had full treatment plans based on volumetric dose calculations. The doses prescribed and reported in this study were not corrected for tissue heterogeneity.

Statistical analysis

The following parameters were studied, including age, gender, performance status, sequential chemotherapy, concurrent chemotherapy, presence of subcarinal lymph nodes, mean dose to the entire esophagus, maximal esophageal point dose, pretreatment weight loss, and percentage of volume of esophagus receiving >55 Gy. Patients were defined as having acute esophageal injury according to RTOG criteria if the symptoms developed during treatment or within the first 3 mo after RT, while those were defined as having late esophageal injury if the symptoms persisted or occurred after 3 mo of follow-up. The patients and treatment/dosimetric factors were coded and correlated with acute and late grade 3-5 esophageal injury by univariate and multivariate regression analyses. Statistical analysis was performed using SPSS 10.0 for Windows.

RESULTS

Twenty-five (12%) of the two hundred and eight patients developed acute (14) or late (11) grade 3-5 esophageal injury. Nine patients developed both acute and late grade 3-5 esophageal injury. Two patients died of perforation (grade 5 esophageal injury). The incidence of acute and late esophageal injury is summarized in Table 4.

Univariate analysis showed that concurrent chemotherapy, maximal point dose to the esophagus ⩾60 Gy, subcarinal lymph nodes and mean esophageal dose ⩾40 Gy were associated with the risk for grade 3-5 esophageal injury, whereas mean esophageal dose ⩾40 Gy and subcarinal lymph nodes did not retain significance on multivariate analysis (Table 5).

Among the 208 patients, 54 (26%) received concurrent chemotherapy, 23 (92%) of the 25 patients who developed grade 3-5 esophageal injury received concurrent chemotherapy ($P = 0.0001<0.01$). Sequential chemotherapy was not associated with the grade 3-5 esophageal injury. Grade 3-5 esophageal injury did not occur in patients who received a maximal dose to the esophagus <60 Gy ($P = 0.0001<0.01$). Only two patients who did not receive concurrent chemotherapy developed grade 3-5 esophageal injury.

Table 1 Patient characteristics

Age (yr)	Gender (%)	Performance (%)	Weight loss (%)	Histologic type status (%)
Range 35–87	Male (70)	KPS⩾70 to 95	<5–75%	Squamous cell carcinoma (60)
Median 66	Female (30)	KPS<70 to 5	⩾5–25%	Adenocarcinoma (14)
				Undifferentiated large cell (24)
				NSCLC, OT (2)

KPS, Karnofsky performance status; NSCLC, non-small-cell lung cancer; OT, otherwise type.

Table 2 Concurrent chemotherapy agents used

Patients (*n*)	Concurrent chemotherapy
25	Cisplatin and etoposide
4	Cisplatin
2	Cisplatin, etoposide, and gemcitabine
6	Cisplatin and 5-fluorouracil
1	Cisplatin and Navelbine
5	Cisplatin, Navelbine and gemcitabine
5	Carboplatin and Taxol
3	Gemcitabine
3	Taxotere

Table 3 RTOG grading for acute esophageal injury

Grade	Description
0	No change
1	Mild dysphagia or odynophagia, requiring topical anesthetic, non-narcotic agents, or soft diet
2	Moderate dysphagia or odynophagia, requiring narcotic agents or liquid diet
3	Severe dysphagia or odynophagia with dehydration or weight loss (>15% of pretreatment baseline), requiring nasogastric feeding
4	Complete stricture, ulceration, perforation or fistula
5	Death

RTOG, Radiation Therapy Oncology Group. During the follow-up period, chest X-ray examination was performed at intervals of 2-3 mo. CT scan of the chest was carried out every 2–3 mo after treatment, or earlier if clinically indicated.

Table 4 Distribution of acute and late esophageal injury

Pt.no.	Late esophageal injury	Acute esophageal injury
1	3	3
2	1	3
3	3	3
4	3	3
5	1	3
6	2	4
7	3	3
8	3	1
9	3	5
10	3	1
11	2	3
12	3	3
13	3	3
14	4	5
15	0	3
16	3	3
Total	11	14

RTOC, Radiation Therapy Oncology Group; Pt. no., patient number.

Table 5 Analysis of factors predicting esophageal injury

Variable	Univariate (*P*)	Multivariate (*P*)
Concurrent chemotherapy	0.0001	0.0090
Maximal dose point ⩾60 Gy	0.0001	0.0010
Mean esophageal dose ⩾40 Gy	0.0341	0.1023
Carinal or subcarinal nodes	0.0145	0.2136
Sequential chemotherapy	0.3680	0.1467
Volume >55 Gy	0.1699	0.1235
Age (yr)	0.3064	0.1354
Gender	0.4947	0.1213
Weight loss	0.3608	0.1302

DISCUSSION

Damage to the esophagus is a major limiting factor in RT of intrathoracic tumors. Radiation-induced esophagitis presents various symptoms such as mild substernal burning sensation, severe pain, odynophagia and dysphagia. Acute change occurs, about 2 wk after initiation of therapy, and is largely limited to the mucosa. Most changes that occur later than 3 mo or more after irradiation are mortal disturbances possibly due to damage to nerves and smooth muscle, stricture may eventually develop[2]. It was reported that abnormalities include abnormal mortality with or without mucosal edema, stricture, ulceration, pseudodiverticulum and fistula, abnormal death occurs 4-12 wk following RT alone and as early as 1 wk after therapy when concurrent chemotherapy is given, strictures often develop 4-8 mo following completion of RT[3]. Radiation-induced esophageal injury occurs more frequently when RT and chemotherapy are combined. Frequent concurrent chemotherapy may complicate identification of the clinical and dosimetric predictors of esophageal injury. RT regimens that escalate the dose or add chemotherapy lay stress on defining the clinical and dosimetric predictors of acute and late esophageal injury. Intensificaiton of additional regimens is not feasible without better dosimetric methods to limit dose-induced esophageal injury. Additional characteristics of the predictors of esophagitis must define the dose limits for radiation and quantify the effect of chemotherapy.

The clinical and dosimetric predictors of acute and late esophageal injury are not typically characterized. Severe esophageal injury has been reported in 46% incidence of acute grade 3-4 esophageal injuries[4]. It was reported that concurrent chemotherapy increases nearly 12-fold risk for esophageal injury[5]. Emami *et al*[6], reported that RT may lead to late stricture and/or perforation of the esophagus. Dillman *et al*[7], reported a similar incidence of esophageal injury (<1%). It was reported that late esophageal injury following aggressive, high-dose conformal RT is common but rarely severe; dosimetric variables addressing the longitudinal and circumferential characteristics of the esophagus have biologic rationale and are predictive of late injury[8]. Patel *et al*[9], found that concurrent chemotherapy and hyperfractionated RT after surgery in patients with NSCLC are significantly associated with acute grade 2 or worse esophageal injury. Werner-Wasik *et al*[10], reported that concurrent chemotherapy and twice-daily RT are associated with higher grades and longer durations of acute esophagitis. Concurrent chemotherapy combined with RT appears to have lower esophageal radiation tolerance, resulting in markedly higher incidence of esophagitis[11].

We found a significant association between concurrent chemotherapy and the development of higher grades of esophagitis. Contrary to the findings of Maguire *et al*[8], we did not find any significant association between the incidence of esophagitis and the the longitudinal and circumferential characteristics of the esophagus. However, Kiura *et al*[12], reported that concurrent thoracic radiation therapy and chemotherapy are effective and tolerable in patients with advanced NSCLC. Singh *et al*[13], found that concurrent chemotherapy is significantly associated with the risk of grade 3-5 esophageal injury in patients with NSCLC. Advances in the delivery of RT and target delineation along with development of radioprotectors, intensity-modulated RT may allow the delivery of high doses to thoracic tumors while minimizing the dose to adjacent normal structures such as the esophagus. The introduction of fluoro-deoxy-glucose positron emission tomography scanning into traditional CT images for 3D treatment planning may improve target delineation, thus allowing reduced clinical target volumes with consequent reductions in the volume of irradiated esophagus. Marks *et al*[14], reported that, without a definitive threshold dose, a differential dose-volume-histogram (DVH) may be useful in predicting the outcome if the dose-response curve for regional organ dysfunction is known. Since the esophagus is a hollow tube, a dose-surface-histogram (DSH) might be a better descriptor than DVH. The relationship between the lumenal organ and the clinical/dosimetric factors is very difficult to investigate, thus both DVH and DSH are not ideal predictors of biologic outcome[8]. Yoshizawa *et al*[15], reported that carboplatin and 5-fluorouracil administered daily with concurrent thoracic radiation therapy in patients with NSCLC induce acceptable injury. Antonadou *et al*[16], found that amifostine, a radioprotector, reduces the incidence of pneumonitis and esophagitis without compromising the antitumor efficacy of radiation treatment in patients with

lung cancer. In our study, concurrent chemotherapy and the maximal esophageal point dose were significantly associated with the risk of grade 3-5 esophageal injury in patients with NSCLC treated with high-dose 3D-CRT. In patients, who received concurrent chemotherapy, the maximal esophageal point dose for grade 3-5 esophageal injury was 60 Gy.

In conclusion, concurrent chemotherapy and the maximal esophageal point dose can predict grade 3-5 esophageal injury.

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