

# Mean esophageal radiation dose is predictive of the grade of acute esophagitis in lung cancer patients treated with concurrent radiotherapy and chemotherapy

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The intention of this research was to define the predictive factors for acute esophagitis (AE) in lung cancer patients treated with concurrent chemotherapy and three-dimensional conformal radiotherapy. The data for 72 lung cancer patients treated with concurrent chemoradiotherapy between 2008 and 2010 were prospectively evaluated. Mean lung dose, mean dose of esophagus, volume of esophagus irradiated and percentage of esophagus volume treated were analysed according to esophagitis grades. The mean esophageal dose was associated with an increased risk of esophageal toxicity (Kruskal-Wallis test,  $P < 0.001$ ). However, the mean lung dose and the volume of esophagus irradiated were not associated with an increased risk of esophageal toxicity (Kruskal-Wallis test,  $P = 0.50$  and  $P = 0.41$ , respectively). The mean radiation dose received by the esophagus was found to be highly correlated with the duration of Grade 2 esophagitis (Spearman test,  $r = 0.82$ ,  $P < 0.001$ ). The mean dose of esophagus  $\geq 28$  Gy showed statistical significance with respect to AE Grade 2 or worse (receiver operating characteristic curve analysis, 95% CI, 0.929–1.014). In conclusion, the mean esophageal dose was significantly associated with a risk of esophageal toxicity in patients with lung cancer treated with concurrent radiotherapy and chemotherapy.

**Keywords:** acute esophagitis; radiotherapy; lung cancer; dosimetric parameters; concurrent chemotherapy

## INTRODUCTION

Lung cancer is the most frequent cause of cancer mortality world-wide. The practice of radiotherapy in the management of lung cancer has evolved tremendously over the past decade. Three-dimensional conformal radiotherapy (3D-CRT) has become the standard of care in many hospitals. In addition, the use of concurrent chemotherapy with radiotherapy is the primary treatment for locally advanced non-small cell lung cancer, which is the most common histological type and presentation. For small cell lung cancer patients, it is beneficial for radiotherapy to be administered early in the course of treatment or concurrently with chemotherapy. However, chemoradiotherapy is a more

aggressive therapy than conventional radiotherapy alone. Chemoradiotherapy may cause a significantly higher incidence of toxicity, most typically acute esophagitis and radiation pneumonitis. These adverse treatment side effects are often dose-limiting factors that affect treatment outcomes and patient quality of life. Concurrent chemoradiotherapy results in a 22–45% rate of severe (Radiation Therapy Oncology Group [RTOG]  $\geq$  Grade 3) acute esophagitis [1]. As a result of the use of concurrent chemoradiotherapy, acute esophagitis that can require hospitalization or radiotherapy breaks can lower local tumor control.

Acute esophagitis has been investigated for the identification of clinical and dosimetric predictors, but not to the same extent as radiation pneumonitis for which considerable

literature already exists. Additionally, results have differed considerably across different institutions regarding which dosimetric factors are more critical than others [2]. The identification of the risk factors for acute esophagitis in lung cancer is crucial for optimizing the quality of radiotherapy treatment planning and minimizing the toxicity of chemoradiotherapy. Many factors found to correlate with an increased incidence of acute esophagitis are concurrent chemoradiotherapy, length of esophagus in the treatment field, and percentage of esophagus volume treated. In the present study, the dosimetric data of patients treated with conformal fractionated radiotherapy for neoplastic lung processes were examined in relation to the incidence of clinically apparent acute esophagitis.

## MATERIALS AND METHODS

### Patient criteria

Between October 2008 and May 2010, patients diagnosed with lung cancer and eligible for chemoradiotherapy were enrolled in this prospective study to evaluate the risk factors for acute esophagitis.

A total of 72 patients with inoperable lung cancer completed treatment with high-dose definitive radiotherapy. Criteria for inoperability were as follows: mediastinal node involvement (N2 or N3), bulky primary disease (T3 or T4) and/or comorbid disease. All patients had pathologically confirmed lung cancer. Criteria for exclusion were: patients with evidence of metastatic disease, those treated with palliative intent, prior thoracic cancer, and receipt of

postoperative radiotherapy. Table 1 shows the characteristics of the patients and tumors.

Each patient had undergone basic laboratory studies as well as CT scans of the chest and brain. In addition, most patients had also undergone whole-body positron emission tomography (FDG-PET).

### Treatment and dosimetric planning

The patients had been treated with concurrent chemoradiotherapy. Concurrent chemotherapy was administered weekly with Cisplatin on Days 1, 8, 15, 22, 29 and 36. Patients also underwent three-dimensional treatment planning, and were simulated on a regular CT simulator in a supine position immobilized with a lung board. CT slices (3 mm thick) were achieved from the level of the mandible to the lower edge of the liver. Treatment planning was completed according to the standards of the International Commission on Radiation Units and Measurements Report No: 50 [3]. Contouring of target volumes and normal organs (esophagus, spinal cord, heart and lung) was performed on each slice. The external surface of the esophagus was delineated on each axial plane of the planning CT scan from the level of the lower end of the cricoid cartilage to the gastroesophageal junction. Patients had their entire esophagus including esophageal internal lumen contoured. Additionally, internal lumina were not contoured. The gross tumor volume (GTV) included all detectable tumors and lymph nodes observed on CT scans. The clinical target volume (CTV) encompassed the GTV plus 0.8 cm expansion margins. Two planning target volume (PTVs) were subsequently described: PTV1 and PTV2. PTV1 was enlarged from the CTV by adding 1.0–1.5 cm margins to account for tumor motion and setup uncertainty. PTV2 was enlarged from the CTV by adding 5–10 mm margins. Prescribed doses were 45 Gy to PTV1 and 55 Gy or 65 Gy to PTV2 as reported by small or non-small cell histology, at single daily fractions of 2.0 Gy. A commercial treatment planning system (Precise Plan 2.15, [2006], Pulb, USA) was used to design 3D-CRT. Beam angles were chosen to reduce lung dose with anterior oblique, posterior oblique and lateral beams used. Multi-leaf collimator shielding was used to conform each beam shape to the PTV. A tissue heterogeneity correction was applied based on the Clarkson integration dose calculation algorithm. Radiotherapy was managed with a linear accelerator using energy of 6 MV or 18 MV X-rays. Maximum acceptable doses for dose-limiting organs were: lung V20 of <35%, and esophageal V45 of <40%.

### Clinical evaluation

During the course of radiotherapy, patients were observed at least weekly and more often if needed for clinical evaluation and treatment of complaints. Acute esophageal toxicity was determined during the weekly visits and at clinical follow-ups after one month and three months

**Table 1.** Characteristics of patients and tumors

Characteristic	Value
Age (year)	
Range	38–79
Mean	59.04
Sex	
Male	64
Female	8
Histology	
Non-small cell	62
Small cell	10
Stage	
IIB	4
IIIA	32
IIIB	26
Localized	10

respectively. Acute esophageal toxicity (symptoms <3 months) was graded by the Radiation Therapy Oncology Group (RTOG) criteria, as shown in Table 2.

**Statistical analyses**

The following parameters were analysed for correlation of acute esophagitis: the mean doses delivered to the

esophagus, the volume of the esophagus irradiated (total esophageal volume that was contoured in PTV), the mean doses irradiated to the lung, the percentage of esophagus volume receiving  $\geq 10$  Gy (V10),  $\geq 20$ Gy (V20),  $\geq 30$  Gy (V30),  $\geq 35$ Gy (V35),  $\geq 40$ Gy (V40),  $\geq 45$ Gy (V45),  $\geq 50$ Gy (V50),  $\geq 55$ Gy (V55),  $\geq 60$ Gy (V60), and the duration of  $\geq$  Grade 2 acute esophagitis.

Spearman’s rank correlation coefficient was used to correlate these parameters with the Grade and duration of acute esophagitis, while the Kruskal-Wallis test was used to test for significance. Additionally, ROC (receiver operating characteristic) curves were used to display the predictive ability of parameters throughout a range of cut points.

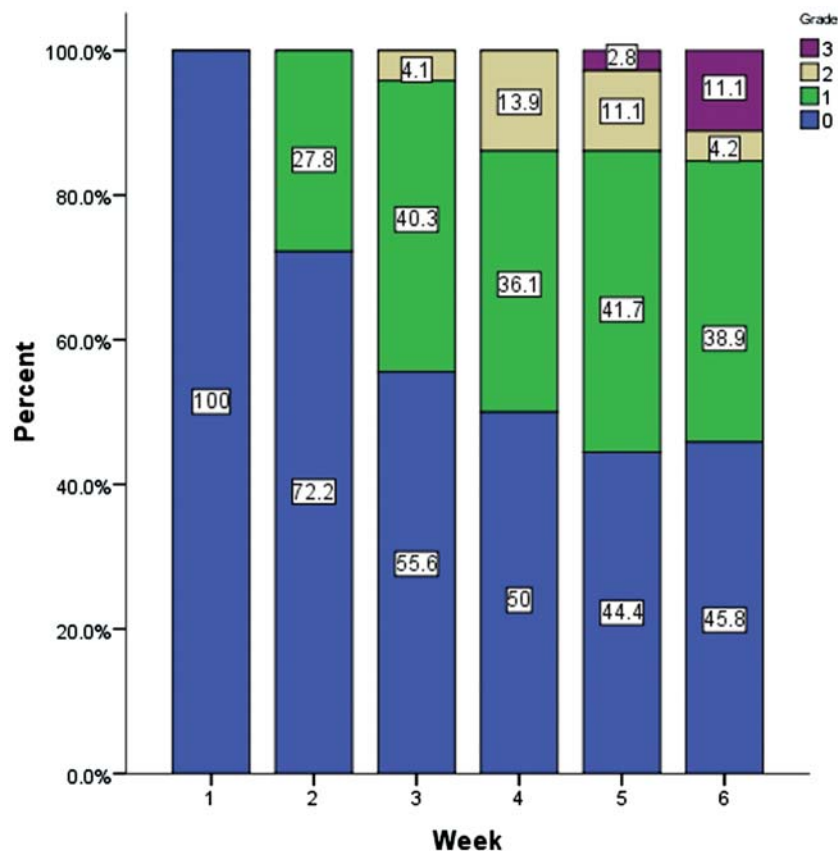
**RESULTS**

From the total of 72 patients included in the study and treated with concurrent radiotherapy and chemotherapy, 33 did not present with any grade of esophagitis during treatment. No patients were hospitalized, and there were no instances of the radiation treatment being interrupted for esophagitis.

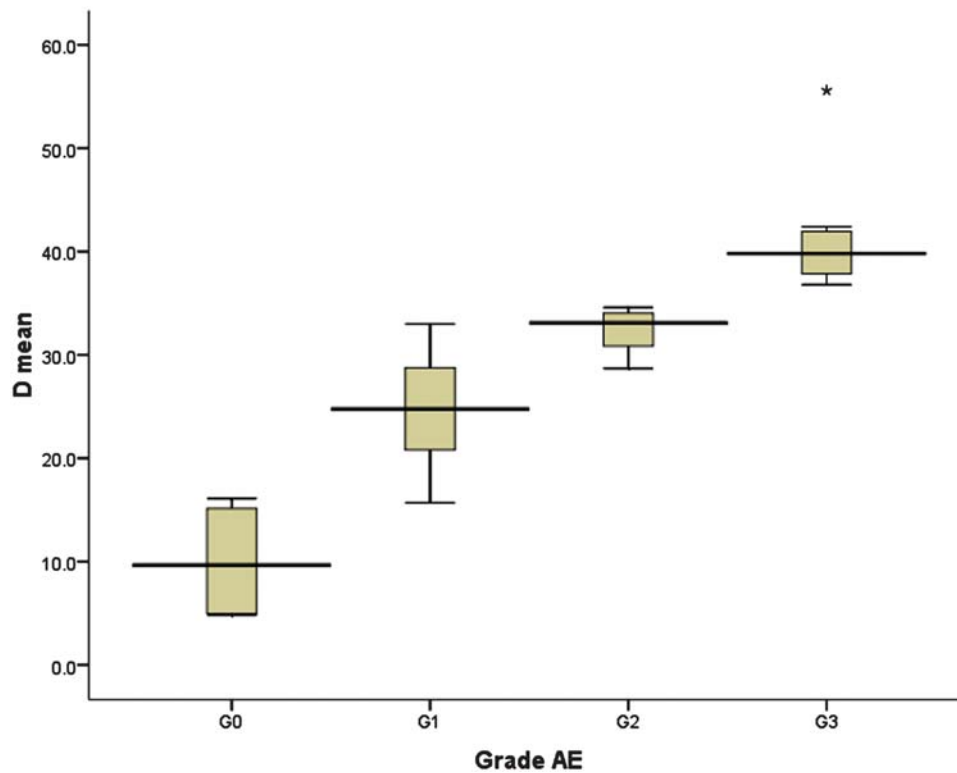
For radiation therapy, the median radiation dose to the PTV2 was 60 Gy (range, 55–62.3 Gy) in 27–30 fractions.

**Table 2.** Radiation Therapy Oncology Group scoring for acute esophagitis

Score	Description
0	No change in baseline
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 pre-treatment baseline), requiring nasogastric feeding
4	Complete obstruction, ulceration, perforation, or fistula
5	Death



**Figure 1.** Distributions of various grades of acute esophagitis during the radiation therapy.



**Figure 2.** Correlations between grade of acute esophagitis and the mean radiation dose received by the esophagus. Kruskal-Wallis test,  $P < 0.001$ .

The rate of acute esophageal toxicity was 54.2% (39/72). The highest esophagitis scores observed during treatment were 38.9% (28 of 72) for Grade 1 esophagitis, 4.2% (3 of 72) for Grade 2 esophagitis, and 11.1% (8 of 72) for Grade 3 esophagitis.

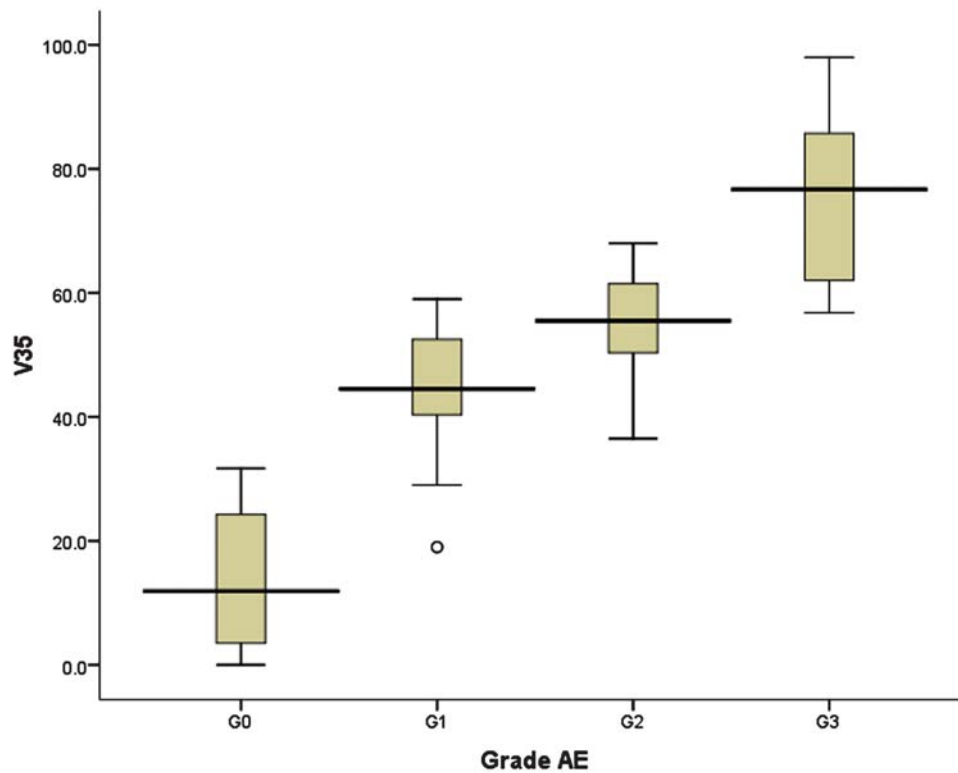
The incidences of the various grades of acute esophagitis during each week of radiotherapy are shown in Figure 1. Grade 1 esophagitis began to appear during the second week of radiotherapy, while Grades 2 and 3 esophagitis were relatively rare. The incidence of Grade 2 and higher esophagitis was 15.3%.

Generally, Grade 2 and higher esophagitis first appeared during the third week of treatment, and the rate continued to increase until the end of treatment. Patients with Grade 3 esophagitis generally experienced it during the fifth week of treatment. The continued presence of esophagitis was not observed at the follow-up visits one month later. The statistical analysis of the possible predictors for esophagitis was tested. As indicated in Figure 2, the mean esophageal dose showed statistically significant correlation with the grade of acute esophagitis ( $P < 0.001$ , Kruskal-Wallis test). However, the mean lung dose and the volume of the esophagus irradiated were not associated with an increased risk of esophageal toxicity ( $P = 0.35$ ,  $P = 0.85$ , respectively, Kruskal-Wallis test).

**Table 3.** Dose–volume parameters of the irradiated esophagus and their association with the incidence of acute esophagitis according to Kruskal Wallis test

Variable	Median	Range	P value
<b>D total lung</b>	59.9	54.5–62.3	0.50
<b>D mean esophagus</b>	27.9	4.8–55.6	<0.001
<b>Esophageal volume</b>	40.1	14.4–83.1	0.41
<b>V10</b>	61.0	10.0–100.0	<0.001
<b>V20</b>	56.8	6.0–99.0	<0.001
<b>V30</b>	48.0	1.0–98.0	<0.001
<b>V35</b>	46.0	0.0–98.0	<0.001
<b>V40</b>	39.0	0.0–97.0	<0.001
<b>V45</b>	24.0	0.0–94.0	0.004
<b>V50</b>	5.0	0.0–82.0	0.13
<b>V55</b>	0.0	0.0–77.0	0.19
<b>V60</b>	0.0	0.0–20.0	0.66

The results of the Kruskal-Wallis tests indicating the relationship between the dosimetric factors of DVH's (dose–volume histogram) and grade of acute esophagitis are shown in Table 3. It was observed that the mean dose



**Figure 3.** Correlations between grade of acute esophagitis and volume of irradiated esophagus  $\geq 35$  Gy (V35), Kruskal-Wallis test  $P < 0.001$ .

to the esophagus and the percentage of organ volume receiving irradiation (i.e. V10, V20, V30, V35, V40, V45) were all significantly associated with acute esophagitis (Figure 3).

Spearman's rank correlation coefficient was used to correlate the mean esophageal dose received with the duration of Grade 2 esophagitis. The mean esophageal dose received was found to be highly correlated with the duration of Grade 2 esophagitis ( $P < 0.001$ ,  $r = 0.82$ ) (Figure 4).

Lastly, the ability of mean esophageal dose to predict the development of acute esophagitis of Grade 2 or worse was tested by ROC curve analysis. The area below the ROC curve for acute esophagitis Grade 2 or worse was 0.97 (95% CI, 0.929–1.014). If mean esophageal dose was  $< 28$  Gy there was a 0.0% occurrence rate of esophagitis Grade 2 or worse, which increased to 60.7% if mean esophageal dose was  $\geq 28$  Gy.

These data can also be used to identify separate points on ROC curves. According to the curve, the mean esophageal dose  $\geq 28$  Gy, represents the cut point with best sensitivity and specificity.

## DISCUSSION

This was a prospective study report of treatment-related acute toxicities of the esophagus in patients with lung

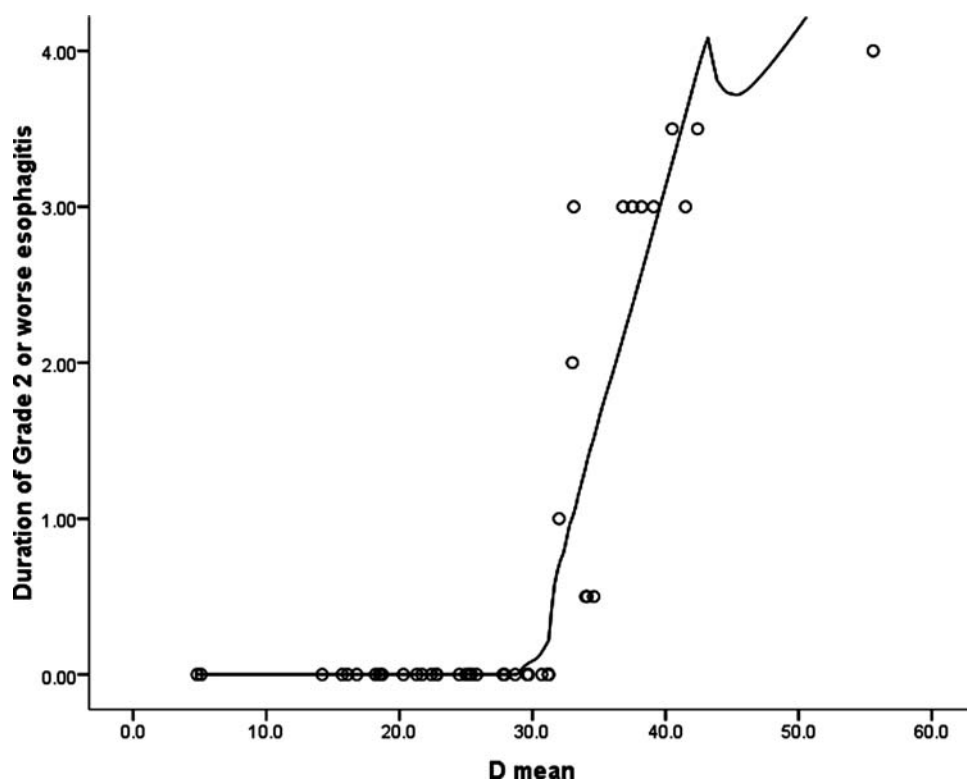
cancer that were administered concurrent radiotherapy and chemotherapy. Several studies have shown that, compared to radiotherapy alone, the addition of concurrent chemotherapy to radiation appears to lower esophageal radiation tolerance [4].

Incidence of severe acute esophagitis was lower than those for other studies of patients with lung cancer treated with 3D-CRT [2, 5]. It is well known that acute esophagitis affects the quality of life of lung cancer patients, and may precipitate a break in radiation treatment. In this study, radiotherapy treatment interruptions due to severe esophagitis were not observed.

The median dose administered to PTV2 was 60 Gy, which was slightly lower than the usual prescribed dose of 63 Gy in conformal radiotherapy. Weekly Cisplatin was used in the study, which was not a standard concurrent chemotherapeutic regimen.

Acute radiation injuries usually occur in the third to fourth week of radiotherapy, and tend to increase in severity toward the end of treatment [6]. These findings also showed that the appearance of Grade 3 or higher acute esophagitis was similar to other published studies [7]. None of the patients experienced Grade 4 or Grade 5 esophagitis.

Although dose-volume parameters are commonly used to analyse the risk of acute esophagitis, there is a significant degree of dissimilarity among the other published studies



**Figure 4.** Correlations between mean radiation dose received by the esophagus and the duration of grade 2 or worse esophagitis. Spearman test,  $r = 0.82$ ,  $P < 0.001$ .

regarding which dose-volume parameters have the most dominant effect on the risk of acute esophagitis [8, 9]. For example, some reports mentioned esophageal volumes  $>35$  Gy associated with acute esophagitis [2, 3]; others mentioned no association between the risk of acute esophagitis and volumes of esophagus [10].

By using DVH parameters, it was found that the risk of Grade 2 esophagitis duration was significantly correlated with the mean esophageal dose. There was no correlation observed between the volume of esophagus irradiated and esophagitis. Furthermore, the mean esophageal dose irradiated  $\geq 28$  Gy was the most statistically significant factor associated with acute esophagitis Grade 2 or worse.

Dose-volume histogram parameters delineating cumulative dose  $>50$  Gy have been identified as being associated with acute esophagitis in several studies. However, some studies have demonstrated the strongest statistically significant correlations with esophagitis at lower doses [11]. The data in this study are consistent with an association with acute esophagitis at lower doses and an increasing effect for greater doses.

At present, it is not possible to identify a single best threshold parameter for esophageal irradiation, because a wide range of parameters associate significantly with mild to severe acute esophagitis. Exempting the entire esophageal length/volume from the high-dose radiation region is

extremely difficult. However, decreasing the radiation dose delivered to a part of esophageal margin might be feasible.

In the department in which this study took place, these esophageal parameters are considered when clinical and dosimetric decisions are being made. Additionally, a higher intake of vegetables and fluids are recommended to the patient and anti-acid medication is prescribed as needed to protect the esophagus. If esophagitis occurs, it can be managed with aggressive nutritional support to prevent the development of dehydration and malnutrition. For patients with Grade 3 or worse esophagitis, tube feeding or total parenteral nutrition is considered.

This study has summarized the Oncology Hospital experience with early toxicities associated with radiotherapy to treat lung cancer, and has analysed dosimetric predictors of acute esophagitis. In the analysis, the mean esophageal dose was significantly associated with a risk of esophageal toxicity in patients. Taking into account the important component of the late effect in the esophagus, the researchers consider it useful for estimating not only the predictors of severe esophageal toxicity, but also those of less severe esophagitis.

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