Dosimetric and Clinical Predictors of Acute Esophagitis in Lung Cancer Patients in Turkey Treated with Radiotherapy

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Abstract

Background: The purpose of this study was to determine the clinical and dosimetric factors associated with acute esophagitis (AE) in lung cancer patients treated with conformal radiotherapy (RT) in Turkey. Materials and Methods: In this retrospective review 104 lung cancer patients were examined. Esophagitis grades were verified weekly during treatment, and at 1 week, and 1 and 2 months afterwards. The clinical parameters included patient age, gender, tumor pathology, number of chemotherapy treatments before RT, concurrent chemotherapy, radiation dose, tumor response to RT, tumor localization, interruption of RT, weight loss, tumor and nodal stage and tumor volume. The following dosimetric parameters were analyzed for correlation of AE: The maximum (Dmax), mean (Dmean) doses delivered to the esophagus, the percentage of esophagus volume receiving ≥10 Gy (V10), ≥20 Gy (V20), ≥30 Gy (V30), ≥35 Gy (V35), ≥40 Gy (V40), ≥45 Gy (V45), ≥50 Gy (V50) and ≥60 Gy (V60). Results: Fifty-five patients (52.9%) developed AE. Maximum grades of AE were recorded: Grade 1 in 30 patients (28.8%), Grade 2 in 20 patients (19.2%), Grade 3 in 3 patients (2.8%), and Grade 4 in 2 patients (1.9%). The most significant relationship between RT and esophagitis were in Dmax (>5117 cGy), Dmean (>1487 cGy) and V10-60 (percentage of volume receiving >10 to 60 Gy). Conclusions: The maximum dose esophagus greater than 5117 cGy and approximately one third (31%) of the esophageal volume receiving >30 Gy was the most statistically significant predictive factor associated with esophagitis due to RT.

Keywords: Acute esophagitis - lung cancer – radiotherapy - side effect

Introduction

Radiotherapy (RT) is used in the treatment of 64% of cases with lung cancer (with a curative intent in 46%) (Tyldesley et al., 2001). Tumors close to the midline and mediastinal lymphadenopathies increase the dose of exposure of the esophagus. For this reason, acute esophagitis (AE) is a frequent adverse effect seen in patients receiving RT for lung cancer. Grade 3-4 AE has been reported in 20-30% in simultaneous chemoradiotherapy (CRT) administrations (De Ruyscher et al., 2012). Parameters predicting the AE in advance would prevent interruptions of treatment and would increase the success of treatment (local control and overall survival). Administration of CRT, hyperfractioned RT, esophageal volume receiving a dose (%) more than 35 Gy (V35), V10, V20, V60, and mean esophageal dose (Dmean), and environmental and volumetric esophageal doses have been faulted for AE development in the literature (Maguire et al., 1999; Werner Wasik et al., 2000; Bradley et al., 2004; Patel et al., 2004; Rose et al., 2009). However, there is no generally accepted predictive factor for AE development. The aim of this study is to evaluate the association between the dose distribution, clinical factors, and AE development in the esophagus during the treatment of lung cancer.

Materials and Methods

Patient characteristics

One hundred and four patients who were planned to receive three-dimensional conformal RT in the Clinic of Radiation Oncology at Osmangazi University School of Medicine between July 2010 and January 2012 were evaluated. Cases with the histopathological diagnosis of non-small-cell lung carcinoma (NSCLC) or small-cell lung carcinoma (SCLC), with T3 or T4 tumors and/or mediastinal lymph node involvement, not operated on for medical reasons or according to the choice of the patient, and with a Karnofsky Performance Scale of 70 and above were included in the study. Cases with multiple primary diagnoses and/or distant metastasis were not included in the study. Cases that developed metastasis during the treatment were excluded from the study. Ninety-seven...
Three-dimensional conformal radiotherapy was planned for all patients. Tomographic planning sections were obtained in 5 mm intervals in the supine position with arms immobilized over the head with a T-bar. Gross tumor volume (primary tumor and lymph nodes with short diameter greater than 1 cm) was contoured according to ICRU-62 using CT and PET-CT (ICRU Report 62, 1999). Clinical target volume (CTV) was calculated by adding 6 mm in squamous cell carcinoma, 8 mm in adenocarcinoma, 3 mm in the presence of pathological lymph nodes, and 8 mm in SCLC. Elective mediastinal nodal irradiation was only used in SCLC. PTV was obtained by adding 1-1.5 cm to the CTV. PTV received a minimum of 93% and a maximum of 107% of the planned dose. Heterogeneity correction was performed. The esophagus was contoured from cricoid cartilage to the gastroesophageal intersection in order to include its external wall. Dose volume histograms were evaluated in all patients. Critical organ dose tolerances were identified as $V_{30}$<50% (lung volume receiving more than 5 Gy was less than 50%), $V_{50}$<30% (lung volume receiving more than 20 Gy was less than 30%), mean lung dose <15 Gy, and maximum spinal cord dose <50 Gy and cardiac $V_{50}$<50% (cardiac volume receiving 30 Gy was less than 50%). Irradiation was performed with linear accelerator equipment (Precise-ELEKTA™) with 6 MV X-rays. Oblique fields following the anterior-posterior fields excluding the spinal cord outside the field were used in all patients. Fields were controlled by electronic portal imaging in the first treatment and followed at weekly intervals. The median dose of RT was 60 Gy (45-62 Gy). Fractions were applied as 1.8-2 Gy/day, total RT 60-70 Gy (over 30 days), in 7-9 treatments per week. Overlapping fields were divided into 2-3 groups in order to reduce the total dose for each field to less than 30 Gy.

Radiotherapy

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### Table 1. Patient Characteristics

| Patient Characteristics | No. of Cases | % |
|-------------------------|--------------|---|
| Median Age (year)       | 61.5 (39-79) | 67.9 |
| Sex (F/M)               | 7-97         | 6.7/93.3 |
| Pathology (NSCLC/SCLC)  | 93/11        | 89.4/10.6 |
| Treatment (CRT/RT)      | 49/55        | 47.1/52.9 |
| Stage                   |              |   |
| IB                      | 2            | 1.9 |
| IIA                     | 3            | 2.9 |
| IIB                     | 11           | 10.6 |
| IIIA                    | 27           | 26  |
| IIIIB                   | 50           | 48  |
| Limited SCLC            | 11           | 10.6 |
| NSCLC                   |              |   |
| N0                      | 18           | 17.3 |
| N1                      | 9            | 8.7 |
| N2                      | 57           | 54.7 |
| N3                      | 9            | 8.7 |
| RT dose                 |              |   |
| ≤60 Gy                  | 36           | 34.6 |
| >60 Gy                  | 68           | 65.4 |
| Tumor localization      |              |   |
| Upper right             | 44           | 42.3 |
| Middle right            | 6            | 5.8 |
| Lower right             | 15           | 14.4 |
| Upper left              | 25           | 24  |
| Lower left              | 14           | 13.5 |

*NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer; CRT: Concurrent chemoradiotherapy; RT: Radiotherapy only

### Toxicity scoring and follow-up

Age and gender of the patients, tumor pathology, type of treatment (only RT/concurrent CRT), number of chemotherapy cycles before RT, localization of the tumor, T and N stage, severity of AE according to RTOG criteria. RTOG scoring system is presented in Table 2. (At the beginning, and the first, second, third, fourth, fifth, and sixth week, and following the first week, and first and second month). Days of interruption of RT, total RT dose, and tumor response results in the second month were recorded in the “RT reporting and oncological follow-up”

### Table 2. Radiation Therapy Oncology Group (RTOG) Criteria for Acute Esophagitis

| 0 | No change compared to beginning |
| 1 | Mild dysphagia or odynophagia necessitating topical anesthetics, nonnarcotic drugs or soft diet |
| 2 | Moderate dysphagia or odynophagia necessitating narcotic drugs or mashed/liquid diet |
| 3 | Severe dysphagia or odynophagia necessitating nasogastric feeding, IV fluids or hyperalimentation (Accompanying dehydration or >15% weight loss) |
| 4 | Complete obstruction, ulceration, perforation or fistula |
| 5 | Death |
system" (IMPAC Medical Systems™, Inc. 100 West Evelyn Avenue Mountain View, CA 94041).

All patients received sucralphate and nystatin suspension (4x5 ml/day) starting with the RT. Follow-up oncology visits were planned for every three months in the first two years, every six months between two and five years, and annually after five years.

**Statistical analysis**

Parameters that may be associated with AE development, such as age (Spearman correlation coefficient) and gender (Fisher’s exact test) of the patients, simultaneous chemotherapy administration (Fisher’s exact test), number of chemotherapy cycles before RT (Fisher’s exact test), total RT dose (Fisher’s exact test), tumor response to RT (Spearman correlation coefficient), pathological type of the tumor (Fisher’s exact test), tumor localization (Fisher’s exact test), T stage (Spearman correlation coefficient), N stage (Spearman correlation coefficient), tumor volume and esophageal volume (Spearman correlation coefficient), interruption of RT (Fisher’s exact test), weight loss during RT (Spearman correlation coefficient) and administered doses and volumes (Spearman correlation coefficient, logistic regression analysis) were evaluated.

Statistical analysis was performed using the SPSS (Statistical Package for Social Science – Version 20.0- for Windows) program. A value of p<0.05 was accepted as statistically significant.

**Results**

Patients’ visits accounted for total of 1040 for 104 patients. The mean number of days of interruption was two days (range 0-10 days), and a median weight of

### Table 3. Frequency of Acute Esophagitis According to Week

| Grade 0 | Grade 1 | Grade 2 | Grade 3-5 |
|---------|---------|---------|-----------|
| Beginning of RT* | 103 | 1 | - | - |
| 1st week | 98 | 6 | - | - |
| 2nd week | 86 | 18 | - | - |
| 3rd week | 66 | 36 | 2 | - |
| 4th week | 49 | 51 | 4 | - |
| 5th week | 50 | 24 | 1 | - |
| 6th week | 80 | 4 | - | - |
| 1 week after RT | 94 | 10 | - | - |
| 1 month after RT | 104 | - | - | - |
| 2 months after RT | 104 | - | - | - |

*RT: Radiotherapy

### Table 4. Associations between Clinical Factors and Acute Esophagitis

| Variable | Correlation Coefficient | p value |
|----------|-------------------------|---------|
| Age | -0.36 | 0.311 |
| Sex (M/F) | - | 0.933 |
| Tumor pathology (NSCLC/SCLC) | - | 0.582 |
| Number of chemotherapy cycles before RT | - | 0.615 |
| (3 chemotherapy cycles/4 or more chemotherapy cycles) | - | 0.536 |
| Concurrent CRT (present/none) | - | 0.711 |
| Tumor localization (upper/middle/lower) | - | 0.911 |
| Tumor volume | - | 0.911 |
| Esophageal volume | - | 0.953 |
| T stage | -0.21 | 0.842 |
| N stage | -0.03 | 0.732 |
| RT dose (>60 Gy) | - | 0.536 |
| Response to RT (regression/stable/progression) | -0.05 | 0.610 |
| Days of interruption of RT (3 days or more days) | - | 0.516 |
| Weight Loss | 0.1 | 0.295 |

*Correlation coefficient; RT: Radiotherapy, NSCLC: Non-small-cell lung cancer; SCLC: Small-cell lung cancer

### Table 5. Association ofDosimetric Parameters with Acute Esophagitis

| Variable | RT Start (r-p value) | 1st wk*** (r-p value) | 2nd wk (r-p value) | 3rd wk (r-p value) | 4th wk (r-p value) | 5th wk (r-p value) | 6th wk (r-p value) | 1 wk after RT (r-p value) |
|----------|---------------------|-----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|--------------------------|
| D<sub>max</sub> (5117cGy) | 0.14-0.14 | 0.04-0.63 | 0.16-0.106 | 0.33-0.00 | 0.32-0.00 | 0.38-0.00 | 0.32-0.00 | 0.23-0.01 |
| D<sub>mean</sub> (13cGy) | 0.14-0.13 | 0.19-0.04 | 0.15-0.11 | 0.17-0.07 | 0.14-0.15 | 0.13-0.18 | 0.22-0.02 | 0.13-0.18 |
| D<sub>mean</sub> (1487cGy) | 0.14-0.14 | 0.12-0.22 | 0.22-0.02 | 0.4-0.00 | 0.47-0.00 | 0.49-0.00 | 0.44-0.00 | 0.21-0.03 |
| V<sub>0</sub> (%) | 0.14-0.15 | 0.10-0.31 | 0.19-0.04 | 0.34-0.00 | 0.45-0.00 | 0.47-0.00 | 0.38-0.00 | 0.13-0.18 |
| V<sub>5</sub> (%) | 0.13-0.18 | 0.11-0.24 | 0.17-0.07 | 0.34-0.00 | 0.44-0.00 | 0.45-0.00 | 0.37-0.00 | 0.14-0.15 |
| V<sub>10</sub> (%) | 0.13-0.17 | 0.13-0.18 | 0.18-0.06 | 0.38-0.00 | 0.48-0.00 | 0.48-0.00 | 0.39-0.00 | 0.18-0.05 |
| V<sub>20</sub> (%) | 0.12-0.21 | 0.13-0.18 | 0.20-0.03 | 0.37-0.00 | 0.43-0.00 | 0.44-0.00 | 0.40-0.00 | 0.21-0.02 |
| V<sub>30</sub> (%) | 0.12-0.19 | 0.04-0.63 | 0.20-0.04 | 0.40-0.00 | 0.45-0.00 | 0.44-0.00 | 0.41-0.00 | 0.28-0.00 |
| V<sub>40</sub> (%) | 0.13-0.19 | -0.02-0.8 | 0.13-0.17 | 0.34-0.00 | 0.37-0.00 | 0.44-0.00 | 0.44-0.00 | 0.31-0.00 |
| V<sub>50</sub> (%) | 0.13-0.17 | 0.008-0.9 | 0.13-0.17 | 0.24-0.01 | 0.25-0.00 | 0.33-0.00 | 0.41-0.00 | 0.23-0.01 |
| V<sub>60</sub> (%) | -0.02-0.7 | 0.11-0.24 | 0.08-0.41 | 0.20-0.04 | 0.17-0.07 | 0.26-0.00 | 0.39-0.00 | 0.30-0.00 |
| V<sub>70</sub> (%) | -0.02-0.7 | 0.11-0.24 | 0.08-0.41 | 0.20-0.04 | 0.17-0.07 | 0.26-0.00 | 0.39-0.00 | 0.30-0.00 |

*Statistically significant correlation present. **week. r: Spearman Correlation coefficient. V<sub>0</sub>: Esophageal volume higher than 10-60 Gy (%)
AE developed in 55 cases (52.8%). The most severe AE occurred in the fourth week of RT in 51 cases as grade 1 (49%) and in 4 cases as grade 2 (3.8%). Ten cases (9.6%) continued to have grade 1 at the first week after RT, while no signs of AE were identified on the first and second month follow-up visits. Grade 3 and above severe acute toxicity were not seen in any cases as presented in Table 3.

AE was detected in 35 of 52 patients (67.3%) with ages older than 61.5 years (median) and in 20 out of 52 patients (38.5%) with ages less than 61.5 years in the fourth week, which is the most frequent time of occurrence of mucositis (r=0.36, p=0.311). AE was seen in 28 of 55 cases (51%) with only RT administration, while 27 of 49 cases (55%) with CRT had AE (p=0.090).

No associations were found between AE and gender (M/F) (p=0.933), tumor pathology (NSCLC/SCLC) (p=0.582), number of chemotherapy cycles received before RT (1-3 chemotherapy cycles/4 chemotherapy cycles or more) (p=0.615), esophageal volume (r=0.00, p=0.953), tumor volume (r=0.00, p=0.911), T stage (r=0.21, p=0.842), N stage (r=0.03, p=0.732), dose of RT (>60 Gy/≥60 Gy) (p=0.536), tumor localization (p=0.711), response rate to RT (regression/stable/progression) (r=0.05, p=0.610), interruption days for RT (p=0.516), and weight loss (r=0.10, p=0.295) (Table 4).

Table 6. Logistic Regression Analysis for Predictors of Acute Esophagitis

| B     | S.E. | Sig. | Exp(B) | 95% C.I. for Exp(B) | Lower | Upper | Lower | Upper |
|-------|------|------|--------|---------------------|-------|-------|-------|-------|
| Maximal esophageal dose (>5117cGy) | 0.002 | 1.000 |
| Esophageal volume (>31%) higher than 30 Gy | 0.008 | 1.036 | 1.000 |

Table 7. Dosimetric Factors Affecting Acute Esophagitis in the Literature

| Reference                      | RT Dose (Gy) | Dosimetric and Clinical Factor |
|--------------------------------|--------------|--------------------------------|
| Bradley et al. (2002)          | 60-74 Gy (1.8-2Gy/day) | CRT, Amax, V2500 |
| Werner-Wasik et al. (2000)     | 45-69.6 Gy* | CRT, HF                        |
| Singh et al. (2003)            | 60-74Gy (2 Gy/ day) | Dmax (≥258 Gy)                |
| Hirota et al. (2004)           | 50-60 Gy (2 Gy/ day) | LETT, V5000                   |
| Maguire et al. (2005)          | 62-85.6 Gy** | HF, pre RT dysphagia           |
| Ahn et al. (2006)              | 30-86.4 Gy***| HF, pre RT dysphagia, Dmax, age |
| Caglar et al. (2007)           | 46-70 Gy (2 Gy/day) | V5000                         |
| Takeda et al. (2008)           | 50-67 Gy (1.8-2 Gy/day) | Vmax (>30%)                  |
| Present Study                  | 45-62 Gy (1.8-2Gy/day) | Dmax (≥51Gy), V2500 (>31%)   |

*98 cases with conventional RT, 7 cases with hyperfractioned RT, **98 cases with (64%) hyperfractioned RT, ***98 cases with (39%) hyperfractioned RT. CRT: Concurrent chemoradiotherapy. HF: Hyperfractionation. LETT, V tumors. Takeda, confirmed the fact that CRT administration alone is not associated with the development of AE in his series of 35 cases (Takeda et al., 2005). In the present study, CRT was not a factor increasing the rate of AE, either. All patients receiving CRT were hospitalized and followed-up by daily patient visits, preventive drugs (sucralphate and nystatin) were administered under the control of the nurses, IV hydration was performed before chemotherapy, and enteral nutritional support was applied when necessary. These factors together may have prevented the progression of the symptoms of AE in this group. In addition, total RT dose (median 64 Gy) is higher than the present study (median 60 Gy) in the studies reporting an enhancing
role of CRT on the rate of development of AE (Table 7) (Werner Wasik et al., 2000; Bradley et al., 2004; Caglar et al., 2010).

The clinical symptoms of AE in the present study were followed-up on. The answer to whether it is clear that there is no organ injury when the individual has no complaint of AE is found in a study of 82 lung cancer patients from Japan. Fields of grade 3 ulcers were seen in the endoscopic evaluation of cases with no AE symptoms or with mild symptoms (RTOG grade 0-1) who received CRT. On the contrary, grade 3 AE symptoms were reported in only 8.5% of the cases who had endoscopic grade 3 ulcers and thus, it was stressed that the esophagus, contradictory to the previous knowledge, was a “quiet” organ in terms of symptoms (Hirota et al., 2001). In our study, the presence of clinical grade 1-2 symptoms do not imply that the real damage is limited to this level. In addition, not only severe AE, but also intermediate and mild AE could be the reason of the late adverse effects according to Dorr et al. this feature (superficial barrier function against mechanical and/or chemical stresses) also is valid for the intestines, oral mucosa, and urinary bladder (Dorr et al., 2001).

Treatment of mild mucositis would prevent possible late adverse effects (Rodriguez et al., 2009). For this reason, such cases should be followed-up on for late adverse effects even if they are asymptomatic in terms of AE.

A comparison of the parameters predicting the development of AE reported in the literature is difficult in many aspects. Variables such as different scoring systems for esophagitis (RTOG and Common Terminology Criteria for Adverse Events CTCAE), different techniques of RT (three-dimensional RT, intensity modulated RT, X-ray, proton treatment), different dose and fraction schemes (conventional and hyperfractionation), different dose-volume histogram parameters (esophageal volume or esophageal surface area), different esophageal contouring protocols (whole organ or external esophageal contour only), differences in the numbers of schemes and cycles of chemotherapy applied simultaneously or before the RT, radioprotector use (amifostine) and different ethnic origins of the patients [Western society (America and Europe) and Far Eastern society (China and Japan)] effect the results.

Another reason for different results originates from the anatomical location of the esophagus. A conversion to the oblique fields of the spinal cord prevention after the first field of lung RT is completed occurs around the fourth week in which AE is maximal. Due to the inclusion of a part of the esophagus immediately in front of the spinal cord in the field, and the exclusion of part of it results in dose-volume histograms with different dosimetric features in this period. In addition, the fractioned dose of the esophagus changes in the oblique boost period since it remains in the partial field, while it receives a 1.8-2 Gy daily dose during the first part of RT. This makes the unit of mean (Dmean) esophageal dose meaningless since it has the same continued fraction and weekly same dose accumulation (Huang et al., 2012). No association was identified in the present study between the Dmean esophageal dose and AE in the regression analysis.

Some other factors that trigger AE are present, apart from RT and chemotherapy. These are esophageal infections (candida and herpes simplex esophagitis), the presence of gastroesophageal reflux disease (reflux complaints are confused with AE and are reported as a complaint of higher grade) and exposure of the stomach to RT (accompanying gastritis symptoms due to the inclusion of the stomach in the field in lower lobe tumors) (Werner Wasik et al., 2010). These additional factors render the identification of the association between RT and AE more difficult. Considering the serial structure of the spinal cord, and esophagus, it is expected to demonstrate findings of toxicity in exceeding doses of the maximal target value, such as the spinal cord.

In the present study, a maximal esophageal dose of greater than 51 Gy is found to increase the frequency of AE. This value is reported as 55 Gy by Singh et al. (2003) in their series of 207 cases from a Western society and 60 Gy by Qiao et al. (2005) in their series of 208 cases comprising a Far Eastern society.

In conclusions, maximal esophageal doses higher than 51 Gy and/or esophageal volumes approximately more than 1/3 receiving a 30 Gy dose are found to be risk factors for AE development in a series of 104 cases with lung cancer receiving RT administration.

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