Mean Regional Dose to the Esophagus Predicts Acute Toxicity Rate for Lung Cancer Patients

Introduction: A number of previous studies have assessed dose volume outcomes for acute radiation esophagitis (AE) in patients treated for NSCLC with mixed results. The absolute and percent of esophageal volume and/or area receiving a given dose were identified as significant correlates of esophageal toxicity over a wide range of doses. As a result, a recent QUANTEC review indicated that there is no consensus dose-volume threshold recommendation for AE [1].

The limitation of using dose-volume metrics extracted from DVHs or DSHs is the lack of spatial information as it relates to the incidence of toxicity. To account for this, the use of circumferential and length metrics have been proposed as additional correlates of esophagitis [2]; however, these metrics are not better than previously identified DVH/DSH metrics. While these techniques introduce some spatial information into the AE models, they are not sensitive to the distribution of dose along the SI axis of the organ. As presented in the current study, dose in subvolumes of the esophagus serve as a surrogate of the differences in the spatial location of dose in the superior/inferior direction of the organ. Dose to the defined regions are incorporated into the LKB NTCP model to investigate the impact on the incidence of AE.

Patient Database and Toxicity Scoring: A total of 541 patients treated for NSCLC between 1999 and 2005 with definitive radiotherapy at the University of Texas M.D. Anderson Cancer Center were included in the current study. Acute radiation esophagitis was assessed by the treating physician and scored according to the Common Toxicity Criteria for Adverse Events version 3.0. For this study, AE grade ≥ 2 (medical intervention) was considered.

Treatment Plan and Dose Distribution Recovery: Patient treatment plans were previously dearchived into the Pinnacle (Phillips Medical Systems, Milpitas, CA) treatment planning database. All of the dearchived plans were later imported into an open source treatment plan analysis system (CERR), which provided means to extract the requisite data for analysis. The 3D dose distribution for the contoured esophagus in each patient was mapped to a common coordinate system. The extreme points of each esophagus were used to define the boundaries of the coordinate system in the anterior-posterior, medial-lateral, and superior-inferior direction. The dose distribution was appropriately masked to the contoured esophagus such that the dose in each voxel outside the structure was 0.

Formulation of the Lyman-Kutcher-Burman Model: The normal tissue complication probability (NTCP) was modeled using the LKB formulation. The volume parameter, n, was set to 1 for the current analysis allowing the model to be written as:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{u^2}{2}} du$$

where MED is the mean esophageal dose, $TD_{50}$ is the dose resulting in 50% complication probability and $m$ is an indicator of the slope of the sigmoid curve.

Esophagus Division Analysis: The esophagus was divided into equal halves, thirds, and fourths along the SI direction of the structure. The mean regional dose (MRD) was calculated in each of these subvolumes and univariate logistic regression analysis was performed to determine the correlation between MRD and the chosen toxicity endpoint. The MRD was also incorporated into the LKB model as a separate additive factor to model NTCP:

$$t = \frac{(MED + C \cdot MRD) - TD_{50}}{mTD_{50}}$$

where MRD is the mean dose in a given region of the geometrically divided esophagus and C is an additional model fit parameter. The sign and magnitude of the fit parameter indicates the relative importance of the regional MED.
Results: Results of the univariate logistic regression analysis are shown in Table I. Significant correlation was determined to exist between AE grade ≥ 2 and MRD in all of the defined esophageal subvolumes except for the inferior third and inferior-most quarter.

Model fit parameters and likelihood ratio test p values for the esophagus region of interest are shown in Table II. There was a statistically significant improvement (p < 0.05) when including the additive MRD for the superior/inferior halves, superior/inferior thirds, and superior-most/inferior-most quarters when the considered endpoint was AE grade ≥ 2.

Discussion: Univariate logistic regression indicates that dose to the superior regions of the esophagus is correlated well with the observed outcome. When the data is modeled using the LKB formulation, inspection of the sign and magnitude of the additional model fit parameter, C, support this trend. The NTCP model fit suggests that a patient with greater dose in the superior portion of the esophagus is at increased risk of experiencing AE. A patient with the same MED but with dose distributed towards the inferior portion of the esophagus would be at lower risk of developing AE.

Inclusion of the MRD in this manner presents a general trend, but is only a significant improvement over the MED model in cases where AE grade ≥ 2 is considered. Further investigation is being considered with AE grade ≥ 3 for an expanded set of 3DCRT, IMRT, and proton patients. Additional methods to incorporate dose in individual esophagus voxels (along the SI axis) into the LKB model are also being explored.

Conclusions and Clinical Significance: This study investigates previously unexplored spatial/regional differences in delivered dose to the esophagus of patients treated for NSCLC. There is evidence to support the notion that dose to the superior portions of the esophagus is more important as it relates to the potential for acute toxicity. The 541 patient cohort is the largest collection used to investigate AE in patients treated for NSCLC, which strengthens the power of the statistical results. As illustrated by this study and planned future work, there is expectation that additional factors affecting incidence of AE can be elucidated, which will ultimately translate to improved patient care.

References