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RADIATION DOSE-VOLUME EFFECTS IN THE ESOPHAGUS

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Publications relating esophageal radiation toxicity to clinical variables and to quantitative dose and dose–volume measures derived from three-dimensional conformal radiotherapy for non–small-cell lung cancer are reviewed. A variety of clinical and dosimetric parameters have been associated with acute and late toxicity. Suggestions for future studies are presented. © 2010 Elsevier Inc.

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1. CLINICAL SIGNIFICANCE

Acute esophagitis (occurring ≤90 days after treatment initiation) is a common side effect of patients undergoing radiotherapy (RT) for thoracic tumors. Concurrent chemoradiotherapy (CCT) or hyperfractionation results in a 15–25% rate of severe (Radiation Therapy Oncology Group [RTOG] Grade 3 or greater) acute esophagitis (1–3) that can require hospitalization, invasive diagnostic tests (*e.g.,* endoscopy), surgical intervention (*e.g.,* percutaneous endoscopic gastrostomy tube) or RT breaks that could lower local tumor control.

Late injury is less commonly reported, perhaps because the patients might not live long enough to manifest toxicity (e.g., the disease-specific survival is relatively short for many thoracic cancers). Dose escalation of standard fractionated RT and hypofractionated RT regimens (4, 5) can increase the risk of late esophageal toxicity, especially if the survival rates improve. Esophageal stricture often requires periodic dilation, usually with good results (6). Death related to late esophageal injury (*e.g.,* tracheoesophageal fistula or esophageal perforation) has been reported in only 0.4–1% of patients (7, 8).

2. ENDPOINTS

The assigned toxicity grade varies with the scoring system used, making interstudy comparisons challenging. In general, Grade 1 toxicities cause minor changes in a patient's lifestyle, and Grade 2 or greater toxicities might require medical intervention. The currently accepted grading system is the Common Terminology Criteria for Adverse Events, version 3 (9); however, the studies cited in the present report mostly used the RTOG scoring system. In the present review, Grade 2 or greater acute esophagitis (because it constituted the endpoint of many studies) and any late esophagitis (Grade 1 or greater), independent of the duration of the late symptoms, were considered clinically significant.

Acute esophagitis occurs during RT and often persists for several weeks after RT. The symptoms of severe esophagitis (Grade 3 or greater) typically peak 4–8 weeks from the beginning of RT (10). Late esophageal damage, typically stricture and associated dysphagia, develops ~3–8 months (range, 5–40) after RT (11). Abnormal esophageal motility can be noted within 3–4 weeks from RT alone and as early as 1 week after starting concurrent chemoradiotherapy (12).

Some of the pitfalls in assigning the acute esophagitis grade are as follows:

1. Esophageal infection can mimic treatment (RT or concurrent chemoradiotherapy)-related esophagitis. Candidiasis (usually suggested by co-existing oral candidiasis) or, rarely, herpes simplex esophagitis are the main culprits.
2. Pre-existing gastroesophageal reflux can worsen the symptoms of esophagitis and should be treated. Constant burning, unrelated to the act of swallowing, and localized in the lower part of the esophagus is more likely related to the reflux than to the treatment-related esophagitis.

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3. Incidental irradiation of the stomach, and associated gastritis symptoms, can occur when a lower lobe lung mass has been treated.
4. The assignment of Grade 2 (brief intravenous fluid for ≤24 hours) vs. Grade 3 (hospitalization) esophagitis might be physician-dependent.

3. CHALLENGES DEFINING VOLUMES

The adult esophagus length is ≈25 cm and is defined by its external contour on axial computed tomography (CT) images. The esophagus remains closed when not involved in swallowing, and its lumen is often not easily identifiable throughout its entire length, particularly in the middle and caudal levels. Administration of a thick barium paste can help localize the esophagus, but the swallowing times are short (10 seconds), and the barium paste might not fully opacify the entire organ. In addition, high-contrast barium can affect the heterogeneity-corrected dose calculations. It is recommended that the entire length of the esophagus, from the cricoid cartilage to the gastroesophageal junction, be identified, requiring that a portion of the neck and upper abdomen be included in the planning CT scan. In some of the studies (8, 11, 13), the cephalad (''cervical'') esophagus was not included, causing the absolute esophageal volume to be ~20% smaller than if its entirety had been contoured.

The esophagus is slightly mobile. In a study of 29 patients undergoing four-dimensional CT scans three times during RT, the cephalad, middle, and caudal esophagus can move ≤5, 7, and 9 mm in the combined anteroposterior and craniocaudal directions, respectively (14). Thus, dose–volume analyses using the planning CT scan (as was done in the studies we reviewed), could have some inaccuracies, although no specific margin recommendations can be given at this time.

The esophageal circumference varies markedly on sequential axial CT images, a reflection of the swallowing act. This appearance does not reflect the anatomic reality of a relatively uniform circumference (15). Thus, conventional dose–volume histograms (DVHs) might not accurately reflect the partial volume doses. In the single study to consider this issue, the predictive value of metrics that were ''corrected'' for this anatomic reality were slightly better predictors of outcome than were the ''traditional'' DVH-based metrics (15). Nevertheless, the use of alternative three-dimensional dosimetric parameters (*e.g.,* dose–surface-area, dose–circumference histograms, ''anatomically corrected'' DVHs) as improved predictors of outcome is of unclear utility (11, 15, 16).

4. REVIEW OF DOSE–VOLUME PUBLISHED DATA

A total 12 studies published between 1999 and January 2009 that assessed the dose–volume outcome in ≥90 patients treated for non–small cell lung cancer were reviewed (7, 8, 11, 13, 16–19, 20–23) (Table 1). All but one study (17) used three-dimensional planning. The endpoint was usually RTOG Grade 2 or greater or Grade 3 or greater. Two studies (7, 8) combined acute and late toxicities in a single analysis. The others either analyzed only acute (13, 16, 17, 19, 20, 22, 23) or analyzed acute and late toxicity separately (11, 18). The studies found a correlation with these endpoints for a variety of dose–volume factors.

The maximal esophagus dose had significant univariate correlation ($p \leq .05$), with severe esophagitis in all the studies that included it as a variable (7, 8, 11, 13, 20). However, it only remained significant in multivariate analyses in some of them (7, 8, 11).

Ten studies (8, 13, 16, 18, 19–24) searched for correlations between severe acute esophagitis and either the absolute volume (aV_{dose}), absolute area (aA_{dose}), or percentage of a reference volume (V_{dose}), or reference area (A_{dose}) receiving more than a specified dose. Eight of these studies (13, 16, 19–24) found significant univariate correlations with exposure over a wide dose range (10–80 Gy; Table 1 and Fig. 1). Multivariate analysis (16, 19, 20, 22, 24) identified fewer dose–volume combinations. Because of the diverse reporting metrics, we could not find a consensus for the dose–volume thresholds. For example, one study (19) found V_{35} was the only dosimetric predictor of RTOG Grade 2 or greater acute esophagitis on multivariate analysis, both with and without CCT, and another study (22) found V_{20} to be the only multivariate significant factor for 215 patients receiving CCT. However, a third study (16) found a much greater dose region (aA_{55} and aA_{80} or aV_{60} and aV_{80}) to be significant.

Some studies found circumferential metrics (*e.g.,* esophageal length receiving full circumference dose >40–66 Gy [19] or 50–65 Gy [11]) to be significant, although not superior to simpler volume or area metrics.

Four studies (7, 8, 11, 22) found a univariate correlation with the mean dose greater than levels ranging from 34 Gy (7) to 40 Gy (8). A 34-Gy mean dose recommendation was adopted in the RTOG Phase III comparison of 60 Gy vs. 74 Gy with CCT in Grade III non–small-cell lung cancer (RTOG 0617).

Dose–volume histogram parameters describing cumulative dose >50 Gy have been identified as highly statistically significantly correlated with acute esophagitis in several studies. Some studies (Fig. 1), however, have shown the strongest statistically significant correlations with esophagitis at lower doses (as low as V_{30}), perhaps owing to technique differences. V_{30} was also implicated in a multivariate modeling study by El Naqa (21). Overall, the data are consistent with some risk of acute esophagitis at intermediate doses (30–50 Gy) and an increasing effect for greater doses.

A main obstacle to obtaining definitive dosimetric recommendations from the published data is the variety of volumetric metrics—the absolute volume or area, relative volume or area, and circumferential measures—all have been analyzed. Reports describing relative metrics might have used different reference volumes (9, 13). Differences in the way other technical factors were handled have less effect. For example, adjusting DVHs for conventional fraction size and the type of tissue heterogeneity correction used are likely to have only minor effect, the latter because the esophagus is embedded in bulky soft tissue and anteroposterior/posteroanterior