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Esophagitis, Treatment-Related Toxicity in Non-Small Cell Lung Cancer

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Abstract

Objectives—Radiation esophagitis represents a significant complication experienced by non-small cell cancer (NSCLC) patients receiving thoracic irradiation. The objective of the current review was to assess the clinical and dosimetrical parameters that may predict radiation esophagitis.

Methods—Studies were identified by searching PubMed electronic databases. Both prospective and retrospective studies were included. Information regarding clinical and dosimetrical parameters predicting for radiation-induced esophagitis was extracted and analyzed.

Results—The esophageal clinical and dosimetric parameters that best predict acute esophagitis remain unclear. In many reports, V_x (the volume of esophagus receiving x Gy) stands out, with values of x ranging from 20–70 Gy. Other studies conclude that the maximal dose received by any point of the esophagus is the best predictor of esophagitis. Another metric implicated with esophageal toxicity in some reports is the proportion of the esophageal circumference or surface area that receives high doses of radiation.

Conclusions—Technological advancements in patient immobilization, setup verification, and radiotherapy delivery are increasingly being employed to limit the toxicity of thoracic irradiation. Future efforts are required to determine how these complex techniques should best be implemented to minimize the risks of acute and long-term esophageal injury.

Keywords

Esophagitis; Radiotherapy; Non-Small Cell Lung Cancer

INTRODUCTION

The esophagus is a critical organ at risk (OAR) when radiotherapy is delivered to the thorax. Acute esophagitis is a common complication in the treatment of lung cancer [1]. Severe esophagitis can necessitate hospitalization, initiation of parenteral feeding, and treatment interruptions. Late sequelae of esophageal irradiation may include stricture formation or ulceration. These complications significantly affect quality-of-life and can negatively impact long term survival [2]. Expertise in the prevention, diagnosis, and management of radiation esophagitis is therefore essential.

PREDISPOSING FACTORS FOR RADIATION-INDUCED ESOPHAGITIS

Most patients who undergo thoracic radiotherapy for non-small cell lung cancer (NSCLC) develop acute esophagitis [1]. The incidence of severe (grade 3) acute esophageal toxicity, however, is uncommon when radiotherapy is given with standard (daily) fractionation, conventional doses, and without concurrent chemotherapy [1, 3, 4]. Intensification of therapy, typically through a switch to hyperfractionated radiotherapy and/or the addition of concurrent chemotherapy, increases the risk of severe acute esophagitis. The early Radiation Therapy Oncology Group (RTOG) experience demonstrates that the addition of concurrent platinum-based chemotherapy to conventionally-fractionated radiation yields severe acute esophagitis rates of 6% when compared with 1.3% for radiotherapy only [1, 4]. Predictably, the combination of hyperfractionated radiotherapy and concurrent chemotherapy yields even higher rates of severe esophageal toxicity. In RTOG studies, 34% of NSCLC patients treated with platinum-based chemotherapy along with twice-daily thoracic irradiation developed severe acute esophagitis [1, 4]. Under the Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) regimen, patients are treated with 36 fractions of 1.5 Gy over 12 consecutive days. In a randomized trial testing the CHART regimen against conventional radiotherapy (60 Gy in 30 fractions over 6 weeks) for NSCLC, hyperfractionated treatment increased severe dysphagia from 3% to 19% [5].

The current standard of care for locally-advanced NSCLC is daily radiotherapy given with concurrent, frequently platinum-based chemotherapy. The choice of systemic agents can significantly affect esophageal toxicity. In a randomized study comparing three cisplatin doublets, severe esophagitis was seen in 52% of patients treated with cisplatin/gemcitabine, compared to 39% of patients treated with cisplatin/paclitaxel and 25% of patients treated with cisplatin/vinorelbine [6]. However, some of the patients in this study were treated using outdated technology (Cobalt Unit) and the original target volume encompassed the mediastinum, even if the contralateral hilum was not treated. As volumes affect toxicity, this may explain the high rate of grade 3–4 esophagitis reported in this study. Moreover, gemcitabine dosage in the concurrent chemoradiotherapy schedule was 600 mg/m² [6], which was nearly twice the recommended dosage in phase I studies [7]. Furthermore, in more recent reports, the weekly gemcitabine dosage concurrently with involved-field radiotherapy have been shown to be associated with low and acceptable toxicity [8, 9].

While most studies report esophageal toxicity in terms of the highest grade reached, some investigators have examined the effects of various treatment regimens on the duration of esophagitis. Ball *et al.* randomized inoperable NSCLC patients in a 2x2 design to receive 60 Gy of thoracic radiotherapy given with daily or twice-daily fractionation, with or without concurrent carboplatin [10]. Interestingly, the median duration of esophagitis (any grade) was nearly doubled in patients receiving hyperfractionated radiotherapy (3.2 months) compared to patients treated with daily irradiation (1.8 months). Use of chemotherapy did not extend the duration of esophageal symptoms [10].

Radiotherapy fractionation schedule and chemotherapy use have been shown to be the most important determinants of esophageal toxicity. Other factors that have been associated with increased risk of esophagitis include the presence of dysphagia before initiation of radiotherapy, presence of N2 disease (likely a surrogate for the volume of esophagus irradiated), low body mass index, and increased age [11–13].

DOSIMETRIC PARAMETERS ASSOCIATED WITH RADIATION-INDUCED ESOPHAGITIS

Thus far, our discussion of risk factors for radiation esophagitis has largely been based on studies that utilized 2-dimensional radiotherapy. Newer treatment techniques such as 3-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) allow radiation oncologists to limit irradiation of OARs such as the esophagus when treating thoracic tumors. Numerous investigators [12, 14–24] have correlated esophageal toxicity with dose-volumetric data for patients who were treated with 3DCRT or IMRT (Table 1). This can provide some guidance for future treatment planning.

The esophageal dosimetric parameters that best predict acute esophagitis remain unclear. In many reports, V_x (the volume of esophagus receiving x Gy) stands out, with values of x ranging from 20–70 Gy [12, 14, 17–21, 23, 24]. Other studies conclude that the maximal dose received by any point of the esophagus is the best predictor of esophagitis [16, 22]. Another metric implicated with esophageal toxicity in some reports is the proportion of the esophageal circumference or surface area that receives high doses of radiation [14, 17].

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) group has recently reviewed the existing literature to identify risk factors for esophageal toxicity [25]. They concluded that some risk of acute esophagitis is present at intermediate doses of 30–50 Gy of thoracic radiotherapy and that the incidence of esophagitis increases with greater radiotherapy doses. Rates of acute grade 2 esophagitis are expected to surpass 30% as V₇₀ exceeds 20%, V₅₀ exceeds 40%, and V₃₅ exceeds 50%, respectively. However, several difficulties in dose-volume analysis were identified. Esophageal circumference has been found to vary on sequential axial CT slices as a reflection of the swallowing act [26]. This does not reflect the anatomic reality of a relatively uniform circumference and raises uncertainty regarding the utility of conventional dose-volume histogram analysis. Another potential source of error is esophageal mobility; during RT the upper, middle and lower portions of the esophagus frequently move up to 5 mm, 7 mm, and 9 mm, respectively [27]. QUANTEC investigators could not identify a single consensus dosimetric constraint to limit the risk of esophagitis.

Current trends in radiotherapy for NSCLC include dose escalation (with standard fraction sizes, with or without concurrent chemotherapy) and hypofractionation (use of large fraction sizes, typically without concurrent chemotherapy). While these measures are expected to improve tumor control [28], they may result in increased toxicity. Early experiences with these strategies provide additional opportunities to evaluate dosimetric predictors of esophageal toxicity.

RTOG 93-11 tested the feasibility of radiotherapy dose escalation for patients with locally-advanced NSCLC [29]. This phase I/II study employed 3DCRT, omitted elective nodal irradiation, and did not allow concurrent chemotherapy. Tested doses ranged from 70.9 to 90.3 Gy. The clinical endpoint of the study was esophageal stricture or perforation. One third of the esophageal volume was allowed to receive 65 Gy, 2/3 was allowed to receive 58 Gy, and the whole esophagus was allowed to receive 55 Gy. One hundred seventy seven patients were evaluated, and there were no reported cases of severe (grade 3) acute esophagitis. Of note, 6 cases of late grade 3 esophageal toxicity occurred. Advanced planning techniques are critical to limit morbidity rates as therapy is intensified.

For early-stage (node-negative) NSCLC patients who are medically inoperable or refuse surgical resection, hypofractionated stereotactic body radiotherapy (SBRT) has emerged as an effective treatment option. For peripheral tumors, the RTOG has adopted a schedule of

54–60 Gy delivered using 3 fractions of 18–20 Gy over 1.5 to 2 weeks period of time [30]. However, high rates of severe (grade 3–5) pulmonary toxicity were reported by using SBRT for centrally located tumors, when doses of 10–20 Gy per fraction were delivered to a total dose of 40–60 Gy using 3 to 4 fractions on consecutive days [31]. Moderately hypofractionated SBRT has been used for centrally located thoracic lesions, delivering 30–63 Gy in 2.5–5.0 Gy fractions; patient deaths from pulmonary causes, potentially grade 5 toxicities occurred in 7.5% of the cases, although the majority of these patients had pulmonary conditions, which may have contributed to the cause of death [32]. Chang *et al.* reported an excellent local control using daily computed tomography-on rail guided SBRT for centrally and superiorly located stage I and isolated recurrent non-small cell lung cancer. The prescribed dose of 40 Gy was escalated to 50 Gy delivered in 4 consecutive days. None of the patients with Stage I disease developed grade 2 radiation pneumonitis, and no esophagitis was reported in any patient [33]. Therefore, for central lesions, phase I studies to determine the maximum tolerated dose in a five fraction regimen are underway. This will help characterize the dose-response relationship for esophageal toxicity following hypofractionated SBRT.

LATE ESOPHAGEAL TOXICITY

In patients who develop acute radiation esophagitis, symptoms commonly persist for 1–3 weeks after the completion of therapy. If it is to occur, late esophageal damage typically develops 3–8 months after completion of radiotherapy and manifests as dysphagia to solids due to narrowing of the esophagus. Esophageal stricture may require periodic surgical dilation of the esophagus, usually with excellent results [34]. Compared to acute esophagitis, late esophageal toxicity is relative rare. In the early RTOG experience of NSCLC patients treated with radiotherapy (standard or hyperfractionated) along with chemotherapy (induction and/or concurrent), severe late esophageal toxicity was seen in only 2% of patients [1]. The reported risk of death due to late esophageal toxicity (usually perforation or tracheo-esophageal fistula formation) is only 0.4–1% [25]. It should be noted that patients with NSCLC have a poor prognosis, and crude late toxicity rates may be slightly misleading.

Ahn *et al.* have shown that the severity of acute esophagitis is a powerful predictor of late esophageal toxicity [11]. Estimated radiotherapy doses that would cause esophageal stricture or perforation in 5% of patients at 5 years ($TD_{5/5}$) are 60 Gy for the entire esophagus, 58 for two thirds of the esophagus, and 55 Gy for one third of the esophagus [35]. Those estimates, however, may have to be revised for the settings of concurrent chemoradiation and/or hypofractionated SBRT, especially as overall survival rates improve [25].

STRATEGIES USED TO PREVENT OR TREAT ESOPHAGITIS

Newer radiotherapy delivery techniques (IMRT, proton beam radiotherapy) typically allow more uniform target volume coverage with improved avoidance of critical normal structures. The dose-response relationship for esophageal toxicity has largely been defined based on experiences with 3DCRT. As IMRT allows radiotherapy dose distributions to be shaped around OARs such as the esophagus, it has the potential to improve toxicity profiles and/or allow safe escalation of target doses.

Grills *et al.* performed a radiotherapy planning study using imaging from 18 NSCLC (stage I–III) patients [36]. As part of their study, they generated optimized 3DCRT and IMRT plans for each patient such that the planning target volume received approximately 70 Gy. They then used normal tissue complication probability (NTCP) modeling to determine the likelihood of toxicities such as radiation pneumonitis, esophagitis, and cardiotoxicity. Among the nine node-positive patients, IMRT decreased the predicted esophageal complication rate from 42% to 19%. The authors concluded that IMRT is beneficial in

selected patients, particularly those with positive lymph nodes or those with target volumes in close proximity to the esophagus. Moreover, in lymph node positive patients, IMRT allowed delivery of radiation doses 25%–30% greater than 3DCRT while maintaining an equal probability of pulmonary and esophageal toxicity. The possibility of dose escalation was severely limited with elective nodal irradiation and the potential for pulmonary and esophageal toxicity was clearly increased [36]. Nowadays, there is a trend towards treating locally advanced NSCLC with involved-field radiotherapy, omitting elective nodal irradiation. More accurate staging of the regional lymph nodes involvement by using positron emission tomography (PET) allows treating only the involved hilar and mediastinal nodes [37]. The concept of elective nodal irradiation for NSCLC has been challenged with recent data showing very low rates of elective nodal failure using involved-field radiation therapy in the era of 3DCRT [38]. Further studies are needed to address this issue.

Another form of radiotherapy that can provide dosimetric advantage over 3DCRT is proton beam radiotherapy. Proton therapy generates a rapidly increasing dose at the end of the beam range (Bragg peak). Proper distribution of proton energies can therefore create a uniform dose across the target volume with essentially no irradiation of normal tissues beyond the target. This may limit the incidence and severity of treatment-related toxicities such as esophagitis [39]. To date, however, clinical experience with proton radiation therapy for NSCLC has been rather limited. Chang *et al.* reported the initial data on 42 patients diagnosed with stage III non-small cell lung cancer and treated with thoracic radiotherapy using proton beam therapy to a total dose of 74 CGE (Cobalt-Gray Equivalent) with concurrent carboplatin and paclitaxel. Esophagitis was reported in only 6.7% of the cases [40]. While these results are encouraging, the use of proton beam radiotherapy for lung cancer should be validated in prospective studies.

As NSCLC target volumes are often extremely close to portions of the esophagus, technical advancements in radiotherapy planning and delivery are unlikely to allow complete esophageal sparing. An alternative strategy to limit radiation toxicity is the administration of a radioprotective agent. The most widely studied of these is the organic thiophosphate amifostine. After administration, amifostine is dephosphorylated to its active metabolite (WR-1065) by alkaline phosphatase. Once inside the cell, WR-1065 (a free thiol) acts as a potent scavenger of the free oxygen radicals induced by ionizing radiation [41]. Early reports indicated that amifostine was effective in preventing radiation esophagitis without compromising tumor control [41–44]. This prompted a multi-institutional, phase III study of chemoradiation with or without amifostine for locally-advanced NSCLC [45]. In that trial, 242 patients were treated with induction chemotherapy (carboplatin and paclitaxel) followed by hyperfractionated radiotherapy along with the same systemic agents. One hundred twenty of those patients were randomized to receive amifostine four times each week. Amifostine did not significantly reduce the incidence of grade 3 esophagitis (30% vs. 34%), but it did improve swallowing dysfunction and pain, based on patient self-assessments [46]. Of note, this trial was designed to “protect” only 40% of radiotherapy fractions, and only 29% of patients on the experimental arm received amifostine according to protocol. Further investigation of this agent, perhaps using subcutaneous administration to improve scheduling and compliance, may therefore be warranted.

CONCLUSIONS

Radiation esophagitis presents a significant complication experienced by NSCLC patients receiving thoracic irradiation. Technological advancements in patient immobilization, setup verification, and radiotherapy delivery are increasingly being employed to limit the toxicity of thoracic irradiation. Future efforts are required to determine how these complex

techniques should best be implemented to minimize the risks of acute and long-term esophageal injury. At present, radio-protective agents are not commonly used.

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Table 1

Predictive Factors Associated with Radiation-induced Esophagitis (Acute or Late)

Study	Number of Patients (n)	Rate of Acute or Late Esophagitis (RTOG Grading System)	Significant Predictive Factors
Maguire <i>et al.</i> [14]	91	Acute: Grade 3 (11%) Late: Grade 1 (9%), Grade 2 (6%), Grade 3 (3%)	V50, maximum percentage of the circumference > 80.0 Gy
Werner-Wasik <i>et al.</i> [3]	105	Acute: Grade 3 (12%), Grade 4 (1%)	CCRT, twice-daily RT
Rosenman <i>et al.</i> [15]	62	Acute: Grade 3 (8%)	Length of esophagus receiving 40 or 60 Gy
Singh <i>et al.</i> [16]	207	Acute: Grade 3 (4%), Grade 4 (0.5%); Late: Grade 3 (5%), Grade 4 (0.5%), Grade 5 (0.5%)	CCRT, maximal esophageal point dose >58.0 Gy
Bradley <i>et al.</i> [17]	166	Acute: Grade 2 (22%), Grade 3 (4%), Grade 4 (0.6%)	CCRT, esophageal surface area receiving 55 Gy, V60
Patel <i>et al.</i> [12]	36	Acute: Grade 2 (33%), Grade 3 (5.5%)	Pre-treatment BMI, V50
Ahn <i>et al.</i> [11]	254	Acute: Grade 3 (8.7%), Grade 4 (0.4%) Late: Grade 2 (2%), Grade 3 (2%), Grade 4 (1%)	Nodal stage N2 or greater, pretreatment dysphagia, twice-daily RT Severity of acute esophageal toxicity
Kim <i>et al.</i> [18]	124	Acute: Grade 3 (12%), Grade 4 (0.8%)	Concurrent chemotherapy, V60 (in patients receiving concurrent chemotherapy)
Takeda <i>et al.</i> [19]	35	Acute: Grade 2 (14%)	V35
Belderbos <i>et al.</i> [20]	156	Acute: Grade 2 (20%), Grade 3 (6%), Grade 4 (0.6%)	CCRT, V35
Chapet <i>et al.</i> [21]	101	Acute: Grade 2 (13%), Grade 3 (3%)	V40 to V70 (Lyman model NTCP)
Qiao <i>et al.</i> [22]	208	Acute: Grade 3 (5%), Grade 4 (0.5%), Grade 5 (1%); Late: Grade 3 (5%), Grade 4 (0.5%)	CCRT, maximal esophageal point dose 60.0 Gy
Wei <i>et al.</i> [23]	215	Acute: Grade 3 (20.5%)	V20
Rodriguez <i>et al.</i> [24]	100	Acute: Grade 1 (26%), Grade 2 (29%), Grade 3 (4%)	30% of the esophageal volume receiving 50 Gy (Rodriguez <i>et al.</i> esophageal index)

Abbreviations: RTOG, Radiation Therapy Oncology Group; CCRT, Concurrent Chemoradiotherapy; RT, Radiation Therapy; BMI, Body Mass Index; NTCP, Normal Tissue Complication Probability