Review Article

Focus on treatment complications and optimal management: radiation oncology

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Background: Esophagitis and pneumonitis are the most important treatment complications and dose-limiting toxicities in non-small cell lung cancer (NSCLC) patients treated with radiotherapy (RT) alone or combined modality therapy.

Methods: A literature research was performed to identify published articles relating clinical and dosimetric parameters associated with significant radiation pneumonitis (RP) and esophagitis in NSCLC patients treated with three-dimensional conformal RT.

Results: Possible clinical parameters associated with acute and or late esophagitis are concurrent chemoradiation, hyperfractionated and accelerated radiation regimens, dysphagia and neutropenia during treatment. Mean dose <34 Gy is currently used as standard dosimetric recommendation. Addition of chemotherapy and hyperfractionation are also associated with the risk of pneumonitis. Both the V20 and the mean lung dose are used as dosimetric parameter to correlate with the risk of high-grade radiation pneumonitis.

Conclusions: A variety of clinical and dosimetric parameters have been associated with acute and late toxicity. Treatment consist mainly in symptomatic relieve. Further research is necessary, as many studies led to different and sometimes even contradictory results.

Keywords: Pneumonitis; esophagitis; toxicity; radiotherapy (RT)

Submitted Apr 28, 2014. Accepted for publication Jun 19, 2014.
doi: 10.3978/j.issn.2218-6751.2014.06.08
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2014.06.08

Chemoradiotherapy is the standard treatment of locally advanced non-small cell lung cancer (NSCLC), which is associated with significant dose limiting toxicities such as radiation pneumonitis (RP) and esophagitis.

Esophagitis

Acute esophagitis (AE) is one of the major complications of radiotherapy (RT) for NSCLC. It may worsen patients' quality of life and cause interruption in their treatments.

The esophagus is lined by non-keratinized epithelium with a lamina propria and muscularis mucosa. Chemotherapy and RT cause damage to the dividing and differentiating cells and limit the proliferative ability of the epithelium, so that it becomes thin or ulcerated (1). Because the cells in the gastrointestinal tractus are rapidly dividing, the tractus is vulnerable for developing gastrointestinal mucositis caused by cancer therapies.

Acute radiation esophagitis during RT was seen from 7-10 days after a single large fraction in animal models (2) and often persists for several weeks after RT. Phillips and Ross noted epithelial regeneration from 1-2 weeks post-RT (3). Chronic changes, typically stricture and associated dysphagia, are seen from 1-8 months post-RT and are caused by failure of the primary peristaltic wave, decreased relaxation of the lower esophageal sphincter, and focal coagulation necrosis of the mucosa and deep muscle.

In patients treated with high-dose thoracic irradiation for the treatment of localized NSCLC, the majority of patients (75%) experienced some transient acute dysphagia, however

the incidence of grade 3 to 4 AE is low. RTOG grade 3 acute toxicity warranting IV fluids or placement of a feeding tube and often resulting in a break in their course of RT was seen in 5-11% of patients (4). With concurrent chemoradiation the incidence is increased as high as 30% (5). Severe late effects are uncommon, but are the source of considerable morbidity. Of nearly 900 patients randomized on the RTOG 83-11 dose escalation trial, only two patients developed grade 3/4 late toxicity (6).

Predicting AE is essential for clinical treatment planning, especially in patients treated with concomitant chemoradiotherapy or dose escalated radiation regimens. Unfortunately, the clinical and dosimetric predictors that relate to the development of acute and late esophageal toxicities in patients treated with high-dose conformal RT for NSCLC are not well characterized.

Emami *et al*. reported in 1991 on radiation doses that may produce stricture or perforation of the esophagus (7): 55 Gy for the entire organ, 58 Gy for two-thirds, and 60 Gy for one-third of the esophagus irradiated.

Clinical predictors

The use of concurrent chemoradiation increases the risk of both acute and late esophageal toxicities. A Radiation Therapy Oncology Group (RTOG) analysis found that concurrent chemotherapy increases the risk of esophagitis nearly 12-fold (5). A meta-analysis (8) showed that concomitant chemoradiotherapy significantly increased grade 3 to 4 AE as compared with sequential chemoradiotherapy, from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1 to 7.8; P<0.001). Several small series report significant esophageal toxicity in patients treated with RT in combination with doxorubicin (9), meanwhile doxorubicin has largely been abandoned in trials of dose escalation for NSCLC. Most modern series of combined modality therapy for lung cancer utilizing induction platinum-based chemotherapy with moderate doses of thoracic RT reveal a relatively low incidence of esophageal toxicity.

Hyperfractionated and accelerated radiation regimens result in increased acute toxicity in comparison to treatment with standard fractionation for this early-responding organ. A trial with continuous hyperfractionated accelerated radiotherapy (CHART) by Saunders *et al*. reported severe acute dysphagia in 19% *vs*. 3% of patients, treated with the accelerated versus the standard conventional regimen respectively (10). Incidence in late toxicity was not significantly different in both fractionation arms. These findings are as might be expected on radiobiologic principles.

In addition to hyperfractionation and concurrent chemotherapy, another clinical factor that was found to correlate with acute toxicity was dysphagia, present prior to the start of RT, and secondary to gastro-esophageal reflux, esophageal compression of ulcers from chemotherapy (4).

Finally the grade of neutropenia during chemoradiation was a significant parameter for developing dysphagia in a predictive model for AE, with higher grades of maximal neutropenia correlating with higher maximal dysphagia (11).

Dosimetric predictors

The dose volume histogram (DVH) is the most commonly used dosimetric tool to predict radiation-induced toxicity for most organs (12). During the last 18 years, many studies reported associations between dosimetric parameters and normal tissue outcomes. The QUANTEC (quantitative analysis of normal tissue effects in the clinic) articles summarize the available data to update/refine the estimates provided by Emami *et al*. (7). For organs such as the esophagus that are structured in series, the maximum dose delivered to any portion of the organ (easily seen on a cumulative or differential DVH) may be predictive of outcome. However, many DVH parameters have often not been validated in independent, prospective trials.

The percentage of organ volume and surface area treated to more than 50 Gy was a factor significantly associated with late esophagitis on multivariate analysis (4). Another retrospective trial however could not confirm these results (13) and found only the maximal esophageal point dose predict for Grade 3-5 esophageal toxicity, as well as the addition of chemotherapy concurrent. For patients who received concurrent chemotherapy, the threshold maximal esophageal point dose for Grade 3-5-esophageal toxicity was 58 Gy, without chemotherapy the radiation tolerance was increased to 69 Gy. The QUANTEC review summarized 11 studies that used 3D treatment planning (14). A single best parameter was not identified due to the diverse range of dose-volume metrics that correlated with acute esophagitis. There appears to be a trend demonstrating increased rates of AE for volumes receiving >40 to 50 Gy. Currently, the ongoing RTOG 0617 is collecting V60 data on all patients and recommends keeping the mean dose <34 Gy (7).

In general, the coverage of the planning target volume is rarely compromised because of limiting esophageal dose, because severe esophagitis generally heals within 3 to 6 weeks

post-treatment, with late severe sequels occurring in less than 1% of patients. A study investigating time of onset of compensatory proliferation in the oral mucosa of the mouse demonstrated that stimulated proliferation, compensating clinically relevant doses, started within a few days after the start of fractionated irradiations (15).

There is no effective prophylactic measure for radiation esophagitis. Dietary changes, such as restriction of alcohol, coffee and acidic foods, are likely to decrease the incidence and severity of acute radiation esophagitis. Management of AE consists mainly in symptomatic relief of dysphagia, with topic or systemic analgesics. In case of gastro-esophageal reflux proton pump inhibitors should be used. Nutrition must be ensured; a nasogastric tube can help prevent malnutrition and dehydration in fragile patients. Late side effects, chronic ulcera, fistula or stenosis, are rare; endoscopic dilatation shows usually good results to ensure nutrition.

Pneumonitis

Radiation-induced lung injury such as RP and pulmonary fibrosis, is the most common side- effect after RT treatment for lung cancer. It can seriously decrease the quality of life of lung cancer patients and can sometimes even be fatal. RP usually develops in the first few weeks to months after RT is initiated and consists of symptomatic changes such as cough, shortness of breath and fever, with or without changes in pulmonary function tests. Pulmonary fibrosis is the permanent scarring of lung tissue that occurs more gradually over months to years in response to the initial tissue injury and leads to permanent impairment of oxygen transfer. The incidence of moderate to severe RP ranges from roughly 10% to 20% with RT or chemoradiotherapy (16).

Clinical predictors

To predict the occurrence or severity of radiation pneumonitis, several clinical factors were investigated. Unfortunately, these studies led to different and sometimes even contradictory results. For example, age, WHO performance status and tumor location are potential risk factor for which conflicting evidence has been published. In different trials a history of smoking increases the risk of RP as a result of preexisting lung damage, but active smoking somehow seems to protect the lungs from RT- induced damage (17,18).

Pulmonary dysfunction before RT may predispose patients for radiation pneumonitis. In some studies chronic obstructive pulmonary disease (COPD) as well as impaired lung function measurements were associated with radiation-induced lung toxicity (19-21), whereas others reported no statistically significant relationship (22,23). A prospective trial shows that about 20% of the patients with dyspnea before the beginning of RT had less dyspnea more than 6 months post-therapy and approximately 30% had more dyspnea (24). The evolution of dyspnea in time shows that some patients have dyspnea during the first 6 months post-treatment, whereas others only develop dyspnea more than 6 months post-radiation. Dyspnea should therefore not be scored at one time-point, but a whole time-line should be investigated.

As for esophagitis, there seems to be an influence of the fractionation regimen on early and late lung toxicity. The prevalence of pneumonitis requiring treatment at the 6-month follow-up was 11.0% after CHART versus 9.2% after conventional RT. At 2 years 16% of the patients receiving CHART and 4% of those treated conventionally had pulmonary fibrosis requiring outpatient treatment (25).

On the basis of general experience, adding chemotherapy might be expected to increase the risk of RP. Nevertheless, the agents most commonly used with RT for lung cancer, such as cisplatin, carboplatin, paclitaxel, and etoposide, have not been consistently shown to increase the risk of pneumonitis (8,19). Drugs such as gemcitabine are not recommended for routine use with concurrent RT in standard practice (26), and the same applies to targeted agents until more mature data become available.

Dosimetric predictors

The risk of RP often limits the dose delivered for treatment of these malignancies. Extensive research has led to the identification of numerous dosimetric parameters associated with lung toxicity. The Vdose (e.g., V20 or V25) parameter is defined as the percentage of CT-defined total lung volume minus the PTV receiving a higher or equal dose compared to the threshold dose (e.g., 20 or 25 Gy). The mean lung dose (MLD) is defined as the average dose of the CT-defined total lung volume. There is strong evidence that both the V20 and the mean lung dose, correlate with the risk of high-grade radiation pneumonitis. The QUANTEC publication reviewed >70 published articles looking at both MLD and V20 parameters. This comprehensive review demonstrated no clear threshold dose for symptomatic RP. The compiled data showed a mean dose–response curve with a 20% risk of RP for a mean lung dose of 20 Gy (14). According to EORTC recommendations, dose volume

constraints for concurrent chemoradiotherapy in non-small lung cancers should be 35% for V20 and 20 Gy for MLD for whole lung (27,28).

Mild to moderate symptomatic RP may resolve with symptomatic treatment such as inhaled corticosteroid therapy. Severe RP is associated with significantly mortality rates that may approach 50% (29).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Billiet C, Peeters S, De Ruysscher D. Focus on treatment complications and optimal management: radiation oncology. Transl Lung Cancer Res 2014;3(3):187-191. doi: 10.3978/j.issn.2218-6751.2014.06.08

