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Management of Normal Tissue Toxicity Associated With Chemoradiation (Primary Skin, Esophagus, and Lung)

Victor Y. Yazbeck, MD*, Liza Villaruz, MD*, Marsha Haley, MD†, and Mark A. Socinski, MD*

*Division of Hematology/Oncology, Department of Internal Medicine, University of Pittsburgh Cancer Institute, Pittsburgh, PA

†Department of Radiation-Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA

Abstract

Nearly one quarter of patients with lung cancer present with locally advanced disease where concurrent chemoradiotherapy is the current standard of care for patients with good performance status. Cisplatin-based concurrent chemoradiotherapy consistently showed an improvement in survival compared with sequential chemoradiotherapy, at the expense of an increase in the toxicity profile. Over the past decades, several encouraging biomarkers such as transforming growth factor-beta and radioprotective agents such as amifostine were studied but without reaching approval for patient care. We reviewed the prevalence and risk factors for different adverse effects associated with the combined chemoradiotherapy modality, especially dermatitis, mucositis, esophagitis, and pneumonitis. These adverse effects can further be divided into acute, subacute, and chronic. Dermatitis is usually rare and responds well to topical steroids and usual skin care. Acute esophagitis occurs in 30% of patients and is treated with proton pump inhibitors, promotility agents, local anesthetic, and dietary changes. Radiation pneumonitis is a subacute complication seen in 15% of patients and is usually managed with steroids. Chronic adverse effects such as radiation fibrosis and esophageal stricture occur approximately 6 months after completion of radiation therapy and are usually permanent. In this review, complications of chemoradiotherapy for patients with locally advanced lung cancer are delineated, and approaches to their management are described. Given that treatment interruption is associated with a worse outcome, patients are aggressively treated with a curative intent. Therefore, planning for treatment adverse effects improves patient tolerance, compliance, and outcome.

Keywords

Chemoradiotherapy; esophagitis; pneumonitis; dermatitis; lung cancer

Lung cancer remains the leading cause of cancer-related mortality. In 2011, there was an estimated 221,000 new cases of lung cancer in the United States, with approximately 160,000 deaths.¹ Approximately 22% of these patients present with locally advanced disease (stage III), with a median survival of 16 months, whereas the 2- and 5-year survival rates are

Reprints: Victor Y. Yazbeck, MD, UPMC Cancer Pavilion, 5150 Centre Ave, Pittsburgh, PA 15232. yazbeckvy@upmc.edu.

Conflicts of Interest

For the remaining authors, none were declared.

only 39% and 24%, respectively.^{1,2} These patients are treated with a combined modality approach that includes combination of chemotherapy and radiation therapy for patients with stage III disease who are not surgical candidates.³ For those undergoing surgery, routine pre-operative chemoradiotherapy is usually avoided and only indicated in selected cases.⁴ Radiation therapy damages cell's DNA through the generation of free radicals by photons and therefore inhibit its capacity to replicate. Whereas most normal cells recover after radiation therapy, cancerous cells lack the capacity to repair radiation-induced damage. This leads to adverse effects in normal tissues that can be divided into acute, subacute, and late effects. Acute toxicities are common, self-limited, occur during the treatment period, and usually resolve within 1 to 2 weeks after completion of the treatment course. Given that radiation therapy induces death in cells undergoing mitosis, the acute adverse effects tend to occur more frequently in normal cells that divide rapidly such as those of mucosal surfaces (e.g., oral mucosa and esophagus) and skin leading to mucositis, esophagitis, and dermatitis respectively. In addition, radiation therapy can induce subacute toxicities such as pneumonitis that usually occur 4 weeks to 3 months after completion of treatment. Late toxicities such as fibrosis, fistula, and secondary cancers occur 6 months or longer after completion of radiation therapy and are often permanent. The combination of chemotherapy with radiation therapy results in a more severe aspect of the toxicities induced by radiation alone.

The current goals of modern radiation therapy are to maximize tumor control and minimize treatment-related toxicities. The addition of chemotherapy to radiation resulted in an improved locoregional control and increased survival by 5% to 10% in patients with locally advanced non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The benefit from adding chemotherapy to radiation is thought to be due to 2 major reasons: radiosensitization and spatial additivity. The former is due to a synergistic effect seen in preclinical models, whereas the latter is due to the addition of systematic benefit from chemotherapy to the local control from radiation. In locally advanced lung cancer, compared to radiation therapy alone, the addition of cisplatin-based sequential chemotherapy to radiation therapy resulted in modest improvement in survival.^{5,6} However, concurrent cisplatin-based chemoradiotherapy showed consistent improvement in survival compared with sequential chemoradiotherapy, albeit at increase in the toxicity profile.^{2,7-9} In a meta-analysis using individual data from patients with NSCLC, concurrent chemoradiotherapy showed an improvement in overall survival (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.74–0.95; $P = 0.04$) compared with sequential radiochemotherapy, arguing for radiosensitization as the major component in the success of the combined modality approach.¹⁰ Compared with the sequential approach, concurrent chemoradiotherapy decreased locoregional progression (HR, 0.77; 95% CI, 0.62–0.95; $P = 0.01$) but without changing the rate of distant progression (HR, 1.04; 95% CI, 0.86–1.25; $P = 0.69$). However, the addition of chemotherapy to radiation resulted in a significant improvement in distant metastasis rate compared with radiotherapy alone.⁶

In this review, we will be describing the different types of chemotherapy and radiotherapy administered to patients with locally advanced lung cancer and their common toxicities. In addition, we will be examining risk factors, potential predictive biomarkers for toxicity,

radioprotective agents, and the current management of common adverse effects from standard chemoradiotherapy.

Chemotherapy

Several classes of chemotherapy possess radiosensitizing proprieties. The most commonly used compounds in combination with radiation therapy for treatment of lung cancer are the platinum (e.g., carboplatin), taxanes (e.g., paclitaxel), vinca alkaloid (e.g., vinblastine), and the antifolates (e.g., pemetrexed). The concurrent use of chemoradiotherapy increases the risk of toxicities, although the fold increase has been quite variable across studies (Table 1). Paclitaxel-based regimen showed an increase in grade 2 or higher lung toxicity with conventional radiotherapy in a phase 1/2 trial,¹¹ whereas no increase was seen in a retrospective study.¹² Radiosensitizing dose of weekly paclitaxel/carboplatin administered with concurrent radiotherapy followed by 2 cycles of the same combination given at a higher systemic dose showed the best median overall survival at 16.3 months but was associated with a greater toxicity profile mainly hematologic, esophageal, and pulmonary.¹³ The current National Comprehensive Cancer Network guidelines recommend concurrent full-dose cisplatin-based chemoradiotherapy regimens (Table 1).⁹ Weekly docetaxel with conventional radiotherapy resulted in 47% grade 3 or higher-grade pneumonitis, including 19% fatal pulmonary toxicity.¹⁴ Other compounds are currently being studied to improve the current outcome of chemoradiotherapy such as the epidermal growth factor receptor inhibitor cetuximab. However, other targeted agents failed in the clinic either owing to inferior survival when added as maintenance therapy after chemoradiotherapy such as gefitinib in SWOG 0023,¹⁵ or owing to toxicities mainly in the form of trachea-esophageal fistulas for bevacizumab.^{16,17} In 2 separate retrospective studies, irinotecan¹⁸ and mitomycin C¹⁹ increased the risk of lung toxicity when combined with conventional or 3-dimensional conformal radiotherapy (3D-CRT), one of the new techniques in radiation therapy that was developed to improve the therapeutic index and increase the accuracy of modern radiation therapy.

Radiotherapy

In patients with NSCLC, the conventional radiotherapy fractionation schedule includes the delivery of 5 daily fractions per week of 1.8 to 2 Gy, for a total of 60 Gy. The interruption of radiotherapy due to toxicity results in significant reduction in locoregional control, overall survival, and metastasis-free survival.²⁰ Strandqvist's²¹ first isoeffect curves in 1944 showed that fractionation resulted in a greater log cell kill of tumor cells while allowing normal tissue time to repair damage between fractions. Several radiotherapy modalities have been developed to improve the radiation dose delivered to the tumor while sparing normal cells. Modified fractionation schedules such as hyperfractionation or accelerated fractionation showed a small improvement in 5-year survival (10.8% vs 8.3%; HR, 0.88), but more studies are needed to determine the optimal radiation schedule to be used in combination with chemotherapy.²² The 3D-CRT allows the precise calculation of dose-volume histograms that determines the maximum safe treatment to be delivered. However, it remains equivocal whether it lowers the risk of radiation induced lung injury compared with conventional radiotherapy.²³ On the other hand, the intensity-modulated radiotherapy (IMRT) increases

the radiation dose delivered to the tumor while reducing irradiation to normal organs by 10% to 20%.²³ Other modalities such as stereotactic radiotherapy showed better efficacy than conventional radiotherapy, with a lower toxicity to normal tissues.²³ However, one of the most challenging aspects of modern radiation oncology is understanding the interaction between different radiation techniques and the many chemical and biological agents used for cancer therapy.

SKIN TOXICITY

Radiation dermatitis is seen more frequently in breast, prostate, perineal, and oropharyngeal malignancies than in lung cancer. In a retrospective review of patients with inoperable NSCLC treated with IMRT, with or without chemotherapy, the incidence of grade 3 or higher-grade dermatitis was 8%.²⁴ There are few controlled trials regarding prevention and treatment.²⁵ Dermatitis risk factors include high body mass index and concurrent chemotherapy.^{26,27} After a single dose of 4 to 5 Gy, there is a decrease in the proliferation of the germinal layer of the epithelium. Erythema appears within several hours, as the capillaries dilate and become more permeable. As radiation therapy progresses, capillary endothelial cells begin to swell and proliferate, and the tunica of the arterioles are disrupted. Maturing keratinocytes demonstrate swelling, nuclear pyknosis, and cytoplasmic vacuolization. Eventually, vascular dilatation, hyperemia, and extravasation occur. Small superficial blisters form, coalesce, and rupture, resulting in moist desquamation. After completion of radiation therapy, the skin undergoes a number of chronic/permanent changes. The density and amount of fibrous tissue increases, and the number of small blood vessels decreases. The epidermis may remain chronically dry owing to damage to the accessory skin glands. Telangiectasias are commonly seen in irradiated skin and result from the loss of microvascular endothelial cells and damage to the basement membrane, leading to contraction of capillary loops into a distorted sinusoidal channel.²⁸ Therefore, early dermatitis skin changes from radiation include erythema and dry and moist desquamation, whereas late effects include telangiectasias, pigmentation changes, hair loss, atrophy, fibrosis, and ulceration. Acute skin reaction in the treatment of lung cancer was more common with the use of lower-energy beams, such as orthovoltage and cobalt-60. With the modern megavoltage linear accelerator, skin reactions beyond simple erythema in lung cancer treatment are rare.

Radiation recall is the rapid onset of skin irritation in a prior-radiated field that occurs soon after starting chemotherapy, especially with doxorubicin, etoposide, gemcitabine, pemetrexed, and paclitaxel. With insufficient evidence to support the current practice, most dermatitis are being treated with topical steroids and dexpanthenol-containing emollients.²⁹ In a randomized double-blind trial, prophylactic use of topical steroids (0.1% methyl-prednisolone) and 0.5% dexpanthenol showed mild clinical benefit over placebo, with a better benefit from topical steroids.³⁰ Hyperbaric oxygen therapy or traditional wound care are good options for the management of soft tissue radionecrosis and osteonecrosis.³¹ However, topical aloe vera gel did not prove to be protective nor therapeutic for patients with radiation dermatitis.³² In 2 randomized trials in patients with breast cancer, deodorants were not associated with an increased risk of radiation dermatitis,³³ whereas exposure of the skin in the radiation field to water and a mild unscented soap was proven to be safe.²⁶

PULMONARY TOXICITY

Approximately 5% to 15% of patients with lung cancer receiving radiation therapy develop radiation pneumonitis, which is a dose-limiting toxicity.³⁴ The trachea and bronchi are relatively radioresistant. Pathologic changes from radiation include thickening of the epithelium and increasing numbers of goblet cells. Clinically, these changes are accompanied by a decrease in ciliary function and may result in coughing. At therapeutic doses of radiation, bronchoscopy reveals an erythematous, hyperemic mucosa and thick secretions, which accumulate and obstruct the lumen. At high-dose external beam radiotherapy, patients are at increased risk for developing bronchial stenosis.³⁵ In contrast to the trachea and bronchi, the gas exchange portion of the lung is relatively radiosensitive. In response to radiation, there are 3 distinct phases of injury: the latent phase, the exudative phase (more commonly known as radiation pneumonitis), and the fibrotic phase. During the latent phase, which occurs up to 3 months after irradiation, the lung appears histologically normal, although there are believed to be intricate subclinical molecular interactions taking place, which lay the groundwork for later manifestations of injury. The exudative phase is characterized by an inflammatory cell infiltrate of macrophages and lymphocytes. Type I and type II alveolar cells desquamate into the air spaces, causing alterations in surfactant composition and the alveolar wall-air interface. As alveolar macrophages and proteinaceous materials fill the alveolar spaces, the interstitium becomes thickened. Pulmonary perfusion and gas exchange decrease. As the acute process subsides, the alveolar exudate organizes and fibroblasts proliferate. This signals the start of the fibrotic phase. Histologically, this appears as scarring of the alveoli, thickening of the alveolar septae, and thickening of the capillary walls. The pulmonary architecture is essentially altered progressively and permanently, with resulting loss of pulmonary function.³⁶ The average tolerance dose TD 5/5 (5% complication rate at 5 years) for the entire lung is 17.5 Gy, and the lung section receiving a radiation dose greater than 20 Gy is at high risk for suffering function impairment.

Patients with radiation pneumonitis usually develop the following symptoms 1 to 3 months after finishing the radiation course: dry cough, congestion, pleuritic chest pain, and fever. However, the diagnosis can be challenging, given other comorbidities in the lung parenchyma in this usually older patient population and radiation injury to adjacent structures such as esophagus and pericardium. Radiation recall pneumonitis can occur to previously irradiated lung parenchyma that is being exposed to certain chemotherapy agents such as doxorubicin, etoposide, gemcitabine, pemetrexed, and paclitaxel.^{37–39}

Risk Factors

Several risk factors for developing radiation pneumonitis have been studied with mixed results. These risk factors can be divided into factors related to the patient such as age, genetic factors, low Karnofsky score, poor pulmonary functional status, tumor site, other lung comorbidities,⁴⁰ and others related to the treatment such as radiation dose rate, absorbed dose, size of individual doses per fraction, volume of irradiated parenchyma, and the addition of concurrent chemotherapy.³⁴ V20 defined as the volume of normal lung (volume of total lung minus planning target volume for radiotherapy) that received 20 Gy or

more has shown to be the single predictor of grade 2 or higher-grade pneumonitis in a multivariate analysis.⁴¹ A secondary analysis of the Cancer and Leukemia Group B trial 30105, where patients received a high dose (74 Gy) of 3D-CRT with concurrent chemotherapy, showed that elevated V20 and regional lymph node involvement at the N3 level were predictive of pulmonary toxicity.⁴² The role of smoking as a risk factor for radiation pneumonitis is controversial.^{40,43} A recent meta-analysis using individual patient data identified several treatment-related risk factors for symptomatic pneumonitis that include a daily dose greater than 2 Gy, V20, lower-lobe tumor location, and concurrent platinum-based chemotherapy in patients older than 65 years (Table 2).⁴⁴

Biomarkers

Radiation pneumonitis occurs approximately 1 month after exposure to radiation when the damage to normal lung is usually irreversible. Identification of patients at risk of developing radiation-induced lung injury could potentially help design preventive approach or alter treatment for this specific patient cohort. Radiation pneumonitis and pulmonary fibrosis are thought to be secondary to cytokine release from radiation damage. Therefore, several cytokines have been studied as potential biomarkers for radiation-induced lung injury. They can be further divided into profibrotic cytokines such as transforming growth factor- β , or inflammatory cytokines such as interleukin-1 α (IL-1 α) and IL-6. High plasma levels of transforming growth factor- β during the course of treatment with conventional⁴⁵ or 3D-CRT⁴⁶ were found to be associated with a higher risk of radiation pneumonitis.⁴⁷ In addition, a high level of IL-1 α , IL-6,⁴⁸ and pulmonary surfactant protein D⁴⁹ or an increase in the levels of serum mucinlike glycoprotein antigen (KL-6)⁵⁰ and cytokeratin 19 fragment (CYFRA 21-1)⁵¹ have been associated with an increased risk of developing radiation pneumonitis.

Radioprotective Agents

Amifostine (WR-1035, Ethiol) is the most widely studied radioprotective agent used to prevent radiation-induced adverse effects to normal cells. After dephosphorylation by the enzyme alkaline phosphatase that is more abundant in normal tissues, the thiol metabolite of amifostine binds to free radicals induced by cisplatin and radiation and also detoxifies cytotoxic platinum-containing metabolites.⁵² It is currently recommended by the American Society of Clinical Oncology as a preventive option for patients with head and neck cancer receiving radiotherapy, with or without chemotherapy, due to its property to decrease acute and late xerostomia.⁵³ Several studies showed a decrease in the rates of pneumonitis, esophagitis, and mucositis in patients treated with amifostine compared with placebo.^{54–56} However, in the largest phase 3 trial, where patients with locally advanced NSCLC received hyperfractionated radiotherapy and chemotherapy, the addition of 500 mg, intravenous, of amifostine 4 times weekly did not result in a decrease in the incidence of radiation pneumonitis.⁵⁷

In a double-blind placebo-controlled study, pentoxifylline resulted in a lower toxicity and better diffusion capacity for patients with lung and breast cancer receiving radiotherapy.⁵⁸ Several other radioprotective agents such as captopril,⁵⁹ carvedilol,⁶⁰ and melatonin⁶¹ as

well as gene therapy⁶² have shown encouraging preclinical data and some early clinical results but are yet to be studied rigorously in well-designed controlled studies.

Treatment

There are no randomized controlled clinical trials evaluating different treatment options for patients with radiation pneumonitis. Based on preclinical data that showed a protective effect of glucocorticoids in murine models of radiation pneumonitis,⁶³ steroids constitute the principal class of treatment. Prednisone is usually given at 50 to 60 mg per day for 1 week followed by an extended taper over 3 to 12 weeks, as it has shown to decrease symptoms and ameliorate lung function.^{40,64} However, patients with previous radiation-induced fibrosis are less likely to benefit from steroids.⁶⁵ Few case reports described the effectiveness of other immunosuppressants such as azathioprine⁶⁶ and cyclosporine⁶⁷ as therapeutic option for patients who are either refractory or intolerant to steroids. Radiation-induced pulmonary fibrosis and necrosis are late and usually permanent complications of radiation therapy. Their management consists on eliminating local and general aggravating factors and controlling acute and chronic inflammation with steroids. Therefore, the efforts of radiation oncologists have focused on prevention by limiting the volume and dose of radiation delivered to the lung, particularly the lower lobes, where most gas exchange occurs. Interestingly, pentoxifylline and tocopherol showed the possibility of reversing radiation-induced breast fibrosis.⁶⁸

GASTROINTESTINAL TOXICITY

Approximately 20% of patients with lung cancer treated with chemoradiotherapy develops stomatitis that usually begins 2 weeks after completion of treatment.⁷ Until today, there is no approved prophylactic agent, and management is mainly symptomatic. Pain responds usually well to topical anesthetics such as viscous lidocaine (Xylocaine). Patients are encouraged to adopt a bland diet and avoid alcohol, coffee, and any dry, salty, or acidic food. For the minority of patients who develop xerostomia, using pilocarpine along with artificial saliva or petroleum lubricants for the lips can provide some relief in addition to routine mouth washes with 1 quart of water mixed with 1 teaspoon of baking soda and ½ teaspoon of salt. Patients should be reminded to remove their dentures before rinsing. If no relief, then they should try “magic mouthwash” that contains oral coating agents and topical anesthetics. These patients are at higher risk for *Candida* and herpes infection. Those who develop oral candidiasis, systematic antifungal agents (e.g., fluconazole), or local antifungal washes like nystatin powder are adequate treatment options. Patients who develop herpes simplex infection respond well to treatment with acyclovir.

Radiation esophagitis occurs in 30% of patients receiving chemoradiotherapy to the lung and is a dose-limiting acute adverse effect.² Pathologically, the esophagus exhibits pseudomembranous inflammation in response to irradiation. Subjectively, patients present with dysphagia, odynophagia, and substernal discomfort that start 2 to 3 weeks after beginning treatment and may be confused with *Candida* esophagitis. The rate of severe (grade 3) esophagitis varies depending on the radiosensitizing effect of the particular chemotherapy and the dose of radiation delivered to the esophagus. The location of the

tumor is also a factor, as a centrally located tumor will require a higher esophageal dose than a peripherally located one. In addition, accelerated programs of radiation therapy, such as twice-daily treatment, will intensify esophagitis. The dose to the esophagus and the volume irradiated are 2 important factors in the treatment planning. The TD 5/5 for the entire esophagus is 55 Gy and for one third of the esophagus is 60 Gy. Appropriate strategies can be taken in the planning phase to reduce the risk of esophagitis. These involve limiting esophageal dose and volume with techniques such as IMRT.

Several agents are used for symptom control including topical anesthetics such as viscous lidocaine (Xylocaine), promotility agents (e.g., reglan) and proton pump inhibitors (e.g., omeprazole).⁶⁹ In addition, dietary changes help decrease both the incidence and severity and include a bland diet and avoidance of irritative substances to esophagus such as acidic or spicy foods, tobacco, coffee, and alcohol (Table 2).⁷⁰ Esophageal stricture is a late complication and is usually managed by endoscopic dilatation. Patients are advised to continue antacids and prokinetic medications to decrease reflux and prevent restenosis. In a phase 2 trial, amifostine failed to reduce esophageal toxicity in patients with limited SCLC receiving concurrent chemotherapy and twice-daily radiotherapy.⁷¹ Recent research has focused on radiation damage protectors and mitigators for normal tissue protection during fractionated radiotherapy. Several such molecules have been discovered, including nitroxide-linked hybrid molecules, p53/mdm2/mdm4 inhibitors, and kinase inhibitors.⁷² Laboratory and animal studies have shown that using manganese superoxide dismutase-plasmid/liposome gene therapy decreases the severity and incidence of late esophageal stricture.⁷³ Currently, clinical trials are under way to examine the role of these new methods in improving radiation therapeutic ratio.

SUMMARY

The current management of locally advanced lung cancer consists of combined modality treatment with radiation and chemotherapy for local control and chemotherapy for eradication of distant micrometastasis. Concurrent chemoradiation is the current standard for patients with good performance status, however, at the cost of increased toxicities. The addition of chemotherapy accentuates radiation therapy adverse effects mainly dermatitis, mucositis, esophagitis, and pneumonitis. Several clinical and treatment-related risk factors have been studied: the volume of irradiated normal lung and the received dose being the major risk factors. Several novel radiation techniques have been developed to spare normal tissues the radiation effect while delivering a higher dose to the tumor. In addition, many potential predictive biomarkers of toxicity have been identified but with a questionable clinical use, as they have not been studied rigorously in prospective trials. Several radioprotective agents showed encouraging preclinical data and early clinical effect, but more solid clinical studies are needed before they can be formally approved for patient care.

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TABLE 1
Incidence of Adverse Effects From Combined Chemoradiotherapy in Locally Advanced NSCLC

Study	No.	Type of Radiation	Daily Fractions	Total Dose (Gy)	Type of Concurrent Chemotherapy	% Grade >2 (Concurrent vs Sequential)				
						Dermatitis	Pneumonitis	Stomatitis	Esophagitis	
Furuse et al ⁷ (1992–1994)	314	2D-CRT Cobalt-60	2 Gy	56	Cis 80 mg/m ² days 1, 29 Vd 3 mg/m ² days 1, 8, 29, 36 Mit 8 mg/m ² days 1, 29	NR	1.2 vs 1.2	0.6 vs 0	2.5 vs 1.8	
Fournel et al ² (1996–2000)	205	2D-CRT	2 Gy	66	(Cis 20 mg/m ² + Et 50 mg/m ²) days 1–5, 29–33 Consolidation: Cis 80 mg/m ² days 78, 106, Vn 30 mg/m ² weekly days 78–127	NR	5 vs 11	5 vs 3	32 vs 3	
Zatloukal et al ⁸ (1997–2001)	102	Cobalt-60	2 Gy	60	Cis 80 mg/m ² day 1 Vn 12.5 or 25 mg/m ² days 1, 8, 15*	NR	4 vs 2	NR	18 vs 4	
Belderbos et al ^{7,4} (1999–2003)	158	Accelerated, HD-CRT	2.75 Gy	66	Cis 6 mg/m ² daily	NR	18 vs 14	NR	17 vs 5	
Curran et al ⁹ (1994–1998)	204	2D-CRT	1.8 Gy × 252 Gy × 9	63	Cis 100 mg/m ² days 1, 29 Vb 5 mg/m ² weekly ×5	NR	4 vs 9	11 vs 1	23 vs 4	
	203	Hyperfractionated	1.2 Gy BID	69.6	Cis 50 mg/m ² days 1, 8, 29, 36 Oral Et 50 mg PO BID ×10 weeks on days 1, 2, 5, 6	NR	3 vs 9	23 vs 1	45 vs 4	

*Four cycles of a 28-day cycle: For cycle 1, 4 (Vn dose, 25 mg/m²); for cycle 2, 3 (Vn dose, 12.5 mg/m²).

BID indicates twice daily; Cis, cisplatin; Et, etoposide; HD-CRT, high-dose CRT; Mit, mitomycin; NR, not reported; 2D-CRT indicates conventional or 2-dimensional CRT; Vd, vindesine; Vn, vinorelbine; Vb, vinblastine.

TABLE 2

Chemoradiotherapy to the Lung: Toxicity, Risk Factors, and Treatment Options

Adverse Effect	Incidence	Risk Factors	Treatments
Skin			
Dermatitis ^{25,28}	8%	Obesity, high BMI	Topical steroids, usual skin care with mild, unscented soap
Radiation recall	NR	Chemotherapy drugs (e.g., etoposide, gemcitabine, pemetrexed, paclitaxel)	Topical steroids, usual skin care with mild, unscented soap
Pulmonary			
Subacute			
Pneumonitis ^{43,45}	5%–15%	Age older than 65 and platinum regimens	Steroids
		Higher radiation dose	
		Higher V20	
		Higher nodal stage	
		Lower lobe tumors	
Chronic			
Bronchial stenosis ³⁶	8%–80%	Higher radiation dose	Stent, laser photocoagulation, cryocoagulation
Fatal hemoptysis ⁷⁵	7%	Higher radiation dose	Multidisciplinary approach
Pulmonary fibrosis and necrosis ²⁵	7%	Higher radiation dose	Steroids
			Avoid aggravating factors
Gastrointestinal			
Acute			
Mucositis ⁹	20%	Higher radiation dose	Viscous lidocaine (Xylocaine), Bland diet Avoid acidic foods, alcohol, or coffee
Oral candidiasis	NR	Higher radiation dose	Fluconazole, nystatin
Esophagitis ^{2,9}	20%–30%	Higher radiation dose	Proton pump inhibitors
		Hyperfractionated radiotherapy	Promotility agents Viscous lidocaine (Xylocaine) Bland diet Avoid acidic foods, alcohol, or coffee
Chronic			
Esophageal stricture ⁷⁵	21%	Higher radiation dose	Endoscopic dilatation

V20 indicates Volume of normal lung (volume of total lung minus planning target volume for radiotherapy) that received ≥20 Gy.