

Pulmonary Effects of Antineoplastic Therapy

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Pulmonary toxicity is common after cancer therapy and can result from all therapeutic modalities. The consequential decrease in lung function ranges in severity from subclinical to life-threatening or even fatal and can manifest in the acute setting or many years after completion of therapy. Radiation effects are due to direct insult to the pulmonary parenchyma and, for younger children, impaired thoracic musculoskeletal development. Radiation pneumonitis can occur in the acute/subacute setting, as well as fibrosis with compromised gas exchange as a late effect of direct lung irradiation; thoracic wall malformation can cause restriction of function as a chronic sequela. The pulmonary effects of cytotoxic drugs usually present as acute effects, but there is the potential for significant late morbidity and mortality. Of course, surgical interventions can also cause both acute and/or late pulmonary effects as well, depending on the specific procedure. Although treatment approaches for the management of pediatric cancers are continually adapted to provide optimal therapy while minimizing toxicities, to a varying degree all therapies have the potential for both acute and late pulmonary toxicity. Of note, the cumulative incidence of pulmonary complications rises with increasing time since diagnosis, which suggests that adult survivors of childhood cancer require lifelong monitoring and management of potential new-onset pulmonary morbidity as they age. Knowledge of cytotoxic therapies and an understanding of lung physiology and how it may be altered by therapy facilitate appropriate clinical care and monitoring of long-term survivors.

11.1 Pathophysiology

11.1.1 Development of the Lung

An understanding of the pathophysiology of lung toxicity due to cancer therapies requires an understanding of the development of the lungs.

Lung development is a complex process [105] that begins on day 26 of gestation and continues for at least several years postnatal. During the embryonic period, the primitive lung bud arises from the foregut, elongates caudally, and branches to form the major airways. The pseudoglandular phase follows; the process of

branching continues and the smaller airways are formed. Fetal breathing movements are identified as early as 8 weeks, and by the end of this phase, the two lobes of the left lung and three lobes of the right lung can be identified. Cartilage and smooth muscle cells are present, and about half of the epithelial cell types that will eventually comprise the mature lung are identifiable. The airway branching is completed, the interstitial tissue decreases, and prospective gas exchange regions begin to appear during the canalicular phase. A differentiation process occurs in the cuboidal epithelial cells, and Type I and II pneumocytes appear. Type I pneumocytes are the functional exchange unit of the lung, while Type II pneumocytes produce surfactant, a phospholipid substance that serves to decrease surface tension within the Type I cell and prevent it from collapsing. Vascularization of the lung occurs throughout development, and, at this point, the capillaries can be found in close proximity to the pneumocytes. The saccular phase of development extends from 24 weeks through 38 weeks gestation. During this time, there is continued thinning of the connective tissue between the potential air spaces, further maturation of the Type II pneumocytes, and increased surfactant production. Primitive alveoli, lined by both Type I and Type II pneumocytes, can now be identified as pouches in the walls of the saccules and respiratory bronchioles (Table 11.1).

The alveoli phase of development extends from 36 weeks gestation through about 3 years of age. At birth, there are few alveoli present, but potential airspaces are identifiable as smooth-walled ducts and saccules with thickened septa. Inflation of the saccules occurs at birth. The septa become thin and grow into air spaces, forming partitions within the pouches. Within a few months the infant's alveoli resemble those of the adult, with greatly increased surface area available for gas exchange. Completion of the vascularization process during this time results in single capillary networks associated with each area of gas exchange [118, 150]. After birth, minor structural changes continue to occur. The alveolar surfaces become more complex, and the alveoli become more numerous with the increase in body size.

Table 11.1 Prenatal and Early Childhood lung development

Stage	Weeks	Major developments
Embryonic	4–9	Formation of major airways
Pseudoglandular	5–17	Formation of bronchial tree and portions of respiratory parenchyma
		Birth of the acinus
Canalicular	16–27	Last generations of the lung periphery formed
		Epithelial differentiation
		Air–blood barrier formed
Saccular	24–38	Expansion of air spaces
		Surfactant detectable in amniotic fluid
Alveolar	36–3 years	Secondary septation

The most rapid phase of pulmonary growth occurs within the first few years of life, followed at 4–6 years of age by a slow growth phase. According to autopsy studies [99], the maximum numbers of alveoli are achieved by approximately 8 years of age. After this point it is believed that alveolar surface volume increases without an increase in alveolar number [149]. However, recent studies have suggested that formation of new alveoli may continue into adolescence [99]. In regard to musculoskeletal development, radiographic measurement of lung diameters demonstrates linear growth during childhood and a spurt at puberty [142].

11.1.2 Pathophysiologic Changes Induced by Cytotoxic Therapy

Primary lung malignancies are very rare in children; however, the lung is a common site for metastases, sometimes even years after the completion of definitive therapy. Therapy-related pulmonary toxicity is due to either local therapies (radiation or surgery) directed at the lung parenchyma and chest wall or chemotherapy that is administered systemically but likewise negatively

affects these organs and structures. Of course, many patients receive multimodality treatment that potentially compounds acute and late toxicity.

The pathogenesis of pulmonary toxicity secondary to cytotoxic therapy is largely based on animal experimentation. However, it is believed to occur through one of four mechanisms of injury: (1) DNA damage from the drug or radiation itself, (2) damage inflicted by free radical generation, (3) allergic response to the cytotoxic agent, and (4) subsequent injury induced by the inflammatory response to the primary damage itself. Pulmonary fibrosis, which mediates many of the long-term effects, can arise from collagen deposits that occur after cellular damage. In addition, the breakdown of actual lung tissue can trigger an inflammatory reaction that activates increased production of elastin by actin-expressing smooth muscle cells. This also results in pulmonary fibrosis. While there are several postulated means of injury to the pulmonary tissue, the common finding in all is diffuse alveolar damage. The cytotoxic changes start as endothelial blebs in the alveolar capillaries and lead to capillary leak syndrome. These are then associated with interstitial edema. There is destruction and a resulting decrease in number of Type I pneumocytes, as well as reactive changes and proliferation of Type II pneumocytes. More recently, progress has been made in understanding the molecular and cellular events after radiation lung injury, leading to clinically and histologically recognizable changes. The process appears to be dynamic and to involve proinflammatory cytokines, profibrotic cytokines, chemokines, and adhesion molecules in modulating and recruiting immune cells to the sites of radiation lung injury [24]. Long-term effects on the lungs are the result of this complex process.

11.1.2.1 Pathophysiology of Chemotherapy-Induced Disease

Drug-related pulmonary disease may be the result of toxicity, allergy, or idiosyncrasy [39]. Toxicity, with a dose–response, has been shown for bleomycin, chlorambucil, and the nitrosoureas. Pulmonary damage, likely mediated

through allergic mechanisms, is caused by cyclophosphamide, methotrexate, procarbazine, and bleomycin. Pulmonary disease has also been associated with mitomycin, cytosine arabinoside, the vinca alkaloids, and alkylating agents.

Bleomycin may be the most commonly recognized cause of pulmonary toxicity; the pathogenesis of bleomycin injury has been studied extensively [29, 58, 71]. Lung injury following low-dose bleomycin may be idiosyncratic, possibly attributable to genetically impaired drug metabolism. Having inherently low levels of bleomycin hydrolase [76], an enzyme that inactivates bleomycin, the lung is particularly vulnerable to bleomycin injury. Mouse data demonstrate that strain sensitivity to bleomycin is related to different levels of bleomycin hydrolase activity [62]. Hence, individual variations in bleomycin sensitivity may be explained at least in part by genetically determined levels of bleomycin hydrolase activity. Free radical formation and oxidative damage also play a role in bleomycin-induced lung injury. Fibrosis after bleomycin therapy develops under the influence of immune processes that include activation of effector cells, including alveolar macrophages, and release of cytokines. Tumor necrosis factor may play a pivotal role [82, 106]. Pathology demonstrates endothelial and Type I cell necrosis with Type II hyperplasia and hyaline membranes. Bleomycin-induced pulmonary effects usually occur during or within a year of treatment.

Alkylating agents, such as the nitrosoureas, are known to cause late-onset pulmonary fibrosis. The fibrosis noted after nitrosourea therapy demonstrates less inflammation than bleomycin-induced fibrosis, but consistency in Type I depletion and Type II hyperplasia with excess collagen deposition. The formation of free radicals and lipid peroxidation of phospholipid membranes may also be the mechanism by which cyclophosphamide and mitomycin damage the capillary endothelium [28]. Permeability increases, resulting in interstitial edema. Hyaline membranes form as plasma proteins, and fluid enters the alveoli through the denuded epithelium. Type I pneumocytes swell, become necrotic, and are replaced by cuboidal cells. Proliferation of fibroblasts then occurs. This process may evolve

slowly, with fibrosis increasing over a period of years. Interstitial pneumonitis (either the desquamative type that appears to be an earlier stage or the usual type with fibrinous exudation, hyaline membranes, and interstitial fibrosis) is also seen with alkylating agents. This pneumonitis may lead to the development of chronic pulmonary fibrosis that is characterized by the enhanced production and deposition of collagen and other matrix components. Pulmonary veno-occlusive disease, with vasculitis and intimal fibrosis resulting in pulmonary hypertension, has been reported after either bleomycin or mitomycin [34].

11.1.2.2 Pathophysiology of Radiation-Induced Disease

Similar histopathologic changes and resultant physiologic abnormalities are found in the lung following radiotherapy and chemotherapy. Subclinical injuries resulting from radiation to the lung are most likely present in all patients, even after very small doses of radiation. Studies of the immunological regulation of inflammation after radiation in animals have revealed a complex interaction between local tissues, resident cells, and circulating immune cells, mediated through chemokines, adhesion molecules, inflammatory cytokines, and fibrotic cytokines. Chemokine monocyte chemoattractant protein-1 (MCP1) [66], adhesion molecules (intercellular adhesion molecule-1 [ICAM-1]) [56, 69], and interferon-inducible protein-10 (IP-10) [66] appear to be involved in initiating radiation lung injury [24, 54, 56, 66, 124, 128, 148]. Afterward, there appears to be a cascade of proinflammatory cytokines and fibrotic cytokines (Fig. 11.1) [129].

In the first few days to weeks after irradiation, ultrastructural alterations in the capillary endothelial lining become evident. The cells become pleomorphic and vacuolated and may slough, thereby producing areas of denuded basement membrane and occlusion of the capillary lumen by debris and thrombi [51, 79, 86, 116]. There is exudation of proteinaceous material into the alveoli, leading to impairment of gas exchange. Studies have shown that radiation-induced lung injury is characterized by alveolar infiltrates of mononuclear cells, primarily CD4+ T cells and

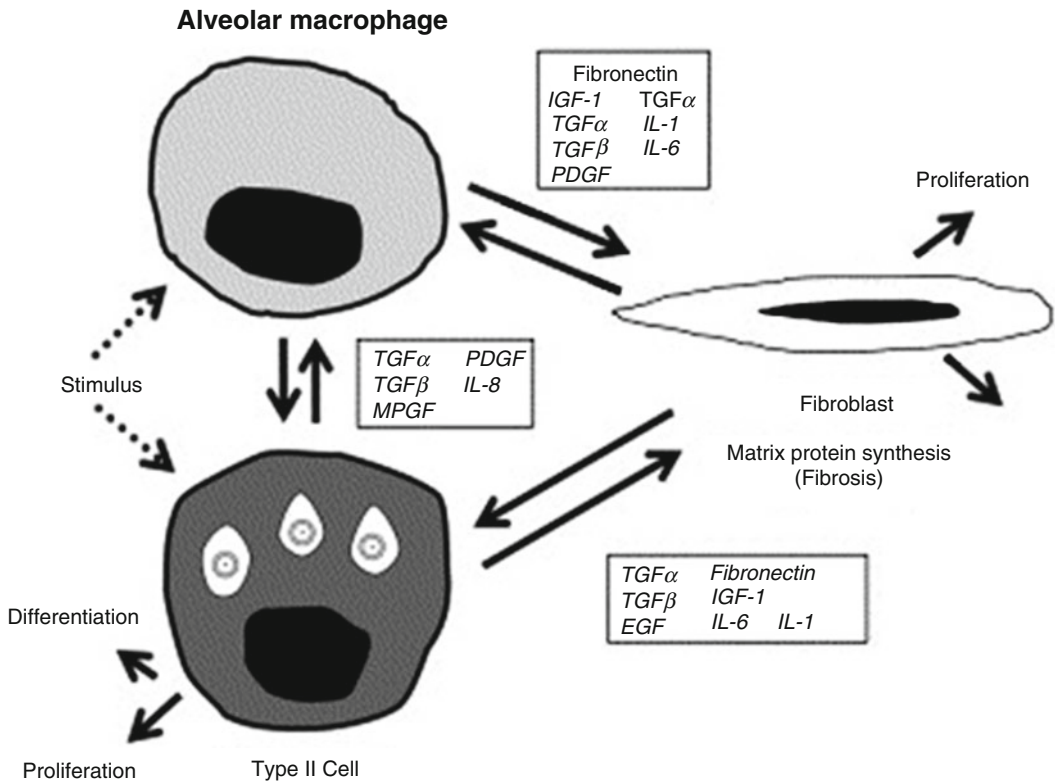


Fig. 11.1 Cell-cell interaction and control of gene expression by growth factors in lung injury (With permission from Rubin et al. [129])

macrophages/monocytes (mononuclear alveolitis), and that there is a relative scarcity of neutrophils [40, 43], a common marker for infectious processes. Lavage fluids obtained from bronchoscopy have confirmed this finding in patients with active pneumonitis [84, 98, 124]. In a few weeks the interstitial edema organizes into collagen fibrils, which eventually leads to thickening of the alveolar septa. These exudative changes may resolve in a few weeks to a few months. However, depending on the volume of lung parenchyma irradiated, the total dose, and the dose per fraction, the changes can result in an acute radiation pneumonitis.

Although no specific lesion is entirely characteristic of pneumonitis, current evidence suggests that damage to the Type II pneumocyte and to the endothelial cell is closely linked to the pneumonitic process [21, 113, 151, 152]. The type II pneumocyte, which produces surfactant and maintains patent alveoli, has been well studied.

After radiation exposure a rapid decrease in the content of cytoplasmic surfactant-containing lamellar bodies occurs, followed by the ultimate sloughing of some of the cells into the alveolar lumen [111, 112]. Changes in the surfactant system that lead to alterations in alveolar surface tension and low compliance are most likely a direct result of the radiation [113, 130, 131], although it has been postulated that the changes indirectly result from exudation of plasma proteins [52]. Endothelial cell damage results in changes in perfusion and permeability of the vessel wall. Endothelial leakage and increased permeability allow immune cells to undergo transendothelial migration and extravasation from the vascular compartment into the alveolar space.

Late lung injury is characterized by progressive fibrosis of the alveolar septa, which become thickened by bundles of elastic fibers. The alveoli collapse and are obliterated by connective tissue. The mechanisms of chronic injury may be related

to the effects of radiation on the pulmonary vasculature (endothelial cells) or somatic cells. The nature of the triggering event in the pathogenesis of radiation-related lung fibrosis is complex. The classic hypothesis that fibrosis is a connective tissue replacement process following parenchymal cell death has been challenged, and the exact mechanisms of early injuries leading to the late effects are not entirely understood. Cytokine-mediated multicellular interactions that initiate and sustain the fibrogenic process take place within hours to days after radiation in animal research models. Experimental data suggest that the progression of the initial lung injury to the pneumonitic phase may be the result of a cytokine and cellular interaction, which subsequently regulates the fibrotic phase of the presentation [24, 127–129]. In addition, it has been recently hypothesized that chronic hypoxia, and the perpetual injury to normal tissue through reactive oxygen species, may also be a contributing mechanism to chronic and progressive fibrosis [158]. Studies in animals have confirmed the protective effect of fractionated radiation therapy, which is several small doses of radiation as compared to a comparable dose delivered in a single large treatment, indicating a significant degree of recovery of lung tissue between fractions [141, 160].

11.1.2.3 Categorization of Pulmonary Disease

Lung disease may be categorized as follows: interstitial, obstructive, restrictive, or a combination. Most long-term toxicity is the result of interstitial disease, which involves inflammation and fibrosis of the alveolar walls and changes in the capillary endothelium and alveolar epithelial lining cells, as described below. The histologic hallmarks of interstitial lung disease are proliferation of fibroblasts and excessive deposition of collagen [135]. Interstitial lung disease also may impact the small airways. As alveolar–capillary membrane destruction is an integral part of interstitial disease, pulmonary function tests demonstrate a decrease in the measured diffusing capacity [135].

Pulmonary disease after chemotherapy or radiation therapy may also have an obstructive

component. Obstructive diseases result from airway narrowing. This may be due to bronchospasm, mucus, or luminal narrowing as a result of edema and inflammation or scarring [97]. Airway narrowing due to disease can be detected as a decrease in expiratory airflow. Pulmonary function tests demonstrate a decrease in the ratio of the volume exhaled in 1 s (FEV1) to the total exhaled forced vital capacity (FVC).

Restrictive lung diseases occur as a result of alterations in the elasticity of the pulmonary system [42], which may be due to parenchymal disease originating in the lung or from structural anomalies of the chest wall. In the healthy lung, collagen and elastin fibers contribute to the formation of an organized web, which has a significant ability to stretch and recoil [42]. Disruption of this organization from inflammation and fibrosis occurs as a result of injury and response to cytotoxic therapy, thereby decreasing the elasticity of the lung and resulting in restrictive disease. Additionally, in the child, cytotoxic therapy may impair the proliferation and maturation of alveoli, leading to inadequate alveoli number and lung growth and resulting in chronic respiratory insufficiency.

Restrictive lung disease may also occur as a result of growth impairment of the lung or musculoskeletal structures, which is predominantly a consequence of radiation therapy. Inhibition of growth of the thoracic cage (i.e., muscle, cartilage, and bone) can limit chest wall compliance, with resultant restrictive problems. Naturally, younger children are more vulnerable to chronic respiratory damage from impairment of the normal growth and development of the lungs and the thoracic cage.

In restrictive respiratory disease, pulmonary function testing demonstrates an increased FEV1/FVC ratio with an increased maximal expiratory airflow. With more advanced restrictive disease, total lung capacity, vital capacity, and lung volumes are decreased, with evidence of uneven distribution of ventilation [97]. Please refer to Sect. 11.3.1 for a detailed discussion of pulmonary function tests.

11.2 Clinical Manifestations

11.2.1 Long-Term Effect in Pediatric Population

Potential pulmonary complications of therapy leading to a range of respiratory manifestations have been reported by the Childhood Cancer Survivor Study. Study participants were asked whether they had ever been told by a physician, or other healthcare professional, that they have or had a particular diagnosis, such as pulmonary fibrosis. This self-report study demonstrated that long-term survivors described a statistically significant increased relative risk of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, use of supplemental oxygen, abnormal chest wall, exercise-induced SOB, bronchitis, recurrent sinus infection, and tonsillitis for all time periods, including during therapy, from the completion of therapy to 5 years off therapy and >5 years after therapy. Significant associations existed between the development of fibrosis and treatment with radiation therapy and between the use of supplemental oxygen, recurrent pneumonia, chronic cough, and pleurisy and treatment with radiation therapy and/or multiple chemotherapy agents [92]. In regard to mortality, a large retrospective study of greater than 20,000 5-year survivors of childhood cancer reported a significant excess rate of deaths largely due to treatment-related causes rather than progression or recurrence of the primary disease; furthermore, pulmonary causes accounted for excess mortality risk (standard mortality ratio, 8.8) second only to death from secondary malignancy (standard mortality ratio, 15.2) [7].

Pulmonary toxicity is frequently reported in survivors of Hodgkin lymphoma, but it also complicates the cure of survivors of germ cell tumors, rhabdomyosarcoma, neuroblastoma, bone tumors, and acute lymphoblastic leukemia (ALL) [16, 55, 61, 67, 72, 94, 101, 102]. Although many of the patients that have been studied received radiation therapy, the intensified use of chemotherapy accounts for some or all of the toxicity in subsets of survivors. In fact, pulmonary complications are

a major cause of morbidity and mortality following hematopoietic stem cell transplant [145], which is now an established treatment approach for many pediatric malignancies.

Studies with long-term follow-up suggest that the cumulative incidence of pulmonary complications increases with increasing time since treatment [63]. This appears to be far in excess of decreases in lung function with normal aging, suggesting that the effects of early lung injury from cancer therapy compound expected decreases and that survivors should be monitored indefinitely for new-onset pulmonary morbidity as they age.

11.2.2 Radiotherapy: Clinical Presentations

Pneumonitis and pulmonary fibrosis are the two most important consequences of irradiation of the lung. Pulmonary fibrosis occurs in almost 100 % of patients receiving high doses of radiation, but it may not be of clinical significance if the volume is small. The clinically significant presentation of pulmonary toxicity is usually pneumonitis, due to its prevalence and potential morbid outcome. The presentation varies with the type of lung injury present. Often there are complaints of a nonproductive cough, fever, and dyspnea. However, the presentation can also be quite acute with respiratory insufficiency and acute respiratory distress syndrome (ARDS). Other presentations include bronchospasm, pleural effusion, bronchiolitis obliterans, pulmonary veno-occlusive disease, sarcoidosis, pulmonary alveolar proteinosis, pneumothorax, and pulmonary hemorrhage.

When radiation therapy is the only modality used, radiation pneumonitis follows the completion of the definitive course of treatment. Cough, pink sputum, dyspnea, and pleuritis are common complaints during the subacute pneumonitic phase, which generally occurs 1–3 months after completion of radiation. When chemotherapy is administered in conjunction with radiation, as in total body irradiation (TBI) and BMT-

conditioning regimens, reactions can occur during treatment. The fibrotic phase of radiation injury starts 3–6 months after completion of radiation and is progressive. The clinical manifestations of fibrosis are worsening dyspnea, increasing probability of oxygen dependence, and declining pulmonary function test results.

11.2.2.1 Subacute Radiation Pneumonitis

Subacute pneumonitis is a pneumonopathy that usually occurs 1–3 months after the completion of radiation. It is well described in the adult literature after the treatment of lung cancer [5, 6, 122], but little of the data from such studies are relevant to modern pediatric cancer therapies. Pneumonitis can occur unexpectedly, with little or no warning. Because of this, many attempts have been made to identify clinical risk factors. The factors that influence risk include total lung radiation dose, irradiated lung volume exceeding 20 Gy vs 25 Gy vs 30 Gy, mean lung dose, fractionation of radiotherapy, daily fraction size, performance status, pre-treatment pulmonary function, gender, low pre-treatment blood oxygen, and high C-reactive protein [49, 59, 64, 74, 123, 125, 136].

Symptoms of subacute pneumonitis syndrome include low-grade fever and nonspecific respiratory symptoms such as congestion, cough, and fullness in the chest. In more severe cases, dyspnea, pleuritic chest pain, and nonproductive cough may be present. Later, small amounts of sputum, sometimes bloodstained, may be produced. Physical signs in the chest are usually absent, although a pleural friction rub or pleural fluid may be detected. Evidence of alveolar infiltrates or consolidation is sometimes found in the region corresponding to pneumonitis. This results from an acute exudative edema that is initially faint but may progress to homogenous or patchy air space consolidation. Frequently there is an associated volume loss in the affected portion of the lung.

CT studies of the lung have been used to evaluate lung density in this situation. Because of its sensitivity to increased lung density, CT has been favored for radiographic detection of pulmonary damage in humans [81, 85, 155]. CT findings

demonstrate a well-defined, dose–response relationship [85]. Four patterns of radiation-induced changes have been defined in lung on CT: homogenous (slight increase in radiodensity), patchy consolidation, discrete consolidation, and solid consolidation [81]. These patterns, corresponding to both pneumonitic and fibrotic phases, have varying timetables and may appear weeks to years after radiotherapy.

11.2.2.2 Radiation Fibrosis

In contrast to the acute reaction, clinically apparent chronic effects of cytotoxic therapy may be observed from a few months to years following treatment, even though histologic and biochemical changes are evident sooner. Pulmonary fibrosis develops insidiously in the previously irradiated field and stabilizes after 1–2 years.

The clinical symptomatology related to the radiographic changes is proportional to the extent of the lung parenchyma involved and preexisting pulmonary reserve. After thoracic radiation, restrictive changes gradually develop and progress with time [51]. Gas exchange abnormalities occur approximately at the same time as the changes in lung volumes. These abnormalities consist of a fall in diffusion capacity, mild arterial hypoxemia that may manifest only with exercise, and a low or normal PaCO₂ level. The changes appear to be consistent with a parenchymal lung defect and ventilation–perfusion inequality that results in a component of effective shunt [52]. Radionuclide evaluations have demonstrated that underperfusion, rather than underventilation, is the cause of these inequalities, reflecting radiation injury to the microvasculature [119, 120, 157]. Larger doses of irradiation cause reductions in lung compliance that start at the time of pneumonitis and persist thereafter [117]. The compliance of the chest wall is usually much less affected in adults and adolescents than in young children, in whom interference with growth of both lung and chest wall leads to marked reductions in mean total lung volumes and diffusion capacity (DLCO) [165]. Whole-lung irradiation in doses of 11–14 Gy has resulted in restrictive changes in the lungs of children treated for various

malignancies [10, 83, 93]. Consequently, RT in younger children, particularly those younger than 3 years old, results in increased chronic toxicity [93]. One to 2 years after radiation, clinical symptoms stabilize and are often minimal if fibrosis is limited to less than 50 % of one lung [134]. A mild deterioration in pulmonary function may be demonstrated as fibrosis develops. There is a reduction in maximum breathing capacity that is particularly evident in patients with bilateral radiation fibrosis. Tidal volume usually decreases, and breathing frequency tends to increase, resulting in an overall moderate increase in minute ventilation [139]. Most studies have found these changes to persist indefinitely, with little recovery unless there are concurrent improvements in pulmonary function with lung tumor response [41, 45, 50]. Functional compensation by adjacent lung regions [100] limits the effect of radiation on pulmonary function tests when small volumes of lung are irradiated. Dyspnea and progressive chronic cor pulmonale leading to right heart failure may occur when >50 % of a lung is irradiated.

Radiologic changes consistent with fibrosis are seen in most patients who have received lung irradiation, even if they do not develop acute pneumonitis. Chest radiographs have linear streaking, radiating from the area of previous pneumonitis and sometimes extending outside the irradiated region, with concomitant regional contraction, pleural thickening, and tenting of the diaphragm. The hilum or mediastinum may be retracted with a densely contracted lung segment, resulting in compensatory hyperinflation of the adjacent or contralateral lung tissue. This is usually seen 12 months to 2 years after radiation. When chronic fibrosis occurs in the absence of an earlier clinically evident pneumonitic phase [113, 126, 140], chest radiography generally reveals scarring that corresponds to the shape of the radiation portal. Eventually, dense fibrosis can develop, especially in the area of a previous tumor [127]. CT is currently favored to image regions subjected to RT [81, 85, 155]. Magnetic resonance imaging (MRI) is being explored and may have promise in accurately distinguishing radiation fibrosis from recurrent tumor. Although radiation tolerance doses

may be exceeded, not all patients will develop complications, given that the sensitivity to radiation varies from patient to patient.

11.2.2.3 Radiation Tolerance Doses and Tolerance Volumes

Radiation-associated sequelae are dependent on radiation dose and fractionation, as well as volume of lung exposed. With high doses exceeding clinical thresholds (8.0–12.0 Gy, single dose), pulmonary reactions clinically express themselves as a pneumonitic process 1–3 months after the completion of thoracic irradiation. Lethality can occur if both lungs are irradiated to high doses (approximately 8–10 Gy, single dose, or greater than 20–25 Gy in a fractionated schedule) or if threshold doses of drugs are exceeded. Recovery from pneumonitis usually occurs, however, and is followed almost immediately by the second phase, which is progressive fibrosis. The clinical pathologic course is biphasic and again dependent upon the dose and volume of lung exposed. Lower doses of lung irradiation (approximately 7 Gy, single dose, or 15–18 Gy in a fractionated schedule) produce subclinical pathologic effects that can be expressed by added insult, such as infection or drugs.

Single Dose, Whole Lung Volume Total body irradiation (TBI) in the setting of bone marrow transplantation (BMT) and half-body irradiation (HBI) initially used single doses of 8.0–10.0 Gy, without lung correction factors for lung density [44, 45, 47, 50–53, 57, 58, 68, 69, 71]. Death resulting from interstitial pneumonitis was often attributed to secondary opportunistic infection after BMT for leukemia. Pulmonary failure 1–3 months later was mistaken for lymphangitic carcinomatosis after HBI. At autopsy, radiation pneumonopathy became evident. Studies of fatal pneumonitis following TBI and HBI conducted by Keane et al. [71] and Fryer et al. [44] provided precise dose–response curves for injury, both with and without lung inhomogeneity correction. The threshold dose for fatal pneumonitis was 7.0 Gy with the TD5 (tolerance dose for 5 % probability of death) at 8.2 Gy, the TD50 at 9.3 Gy, and

the TD90 at 11.0 Gy, corrected for pulmonary transmission. The dose–response is so sharp that a difference of 2.0 Gy could change zero mortality to 50 % lethality.

Fractionated Dose, Whole Lung Volume The tolerance of the whole lung to fractionated doses of radiation is well described, particularly in Wilms’ tumor patients [10, 15, 83, 93, 115, 165]. In the absence of chemotherapy and with daily doses of 1.3–1.5 Gy, the TD5 is 26.5 Gy and the TD50 is 30.5 Gy. Young children experience more chronic toxicity at lower doses than older children and adults because of interference with lung and chest wall development, in addition to fibrosis and volume loss [96]. After 20 Gy, mean total lung volumes and DLCO are reduced to 60 % of predicted values [165]. Even within the dose range currently used for whole lung irradiation (11–14 Gy), restrictive changes occur [10, 83, 93].

Whole Lung Volume, Dose Rate Dose rate has a profound impact on lung damage, with a decrease in the incidence of injury from 90 % to 50 % with decrease in dose rate from 0.5 to 0.1 Gy per minute [44, 71].

Fractionated Dose, Partial Lung Volume Clinical tolerance of partial lung volumes to fractionated radiation is not well quantified. There are, however, some relevant data from Mah and colleagues [85]. They showed that, using an increase in lung density within the irradiated volume on CT in the posttreatment period as an endpoint, each 5 % increase in effective dose was associated with a 12 % increase in the incidence of pneumonitis. Doses above 30 Gy over a period of 10–15 days, and 45–50 Gy over a period of 25–30 days, caused radiographic changes in 30–90 % of patients. The need for a clinical guideline in estimating radiation injury prompted the collaborative work by a task force to address the normal tissue tolerance in the standard, fractionated radiation setting. Information was obtained from a diverse group of patients afflicted with various diseases of the thoracic region, but mostly from patients with Hodgkin’s disease, lung cancer, or a disease requiring large-volume

Table 11.2 Lung tolerance dose (TD) in fractionated radiotherapy

Lung volume	TD 5/5 ^a	TD 50/5 ^b
1/3	4,500 cGy	6,500 cGy
2/3	3,000 cGy	4,000 cGy
3/3 (whole lung)	1,750 cGy	2,450 cGy

^aThe probability of 5 % complication within 5 years of treatment

^bThe probability of 50 % complication within 5 years of treatment

irradiation (hemibody or total body radiation) [37]. The doses agreed on by the physicians in the taskforce are shown in Table 11.2. It is important to note that these values were defined for adult, not pediatric, patients.

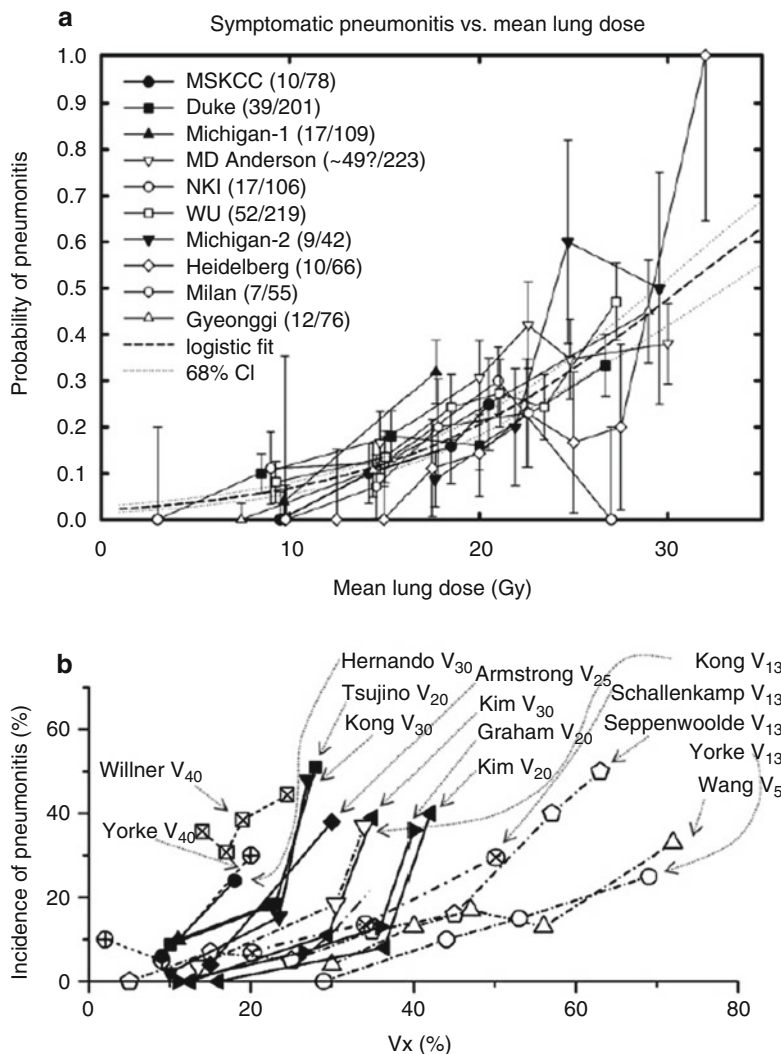
More recently, as part of the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) effort, a logistic regression fitted to radiation pneumonitis vs mean lung dose was created from data from all published studies, again, predominantly involving adult patients, of a significant size that had extractable complication rates binned by mean dose (Fig. 11.2). The authors note that some of the variation around the fitted curve is possibly explained by differences in patient selection, as well as differences in the grade of RP reported in the various studies; however, there is a relatively small 68 % confidence interval (stippled lines). Of importance is the gradual increase in dose–response, which suggests that there is no absolute “safe” mean lung dose below which pneumonitis is certain not to develop.

An international effort similar to the above QUANTEC analysis is currently underway specific to the pediatric population.

11.2.3 Chemotherapy: Clinical Manifestations

As increasing numbers of patients are cured with chemotherapy, reports of agents responsible for acute, and possibly chronic, pulmonary toxicity are expanding. Drug-related lung injury is most commonly an acute phenomenon, occurring during or shortly after the chemotherapeutic agent(s) is administered [28].

Fig. 11.2 Rate of radiation pneumonitis after fractionated partial lung radiotherapy (RT) related to (a) mean lung dose and (b) different values of Vx. Confidence intervals shown are ± 1 standard deviation (With permission from Marks et al. [87])



11.2.3.1 Patterns of Toxicity

Three typical patterns of pulmonary toxicity have been described: acute hypersensitivity (or inflammatory interstitial pneumonitis), noncardiogenic pulmonary edema, and pneumonitis or fibrosis.

Hypersensitivity reactions are rare but can be induced by such agents as methotrexate, procarbazine, bleomycin, BCNU, and paclitaxel. Cough, dyspnea, low-grade fever, eosinophilia, “crackles” on exam, and interstitial or alveolar infiltrates are noted. These reactions occur during therapy and usually resolve with discontinuation of the offending drug and, potentially, corticosteroid use.

Noncardiogenic pulmonary edema, characterized by endothelial inflammation and vascular

leak, may arise upon initiation of treatment with methotrexate, cytosine arabinoside, ifosfamide, cyclophosphamide, and interleukin-2 [28, 77, 146]. All-trans retinoic acid (ATRA) syndrome, a potentially fatal cytokine release syndrome, occurs in 23–28 % of patients receiving ATRA. Pulmonary edema has also been described in patients treated with bleomycin who are exposed to supplemental oxygen. These acute reactions generally have a good prognosis. Hypersensitivity reactions and noncardiogenic pulmonary edema are unlikely to result in late-onset pulmonary toxicity.

Drug-induced pneumonitis or fibrosis has a similar clinical presentation to that described after

RT. Bleomycin, the nitrosoureas, and cyclophosphamide are most commonly the etiologic agents, although methotrexate and vinca alkaloids have also been implicated [28]. This syndrome is particularly worrisome because symptoms may not be detectable until months after a critical cumulative dose has already been reached or exceeded. In addition, persistent subclinical findings may indicate a potential for late decompensation.

11.2.3.2 Specific Agents

Bleomycin The incidence of bleomycin pulmonary toxicity is 6–10 %, with a mortality of 1–2 %. One study in children with rhabdomyosarcoma exposed to bleomycin demonstrated an incidence of toxicity of 70 % based on decreased DLCO [67]. A risk factor for bleomycin-induced pulmonary toxicity is the cumulative dose with a 10 % risk at doses of 400–500 IU/m² [14, 132] although injury may occur at doses as low as 20 IU/m². The elderly [14] and children or adolescents [44] may be more sensitive, especially when bleomycin is administered in conjunction with RT. Of children treated for Hodgkin's disease with 70–120 IU/m² of bleomycin [44], 9 % had grade 3 or 4 pulmonary toxicity, according to DLCO. Three patients (5 %) had clinical symptomatology, and one patient died. Only one patient had received RT. Although pediatric trials now use a significantly lower maximal dose than many adult studies, 80 % of the drug is excreted by the kidney, which can result in an increased risk of toxicity due to renal insufficiency [114, 143]. Other chemotherapeutic agents such as cisplatin, cyclophosphamide, doxorubicin, methotrexate, and vincristine [8, 121] may also increase risk. Exposure to high levels of oxygen or to pulmonary infection, especially within a year of treatment, is associated with a risk for immediate progressive respiratory failure [47]. Risks associated with surgery after treatment with bleomycin may be due to fluid overload [35]. These risks may persist for longer periods of time. There may be a potential increase in pulmonary toxicity with the use of granulocyte colony stimulating factor (G-CSF), which is mediated via the increased numbers of neutrophils [30].

Patients with acute bleomycin toxicity most commonly present with dyspnea and a dry cough. Fine bibasilar rales may progress to coarse rales involving the entire lung. Radiographs reveal an interstitial pneumonitis with a bibasilar reticular pattern or fine nodular infiltrates. In advanced cases, widespread infiltrates are seen, occasionally with lobar consolidation [132]; however, the consolidation may involve only the upper lobes. Large nodules may mimic metastatic cancer [89]. Loss of lung volume may occur. Pulmonary function testing reveals a restrictive ventilatory defect with hypoxia, hypocapnia, and chronic respiratory alkalosis due to impaired diffusion and hyperventilation [154]. The DLCO is thought by some to be the most sensitive screening tool for bleomycin toxicity [154]. In patients who develop mild toxicity, discontinuation of bleomycin may lead to a reversal of the abnormalities [32], but some patients will have persistent radiographic or pulmonary function abnormalities [9, 107, 164].

Nitrosoureas The risk of nitrosourea pulmonary toxicity is age and dose dependent with patients who have received higher doses of nitrosoureas (e.g., greater than 1,500 mg/m² in adults and 750 mg/m² in children) more likely to present with an interstitial pneumonitis identical to that seen after bleomycin therapy [1]. Fibrosis may be early onset or late onset. Radiation therapy also increases risk, as does underlying pulmonary abnormality, such as chronic obstructive pulmonary disease, although this is rarely a factor in children. Bone marrow transplant patients may develop pulmonary fibrosis with BCNU as one of the contributing etiologies [103]. As part of a preparative regimen including etoposide and melphalan, BCNU at 600 mg/m² was associated with unacceptable pulmonary toxicity, but doses of 450 mg/m² were tolerated in the acute period [2]. Chemotherapy prior to bone marrow transplant may induce inflammatory changes that render the lung more susceptible to further, potentially irreversible, injury with high-dose therapy [12]. Although pulmonary fibrosis has been most commonly associated with BCNU, it has been described after other nitrosoureas as well [13, 33]. Bibasilar rales

with a bibasilar reticular pattern may be seen on chest radiograph, and restrictive ventilatory defects are seen as well. Abnormalities may be restricted to the upper lobes. A decreased diffusion capacity may precede all other signs [137]. Discontinuation of therapy may alter the course of BCNU-induced pulmonary disease. However, once pulmonary infiltrates are noted, the disease may be irreversible [162]. In a documented study, 47 % of survivors of childhood brain tumors treated with BCNU and radiation died of lung fibrosis, 12 % within 3 years of treatment, and the remainder 6–17 years posttreatment. Additional patients were known to have pulmonary fibrosis and remained at risk for late decompensation. In this study, age was a risk factor. The median age of the patients who died was 2.5 years, while the median age of survivors was 10 years. In fact, all patients treated under the age of 5 years had died [104].

Cyclophosphamide Fibrosis after treatment with cyclophosphamide is rare, with a reported incidence less than 1 %. However, one study [72] found that 4 of 15 children treated with high-dose cyclophosphamide without mediastinal RT had significantly decreased forced vital capacities; 2 of these children also had a decreased FEV1. In addition, one of the children had pulmonary fibrosis and a chest wall deformity. Two children who received more than 50 g/m² of cyclophosphamide had delayed (greater than 7 years) fatal pulmonary fibrosis, with severe restrictive lung disease. Severely decreased anteroposterior chest dimensions in these patients were attributed to inability of the lung to grow in accordance with body growth. Fibrosis may also develop late after prolonged treatment with relatively low doses of cyclophosphamide. Although there may be recovery if symptoms occur during therapy and the drug is discontinued with administration of corticosteroids, the course may be one of progressive fibrosis nonetheless.

Hematopoietic Stem Cell Transplant (HSCT) Patients who are treated with HSCT are at risk of pulmonary toxicity because of multiple potential factors, such as preexisting pulmo-

nary dysfunction; the preparative conditioning regimen, which may include cyclophosphamide, busulfan, carmustine, and total body irradiation (TBI); and the presence of graft-vs-host disease [21, 78, 134, 162]. Although most transplant survivors are not clinically compromised, restrictive lung disease may occur. Obstructive disease is less common, as is the recently described late-onset pulmonary syndrome, which includes the spectrum of restrictive and obstructive disease. Bronchiolitis obliterans, with or without organizing pneumonia, diffuse alveolar damage, and interstitial pneumonia, may occur as a component of this syndrome, generally 6–12 months after transplant. Cough, dyspnea, or wheezing may occur with either normal chest radiograph or diffuse or patchy infiltrates; however, most patients are symptom-free [78, 162]. Cerveri et al. [21] evaluated pulmonary function tests in survivors of pediatric HSCT at baseline and at 3–6, 12, and 24 months after transplant. Before transplant, at 3–6 months after transplant, and at 24 months after transplant, 44 %, 85 %, and 62 % of children, respectively, had abnormal pulmonary function tests. A restrictive abnormality was most common at 3–6 months after transplant.

Other Agents Acute pulmonary effects have occurred with cytosine arabinoside (noncardiogenic pulmonary edema) [3, 57] and vinca alkaloids in association with mitomycin (bronchospasm or interstitial pneumonitis) [29, 53], but delayed pulmonary toxicity has not been described. Hypersensitivity reactions to the anti-metabolites (methotrexate, mercaptopurine, and azathioprine) may cause either a desquamative interstitial pneumonitis or an eosinophilic pneumonitis [77, 155, 159]. Recovery usually occurs within 10–45 days after methotrexate-induced pulmonary toxicity [144].

However, long-term follow-up of 26 childhood leukemia survivors revealed that 17 (65 %) patients had one or more abnormalities of vital capacity, total lung capacity, reserve volume, or diffusion capacity [138]. All children with these deficiencies were diagnosed and treated before age 8. The findings have also been attributed to an impairment of lung

growth, which normally proceeds exponentially by cell division during the first 8 years of life. Other studies have also demonstrated long-term changes in pulmonary function in survivors of ALL treated without spinal radiation or bone marrow transplant [102].

Busulfan can result in late pulmonary fibrosis, with no consistently identified risk factors. Unlike many other agents, the risk does not appear to be dose related. The clinical and pathologic picture is like that of bleomycin-induced fibrosis. The mortality from busulfan fibrosis is high [1]. Although reports of pulmonary toxicity with other agents are rare, pneumonitis and fibrosis should be considered in the differential of patients presenting with respiratory symptoms. New agents may also present a risk for late pulmonary toxicity. See Table 11.2 [1, 90].

11.2.4 Thoracic Surgery

Lung resections are performed in children for a number of reasons, including congenital malformations, infections, bronchiectasis, and metastatic malignancies. Interestingly, the majority of children who undergo lung resection do well with mild sequelae, if any, in adulthood [80]. A large study of 230 patients who were evaluated on average 33 years after pneumonectomy provides interesting data on the long-term compensatory potential and possible mechanisms of recovery in young children and adults following surgery [75]. The study found that children who underwent surgery before the age of 5 years had ventilatory capacity close to what would be predicted for two lungs, which the authors argue suggests that compensatory growth by way of hyperplasia might have been the most important adaptive mechanism in this group. Perhaps more surprisingly, even in the patients who underwent surgery between the ages of 6 and 20 years, a significant difference was still found as compared to the group of patients operated on at an older age, which indicates that in this period compensatory growth, possibly simple hypertrophy, still played an important but gradually decreasing role.

Unfortunately, few studies have investigated pulmonary toxicity specifically in the context of pediatric cancer therapy.

11.2.5 Treatment and Clinical or Environmental Interactions

11.2.5.1 Chemotherapy: Chemotherapy Interactions

In considering the risk of pulmonary toxicity from chemotherapy, the potential for chemotherapy – chemotherapy interactions – must be taken into account. Toxicity is seen at much lower doses than expected with drug combinations such as nitrosoureas and cyclophosphamide [147], bleomycin and cisplatin, or vincristine, doxorubicin, and cyclophosphamide [8, 77, 121]. Vinca alkaloids appear to cause pulmonary toxicity only in the presence of mitomycin [29, 77].

11.2.5.2 Radiation and Chemotherapy Combinations: Interaction and Tolerance

Many antineoplastic agents potentiate the damaging effects of radiation on the lung. Phillips [116] and Wara [160] demonstrated that dactinomycin administration lowered the radiation dose threshold for pneumonitis. Testing the effects of commonly used chemotherapeutic agents, Phillips and colleagues [116] reported that the administration of dactinomycin, cyclophosphamide, and, to a lesser extent, vincristine enhanced the lethal potential of thoracic irradiation. The effect of dactinomycin was seen when given as long as 30 days before irradiation, but it was not seen when given 30 days after the irradiation. The administration of bleomycin and lung irradiation together produces lung toxicity that is more common and severe than when either agent is given alone. Catane [20] found pulmonary toxicity in 19 % of patients, and it was fatal in 10 %. This toxicity appears to be maximal when bleomycin is given concurrently with radiation [36]. Although 500 IU of bleomycin without RT can be lethal in 1–2 % of patients, as little as 30 IU can be fatal when given with RT. The effects of RT are also potentiated by doxorubi-

cin. In addition to the enhanced toxicity observed in skin, intestines, and heart, the lung also appears to be very sensitive to this combination [18, 22]. Of 24 patients with lung cancer treated with low-dose doxorubicin and RT, 13 developed pneumonitis [156].

11.2.5.3 Other Interactions

Although not as well defined, surgical interventions and other factors, such as repeat or chronic infections and toxic environment exposures such as cigarette smoke, can decrease the threshold for development of late pulmonary effects from therapy.

11.3 Detection and Screening

Pulmonary disease occurring in patients treated for cancer can present a diagnostic problem because of the multiplicity of possible etiologies. Progressive cancer, infections, emboli, allergy, irradiation, or drugs (and their interaction) can be causative. Clinical findings, radiologic studies, and pulmonary function tests can be nonspecific; however, these factors represent measurable endpoints to quantify toxicity.

11.3.1 Measurable Endpoints

Symptoms Fever, cough, and shortness of breath are the most common symptoms of radiation-induced pneumonopathy. Temperature, respiratory rate, oxyhemoglobin saturation, frequency of cough, and the nature of sputum produced should all be recorded. Varying degrees of dyspnea, as well as orthopnea, can be present depending on the severity of pulmonary damage. To standardize grading in the literature, the grading criteria in Common Terminology Criteria for Adverse Events (CTCAE), published by the National Cancer Institute and National Institute of Health [27], have been expanded to be useful for the long-term survivor.

Signs The principal signs of both acute and delayed pneumonopathy are the increase in respi-

ratory rate, dullness to percussion of the chest, auscultation of crackles, and, in severe cases, cyanosis.

Radiography Plain anteroposterior (AP) and lateral chest films are useful when the disease involves a large volume of lung. The acute pneumonitic phase manifests as a fluffy infiltrate, and the late fibrotic phase can follow the intermediate phase of contraction. However, routine chest radiography has a low level of reliability in detecting small volumes of pneumonopathy, particularly if they are located close to the chest wall. Chest radiography also lacks the ability to quantify the volume of affected lung vs the total lung volume.

When chronic fibrosis occurs, chest radiography generally reveals scarring that corresponds to the shape of the radiation portal. CT scans have the capability of presenting three-dimensional images and calculating three-dimensional volumes of functional lung in a defined range of Hounsfield units. One can also detect small infiltrates that may be adjacent to the chest wall, for example, in the case of tangential field RT, where infiltrates are calculated as a percentage of the total lung volume. Mah [85] has shown a quantitative relationship between the volume of abnormality on CT and RT dose (converted to a single dose equivalent). Radiographic changes after chemotherapy are often bibasilar fibrosis. Fibrosis confined to the upper lobes has also been described after treatment with BCNU [110] and bleomycin [88].

Pulmonary Function Tests (PFTs) Pulmonary function testing (PFT) is a broad term that encompasses a variety of techniques and tests. The indications for pulmonary function testing include (a) documenting the presence of obstructive or restrictive abnormalities in the course of establishing a diagnosis, (b) monitoring the course of a known pulmonary disease (e.g., cystic fibrosis, asthma, etc.), (c) monitoring for pulmonary toxicity of treatment (e.g., amiodarone, radiation, chemotherapy), (d) monitoring response to therapy, and (e) describing normal and abnormal lung growth.

The values measured in the laboratory are usually normalized with the use of reference equations, most commonly utilizing the subject's height and gender and sometimes modifying for ethnicity and age. With these equations, a predicted value can be calculated for each parameter, and the measured flows can be reported as a percentage of the predicted value or as a standardized deviation score (Z-score). It should be noted that comparing test results between pulmonary function laboratories must be done with caution if different reference equations are used.

Ideally, patients can serve as their own control for the effects of chemotherapy or radiotherapy if measurements are obtained prior to treatment. Abnormal PFTs prior to treatment may also alert the practitioner to patients at higher risk for pulmonary toxicity. Indeed, abnormal lung function has been shown to predict early pulmonary complications [70] and higher mortality following stem cell transplantation in both adults [109] and children [48]. In addition, PFT abnormalities may be present in the absence of clinical symptoms and may herald the development of clinical disease.

11.3.1.1 Spirometry

Spirometry is the measurement of airflow during a maximally forced exhalation. The subject breathes through a mouthpiece connected to a pneumotachometer while wearing noseclips. After inhalation to total lung capacity, the subject is coached to exhale rapidly and forcefully until the lungs have emptied. The test does require the ability to cooperate with the technician. This is commonly expected after age 6, although children as young as 4 have been able to perform spirometry with practice and normative data does exist even for very young children [11].

The test is informative because airflow rates are inversely proportional to the fourth power of the radius of the airway; therefore, even minimally obstructed airways result in greatly reduced airflow rates. Indeed, the hallmark of obstructive lung diseases (such as asthma, obliterative bronchiolitis, and chronic GVHD [108]) is reduced airflows. Properly performed tests are very repro-

ducible within subjects, making them useful for assessing response to treatment over time.

Several parameters can be calculated from these maneuvers. First, the total exhaled volume is termed the forced vital capacity (FVC). The volume exhaled in the first second is termed the FEV₁. The airflow rate between 25 % of the exhaled volume and 75 % of the exhaled volume is termed the FEF_{25-75 %}. The pattern of these parameters can suggest an obstructive defect or a restrictive defect. Specifically, a reduced FEV₁ and FEV₁/FVC ratio may suggest an obstructive defect, while a reduced FVC and normal FEV₁/FVC ratio may suggest a restrictive defect. However, measurement of lung volumes is required to accurately diagnose restrictive disease. To complicate matters, some patients can have both obstructive and restrictive defects.

If an obstructive defect is documented, reversibility can also be assessed utilizing spirometry. Following administration of the bronchodilator (e.g., albuterol), testing is repeated after 15–20 min. Commonly, a 12 % increase in the FEV₁ is considered indicative of a significant response.

11.3.1.2 Lung Volumes

Disease states that affect lung growth would be expected to alter lung volume in addition to airway caliber. These diseases include pulmonary hypoplasia or space-occupying lesions (e.g., lymphoma), bronchopulmonary dysplasia, and, specifically to children and young adults, conditions that alter the growth of the rib cage (thoracic dystrophies and radiation to the chest wall).

Restrictive lung disease is defined by the presence of reduced lung volume, which can be measured utilizing a dilution technique and, more commonly, plethysmography (Fig. 11.3). Both techniques are typically used to measure resting lung volume or functional residual capacity (FRC). A lung capacity is the sum of two or more lung volumes; in the case of FRC, it is the sum of residual volume (RV, the amount of gas remaining in the lung after a maximal exhalation) and expiratory reserve volume (ERV, the amount of gas exhaled from resting lung volume until the lung is empty). In combination with spirometry,

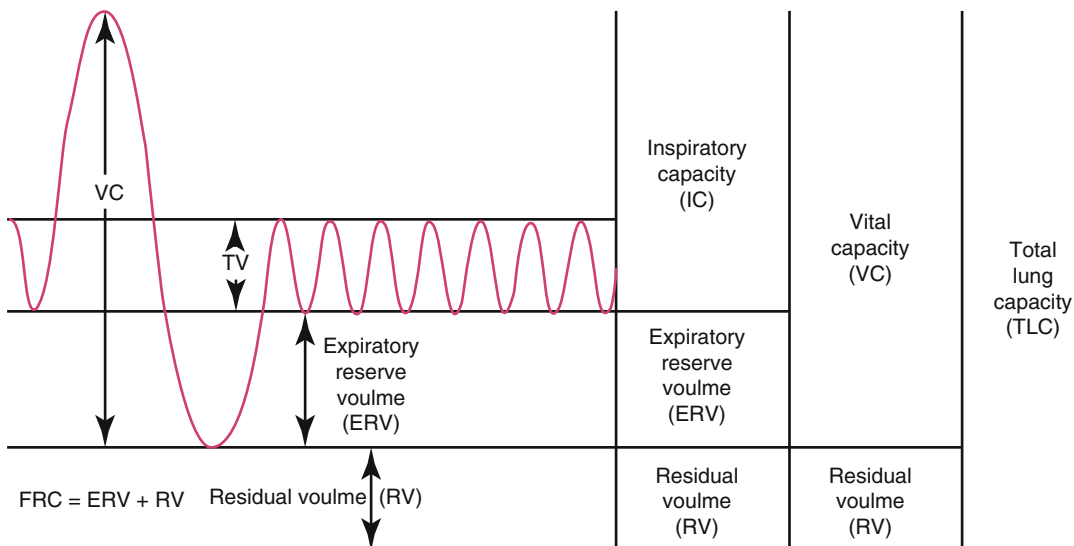


Fig. 11.3 Lung volumes (From Gibson [46])

other lung volumes and capacities can be calculated: total lung capacity (TLC) = RV + FVC.

Plethysmography utilizes the principle of Boyle's Law, i.e., in a closed system, pressure and volume change inversely when temperature is constant. With the subject sitting in a fixed volume chamber ("body box") and breathing on a mouthpiece, a shutter is closed in the inspiratory limb of the breathing circuit. The subject makes continued respiratory efforts, resulting in small changes in the volume of the lung and corresponding inverse volume changes in the box. Pressures in the box and at the mouth are measured, and this allows for calculation of the lung volume at which the panting efforts began. The subject usually begins the maneuvers at the end of a breath, and this "resting" lung volume is termed FRC. Younger children may have difficulty with the maneuver.

The pattern of lung volumes can also assist in diagnosis. Typically, patients with obstructive diseases (including obliterative bronchiolitis) will have an increased RV, especially as a fraction of total lung capacity (RV/TLC). The TLC may be normal or elevated. In contrast, low lung volumes are the hallmark of restrictive lung disease, and these patients will have a reduced TLC and RV.

11.3.1.3 Diffusing Capacity

The diffusing capacity for carbon monoxide (D_LCO) is an integrative measurement that describes the transfer of carbon monoxide (as a surrogate for oxygen) from the alveolus into the red blood cell. This transfer is proportional to the surface area of the alveolar/capillary membrane and the pressure gradient for oxygen between the alveolus and the blood and inversely proportional to the thickness of the alveolar-capillary membrane. The measurement depends on the fact that CO is more soluble in blood than in lung tissue because it binds much more rapidly and tightly to hemoglobin in the blood. Thus, the partial pressure of CO in the blood remains very low, which maintains a diffusion gradient for the gas.

In the single-breath technique for measurement of D_LCO , the patient exhales completely to residual volume and inhales to total lung capacity a gas mixture 0.3 % carbon monoxide and an inert gas (usually helium or methane). The subject holds their breath for 10 s during which CO diffuses into the blood. The uptake of CO (in ml/min) is divided by the partial pressure gradient for CO (between alveolus and pulmonary capillary) to calculate D_LCO (ml/mmHg/min). Alveolar ventilation is calculated from the inspired and expired concentrations of the inert gas, and this is used to calculate a dilution factor

for the inspired CO concentration and to normalize the D_LCO according to lung volume in which the CO is diluted (D_LCO/VA in ml/mmHg/min/L). The measurement should be adjusted for the patient's hemoglobin and, if present in significant amounts, carboxyhemoglobin. The measurement assumes a negligible concentration of carboxyhemoglobin, which may not be true in the presence of hemolysis [100]. Younger children, and subjects with significant restriction or dyspnea, may have difficulty cooperating with this testing. In these patients, oxyhemoglobin desaturation with activity or exercise would be suggestive of diffusion impairment.

Diseases that decrease the surface area for diffusion (emphysema, pulmonary emboli, resection of lung tissue) or diseases that increase the thickness of the alveolar–capillary membrane (fibrosis, pulmonary edema, proteinosis) would both decrease the diffusing capacity of the lung. Increased D_LCO is much less common but can be seen in patients with alveolar hemorrhage (hemoglobin in the airspace appears to make uptake of CO very high), polycythemia, or during exercise (via recruitment of more pulmonary capillaries). This test may be useful in evaluating patients with diffuse lung diseases or assessment of patients with pulmonary vascular obstruction.

11.3.1.4 Musculoskeletal Strength

The respiratory muscles (including the diaphragm, intercostals muscles, and others) contract intermittently 24 h per day to perform the work of ventilation. Many diseases can affect the strength of these muscles, putting patients at risk for hypoventilation, impaired airway clearance of secretions, and respiratory insufficiency. These conditions include primary muscular disorders, conditions affecting nerve transmission to the muscles (neuropathies, including vincristine toxicity), malnutrition, and stretch of the muscles beyond their optimal length–tension relationship (which can occur in hyperinflation). Additionally, bone development is critically important. As noted previously, radiation to the chest wall and certain systemic agents can likewise affect pulmonary function.

Typically, maximal expiratory pressure (MEP, $P_{E\max}$) is measured by having the subject inhale maximally to TLC and blow out as hard as

possible into a mouthpiece connected to a pressure transducer and with an occluded distal end. Similarly, maximal inspiratory pressure (MIP, $P_{I\max}$) is measured by having the subject exhale completely to RV and inhale rapidly against the occluded tube. Usually several repeated maneuvers are required to elicit the maximal effort.

11.3.1.5 Pulmonary Function Tests in Infants

Most of the tests described above have been adapted to infants, with the obvious challenge being that maximal efforts cannot be elicited voluntarily. Infants and toddlers are usually sedated and placed supine with a mask over mouth and nose to measure airflow and pressure at the mouth. These techniques require specialized equipment and expertise not available in all pulmonary function laboratories.

The raised volume rapid thoracic compression technique is one method that has been used to generate maximal expiratory flow by applying a positive pressure externally to the chest. This involves a plastic jacket that encircles the chest and abdomen of the sedated, supine infant and a face mask over the mouth and nose to measure flow. The infant's lung is first inflated to a predetermined pressure (typically 30 cm H_2O), resulting in an end-inspiratory lung volume close to total lung capacity. From this raised lung volume, the jacket encompassing the chest is rapidly inflated from a pressure reservoir, generating a full expiratory flow–volume curve.

Another technique, which is less commonly available, is the forced deflation technique. This involves using a negative pressure (vacuum) to deflate the lungs after an inflation to total lung capacity. This technique is only used in anesthetized, intubated patients. It is a relatively quick and reproducible test that can be accomplished at the time of other operative procedures (central line placement, bone marrow aspiration, etc.).

Lung volumes can also be measured by plethysmographic methods. The infant is placed within a rigid, airtight, plexiglass plethysmograph. The infant breathes through a face mask connected to an airway pressure gauge and a pneumotach to measure flow and volume.

A shutter within the face mask can briefly occlude the infant's airway; continued respiratory efforts alternately compress and rarify the gas within the lung, and Boyle's Law is used to calculate FRC as it is in older children.

Tests to measure diffusing capacity have been adapted to infants [19], although no commercially available equipment is available for this purpose. This is unfortunate, as these measures might be the most sensitive tests to detect early, primarily interstitial, pulmonary toxicity that would precede development of restrictive disease.

Nuclear Medicine Tests To evaluate therapy-induced pneumonopathy, qualitative and quantitative radionuclide studies, consisting of perfusion studies, ventilation studies, gallium scans, and quantitative ventilation/perfusion scintigraphy, have been utilized in some institutions. These nuclear studies have been primarily for research interests and have not been routinely applied to the clinical management of patients.

Laboratory Tests of Serum or Blood Erythrocyte sedimentation rate (ESR) has been evaluated as a potential early marker of pulmonary toxicity from bleomycin [60]. The nonspecific nature of this value may make clinical application difficult, as increases in ESR would also be expected in infection or recurrent disease. Despite the identification of these clinical contributing factors, research has tended to focus on the development of a reliable and simple diagnostic laboratory test that could predict the risk of post-radiation pneumonitis and, in particular, could be administered prior to the start of therapy.

There is a need for early biochemical markers of normal tissue damage that would predict late effects and that would allow the radiation oncologist and medical oncologist to determine whether their treatment is exceeding normal tissue tolerance [126]. If biochemical markers of tissue damage could be detected in the subclinical phase, prior to the accumulation of significant injury, one could terminate therapy or institute treatment to prevent or attenuate later lesions. An ideal marker would be a simple, reproducible,

biochemical test. In the recent years, some circulating cytokine markers have been independently found to be potential predictors of radiation pneumonitis. These include proinflammatory cytokines interleukin-1 α (IL-1 α) and interleukin-6 (IL-6) [25, 26], fibrotic cytokine-transforming growth factor β (TGF- β) [4], and ICAM [65]. Chen and colleagues tested the ability of IL-1 α and IL-6 measurements to predict radiation pneumonitis [23]. The predictive power of IL-1 α and IL-6 appeared to be strongest for the blood samples collected prior to radiotherapy than during RT. While both inflammatory cytokines can serve as diagnostic testing tools, IL-6 was found to be a more powerful predictor than IL-1 α of radiation pneumonitis. The specificity and positive predictive value of IL-6 were as high as 80 % for the blood samples collected prior to RT. The application of these cytokine markers in the predictive diagnosis of radiation pneumonitis may prove to have clinical utility in the near future and deserves further investigation.

In addition to cytokines, the release of many substances into the circulation could reflect and may also predict the degree of RT and chemotherapy injury to the lung. These include the surfactant apoprotein, procollagen type 3 angiotensin-converting enzyme, blood plasminogen-activating factor, and prostacyclin. These various substances have been correlated with either acute or delayed radiation-induced pneumonopathy. Significant additional work is required to evaluate the usefulness of such blood level measurements.

11.4 Management of Established Pulmonary Toxicity Induced by Cytotoxic Therapy

Hopefully in the future, pulmonary toxicity will be prevented rather than managed. Strict attention should be paid to drug doses and cumulative drug-dose restrictions. When RT is given, volumes and doses should be minimized and given in accordance with accepted tolerance. During drug therapy, monitoring of symptoms and signs, PFTs, and chest radiographs can aid in detecting

problems early, and the causative agent can be withdrawn. After bleomycin withdrawal, early stages of bleomycin-induced pneumonitis have clinically and radiographically reversed [89].

11.4.1 Precautions for Minimizing Potential Complications

Assessing baseline pulmonary function prior to therapy is important and especially so for patients with underlying pulmonary pathology such as lung disease of prematurity, chronic obstructive pulmonary disease, and idiopathic lung fibrosis. The detection of abnormalities may allow for better anticipatory guidance and counseling. Counseling on the risks of smoking and environmental tobacco smoke exposure is imperative for these patients, even in the absence of symptoms or abnormalities on evaluation. Patients should also be aware of the potential risks of general anesthesia and notify physicians of their treatment history if they are to undergo anesthesia. For those with compromised lung condition, therapy should be tailored to minimize injury from cytotoxic agents and radiation damage. When following survivors of cancer, vigilant evaluation of symptoms of respiratory compromise is necessary and should be anticipated when thoracic RT or drugs with known pulmonary toxicity have been used. Depending on the findings and other circumstances, lung biopsy may be considered to confirm fibrosis or exclude the recurrence of cancer. Chronic cough, dyspnea, or change in exercise should be further evaluated with chest radiography and PFTs. This is also imperative in patients scheduled for general anesthesia. In the absence of symptoms, chest radiographs and lung function testing are recommended every 2–5 years. The number of potential pulmonary toxic agents, the cumulative doses, and the radiation dose and field size are all factors to be considered in setting follow-up intervals.

11.4.2 Preventative Therapy

The difficult issue in screening is that there is no definitive therapy. Before therapy, the prophylac-

tic administration of steroids has no proven benefit and may present potential risks. A study of inhaled fluticasone propionate, however, demonstrated some potential benefit with reduction of acute pneumonitis in patients treated for breast cancer [91]. Confirmation of this benefit and whether like interventions can reduce long-term pulmonary sequelae requires further study. The role of amifostine as a radioprotector in preventing lung toxicity has been investigated. Amifostine is a sulfhydryl compound that was originally developed as an agent to protect against ionizing radiation in the event of nuclear war [31, 133]. It was also found to protect normal tissues from toxicities of radiotherapy for head and neck tumors [17], alkylating agents, and cisplatin [161, 166]. Recent clinical studies have shown a reduction in pneumonitis using amifostine in chemoradiation treatments for lung cancer [5, 73]; however, further investigation is required until its use becomes standard clinical practice.

There is a lack of studies quantifying the impact of smoking after exposure to chemotherapy and radiation therapy, but it very likely increases the risk of lung damage. In the Childhood Cancer Survivors Study (CCSS), survivors smoked at lower rates than the general population, but more than a quarter reported a history of having ever smoked, and 17 % reported currently smoking [39]. Smokers who responded to the study expressed a higher desire to quit than the general population. Interventions have been developed and studied to decrease smoking and improve smoking cessation in long-term survivors [38, 153]. Similarly, parents and caregivers of children with cancer should be encouraged to avoid exposing their children to environmental tobacco smoke.

Viral respiratory infections can cause significant morbidity in patients with established lung disease. Hand hygiene can help decrease the spread of viral pathogens, and influenza vaccination should be encouraged in non-immunosuppressed patients. Passive immunoprophylaxis against respiratory syncytial virus (with palivizumab) is also available for young children at high risk of pulmonary complications with this infection.

11.4.3 Therapy for Established Toxicity

Corticosteroids play a useful role in the relief of symptoms from pneumonitis caused by a variety of drugs and RT. Severe symptoms necessitating treatment can be relieved markedly and rapidly by corticosteroids in half of affected patients [95, 163, 164]; however, prevention or reversal of the fibrotic phase does not occur. Supportive care with bronchodilators, expectorants, antibiotics, bed rest, and oxygen can be beneficial for relief of symptoms in pneumonitis and fibrosis. In cases of radiation or chemotherapy-induced pneumonitis in which corticosteroids have been used, it is important to withdraw steroids very slowly to avoid reactivation. Patients with very significant restriction (vital capacity <30 % predicted) or diffusion impairment are at increased risk for hypoxemia and may require supplemental oxygen. In addition, they may demonstrate evidence of hypoventilation and in some cases may benefit from noninvasive ventilation.

11.5 Future Studies

We have come to appreciate the complexity of interstitial pneumonitis from cancer therapy, now seen as a process involving an active communication and interaction between resident cell types of the lung parenchyma and circulatory immune and inflammatory cells. There is increasing evidence of immune cells augmenting pneumonitis through complex autocrine, paracrine, and systemic regulatory mechanisms critically orchestrated by cytokines [24, 129].

Further investigation of the molecular mechanisms involved in pneumonitis and fibrosis will allow for timely intervention and proper protection. Interferons and other cytokines that oppose or inhibit fibrosis-promoting growth factors potentially may be used during therapy, resulting in the desired enhanced therapeutic ratio. Chemoprotective agents are being investigated for their ability to reduce the toxicity of chemotherapy, including lung injury. It is essential, of course, that they do not disturb the efficacy of the

treatment. Improvement of radiotherapy targeting and normal tissue sparing, such as three-dimensional conformal radiotherapy and intensity-modulated radiotherapy (IMRT), will minimize radiation to nontarget normal lung tissue. Novel interventions, such as mechanisms to increase the level of bleomycin hydrolase in susceptible patients or viral-mediated transfer of a bleomycin resistance gene, may hold promise for future applications in clinical treatment. What may prove to be the most important is the recognition of those at enhanced risk for long-term pulmonary toxicity as a result of their genotype. Understanding of such risk factors could lead to therapy tailored to an individual risk profile.

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