Antonio M. Esquinas · S. Egbert Pravinkumar
Ayman O. Soubani *Editors*

Mechanical Ventilation in Critically Ill Cancer Patients

Rationale and Practical Approach

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Editors
Antonio M. Esquinas
Intensive Care and Non Invasive
Ventilatory Unit
Hospital Morales Meseguer
Murcia, Spain

Ayman O. Soubani
Wayne State University School of Medicine
Detroit, Michigan, USA

S. Egbert Pravinkumar
Division of Anesthesiology and
Critical Care
The University of Texas
M.D. Anderson Cancer Center
Houston, Texas, USA

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To all our patients, to whom we will always owe at least a little hope

Preface

Survival of critically ill cancer patients admitted to intensive care unit (ICU) for management of acute deteriorations related to underlying malignancy, infections, and treatment-related organ dysfunctions is improving worldwide. In particular outcomes of cancer patients receiving mechanical ventilator support have improved given the timely optimal diagnostic and therapeutic management of critically ill cancer patients with respiratory failure. Advances in the care of deteriorating organ functions in cancer patients, early recognition of acute clinical decline and admission to ICU, use of rapid response teams, and clinical practice algorithms play an important role in the positive outcome of these patients. Furthermore, advances in ventilator support devices, aggressive structured and standardized weaning from mechanical ventilation and intravenous sedatives, use of noninvasive mechanical ventilatory support, and education of health care providers have significantly contributed to the improved survival of cancer patients in the ICU.

This book is focused on the care of cancer patients in the ICU given the increased incidence of cancer and related critical illness. Experts from various countries have contributed to the development of this book by sharing their expertise in their specific area of practice. The book provides an in-depth understanding of the rationale and practice of mechanical ventilatory support in critically ill cancer patients. The book is unique in that it has an international panel of experts focused in the clinical care of cancer patients with critical illness.

The lack of a wider international perspective on ventilatory support in cancer patients triggered the need for this textbook. The chapters are structured in such a way that the reader would appreciate the different aspects of ventilator support such as pre-ICU support, types of ventilatory support, and postoperative ventilatory support. Chapters on ICU end-of-life care, withdrawal of mechanical ventilator support, and health care cost/resource utilization have been included to provide the reader a realistic and wider perspective of ventilatory support for cancer patients.

The book will aid in acquiring knowledge and understanding of ventilatory support for critically ill patients with both solid and hematological malignancies. Coordinating the creation of a book with international authors, like this book, is of no easy task; nevertheless, it has resulted in compilation of knowledge from international authors for a broader view in the management of critically ill cancer patients. We hope that the reader would find this book not only interesting but as a resource of practical knowledge.

The editors would like to acknowledge the willingness of these experts in sharing their experience and knowledge in this area. We would also like to thank Ms. Madonna Samuel and Andrea Ridolfi with Springer Publishing Group for their support throughout the process.

Murcia, Spain — Antonio M. Esquinas
Houston, TX, USA — S. Egbert Pravinkumar
Detroit, MI, USA — Ayman O. Soubani

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Part I

Background and Therapeutic Procedures in Critically Ill Cancer Patients

Epidemiology of Mechanical Ventilation and Acute Respiratory Failure in Cancer Patients

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Dulce Apolinário

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ICU	Intensive care units
NIV	Noninvasive mechanical ventilation
TRALI	Transfusion-related acute lung injury

1.1 Introduction

The number of cancer patients has increased over the last decades, as a result of survival gains achieved by intensive treatments, with an estimated prevalence for 2012 of 32.6 million persons alive who had been diagnosed with cancer in the previous 5 years [1].

With the improved survival of these patients, the complications associated with the oncologic disease and its treatment have also increased, being the lung the organ most frequently involved, resulting in respiratory failure [2].

This chapter reviews the epidemiology and major causes of acute respiratory failure (ARF) in adult patients with malignancies requiring ventilatory support.

D. Apolinário
Resident, Pulmonology Service, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal
e-mail: dulce.apolinario@sapo.pt

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1.2 Discussion and Analysis of the Main Topic

1.2.1 Acute Respiratory Failure in Cancer Patients

Cancer-related complications or treatment-associated side effects can lead to lung damage that can result in respiratory failure [2].

ARF requiring mechanical ventilation is a leading cause of admission to intensive care units (ICU) for patients with malignancies, who are actually more often admitted to the ICU for respiratory complications than the other ICU patients [3]. The frequency of ARF ranges from 5 to 50% in patients with hematologic and solid malignancies and from 42 to 88% among hematopoietic stem cell transplant recipients [2, 4].

This condition has a poor outcome in cancer patients, with high mortality rate, mainly in patients with ARF requiring mechanical ventilation. In patients with hematologic and solid malignancies who require mechanical ventilation, the mortality is 50% and 75%, respectively [2]. Among hematopoietic stem cell transplant recipients requiring mechanical ventilation and ICU admission, the mortality rate is approximately 85% [2]. Notwithstanding, this clinical scenario has changed in the late years, and improved survival rates have been reported: in a Sepsis Occurrence in Acutely Ill Patients substudy, the outcome of patients with solid cancer was similar to ICU patients without cancer, with ICU mortality rates of 20% and 18%, respectively [3]; still, patients with hematological cancer had a worse outcome with the highest hospital mortality rate (58%) [3]. Investigators attribute the increased survival to advances in oncology, hematology, and critical care, in conjunction with more appropriate selection of cancer patients for ICU admission [2, 4].

Various infectious and noninfectious causes, both by complications of the own cancer and by side effects associated with the therapies, can lead to ARF in these patients [2].

1.2.1.1 Infectious Causes

Cancer patients have an increased risk of pulmonary infections due to defects in humoral and/or cell-mediated immunity, neutropenia, use of immunosuppressant drugs, higher risk of aspiration, frequent exposure to antibiotics, and prolonged hospitalizations [2]. The pulmonary infections are the most frequent cause of ARF in patients with cancer, especially in those with severe comorbidities, underlying hematologic malignancies or those undergoing chemotherapy [2, 4].

The majority of pneumonias have bacterial etiology (47%), being the most frequently documented pathogens the gram-positive cocci (40%), like *Streptococcus pneumoniae* (20%), other streptococci (12.5%), and *Staphylococcus aureus* (7.5%); gram-negative bacilli (49%) such as *Escherichia coli* (10%), *Enterobacter cloacae* (10%), Klebsiella pneumonia (4%), *Pseudomonas aeruginosa* (16%), and *Haemophilus influenza* (4%); gram-negative cocci (1%) including *Neisseria sp.* (1%); and intracellular bacteria (10%) like *Legionella pneumophila* (5%), *Mycoplasma pneumonia* (2.5%), *Coxiella burnetii* (1%), and *Chlamydia pneumoniae* (1%) [5].

Opportunistic pulmonary infections are also common in these patients (31%), such as invasive pulmonary aspergillosis (31%), respiratory viral infections (28%), *Pneumocystis jirovecii* pneumonia (27.5%), tuberculosis (5%), mucormycosis (4.5%), *Cytomegalovirus* infection (1.5%), fusariosis (1.5%), *Scedosporium* sp. infection (1%), and *Toxoplasma gondii* infection (1%) [5]. Fungal pneumonia is more frequent in the setting of prolonged neutropenia, corticotherapy, broad-spectrum antibiotherapy, or underlying leukemia or lymphoma [2]. Community respiratory viruses have also been recognized as a cause of pneumonia among hematopoietic stem cell transplantation recipients and patients with hematologic malignancies, more frequently the influenza (33%), respiratory syncytial (31%), and parainfluenza (27%) viruses [6].

The infections are also the major cause of primary acute respiratory distress syndrome (ARDS) in patients with cancer (65.9%), including bacterial infection (58%) and invasive fungal infections (42%), such as invasive pulmonary aspergillosis and *Pneumocystis jirovecii* pneumonia [7]. In patients with septic shock, secondary ARDS can also occur (22.4%) [7].

1.2.1.2 Noninfectious Causes

Although the noninfectious etiology of ARF in cancer patients is less frequent, with values around 22%, and only 7.6% in the subgroup of patients with ARDS, there are numerous causes for it, and the most frequently described findings are pulmonary edema (49%) and pulmonary infiltration by the malignancy (49%) [5, 7].

One of the noninfectious causes is the decompensation of concurrent respiratory and cardiovascular diseases, which may lead to or worsen respiratory failure [2].

Another cause of ARF in these patients is the transfusion-related acute lung injury (TRALI), which usually manifests itself as lung noncardiogenic pulmonary edema in the sequence of blood product transfusion [2].

Antineoplastic agent-induced lung injury is a major problem for cancer patients having a broad spectrum of manifestations (bronchospasm, hypersensitivity reactions, lung fibrosis, diffuse alveolar hemorrhage, acute interstitial pneumonitis, ARDS, capillary leak syndrome, and organizing pneumonia) [2, 4]. In patients who have previously received radiation to the chest, radiation-induced lung injury may occur and is manifested by an early acute phase in the form of pneumonitis (radiation pneumonitis) and a late phase of pulmonary fibrosis [2].

Venous thromboembolism, manifested as either deep venous thrombosis or pulmonary embolism, is a frequent cancer-related medical disorder, present in about 7.8% of patients hospitalized with cancer, especially with advanced malignancies, renal carcinoma, pancreatic, gastric, and brain tumors [8].

In thrombocytopenic patients with acute or chronic leukemia or multiple myeloma, and in recipients of hematopoietic stem cell transplantation, alveolar hemorrhage is also a frequent cause of respiratory failure [2].

The paraneoplastic syndromes, such as myasthenia gravis, Lambert-Eaton myasthenic syndrome, or Guillain-Barré syndrome, can cause respiratory failure due to respiratory muscle weakness, as well as upper airway compromise caused by weakness of the facial, oropharyngeal, and laryngeal muscles [2].

The disease own progression can lead to ARF by direct neoplastic involvement of the respiratory tract, resulting in upper or lower airway obstruction, or even to disseminated parenchymal disease or lymphangitis [4].

In patients undergoing thoracic cancer surgery, ARF may also occur postoperatively due to atelectasis, pneumonia, pulmonary edema, and development of bronchopleural fistula [2].

1.2.2 Mechanical Ventilation in Cancer Patients

Many cancer patients with ARF need mechanical ventilation support, with frequencies of 62.2% in solid tumors and 69.6% in hematological cancers [3]. The identified risk factors for invasive mechanical ventilation in subjects with malignancies admitted for ARF are respiratory disease severity (oxygen flow required and number of quadrants involved on chest x-ray) and hemodynamic dysfunction at ICU admission [9].

Although the prognosis of these critically ill patients is disappointing, especially if they require endotracheal intubation, it is demonstrated that half of the cancer patients with good performance status and nonprogressive disease requiring ventilator support survive, so they should receive full intensive care [10].

In the last years, noninvasive mechanical ventilation (NIV) has been increasingly used as an alternative to invasive ventilation, as it has the benefits to reduce the infectious complications in patients affected by hematologic cancers or those with immunosuppressant drugs, avoid intubation-related trauma, enhance patient comfort, and reduce the need for sedation [2, 4]. Nonetheless, NIV has to be used in appropriate situations because its failure has been associated with increased mortality [4]. NIV may also be a reasonable option in cancer patients with respiratory failure who have refused endotracheal intubation or have a "do not intubate" order [2].

1.3 Conclusion

ARF is frequent in cancer patients due to cancer-related complications and treatment-associated side effects. Various etiologies can lead to ARF in these patients, conducting to diagnosis and management challenges. The pulmonary infections are the most frequent causes, but many noninfectious causes are described, such as decompensation of concurrent respiratory and cardiovascular diseases, pulmonary drug toxicity, radiation-induced lung injury, TRALI, antineoplastic agent-induced lung injury, venous thromboembolism, alveolar hemorrhage, paraneoplastic syndromes, disease progression with airway obstruction, disseminated parenchymal disease or lymphangitis, and complications of thoracic cancer surgery.

Regardless of the cause, ARF is a severe condition and frequently requires ventilatory support and ICU admission. It is still associated with a poor outcome and high mortality, despite the general improved outcome over the last decade.

1.4 Key Major Recommendations

- ARF remains a frequent and severe complication in cancer patients. Despite most of the times being of infectious origin, there are many other possible causes, the knowledge of its epidemiology and main etiologies being essential.
- Many cancer patients with ARF will need mechanical ventilation support and ICU admission.

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Breathlessness in Advanced Cancer Patients: Protocols and Recommendations

2

Manuel Sánchez Cánovas, Juan Gutiérrez Mejía, Alberto Carmona Bayonas, and Paula Jiménez-Fonseca

2.1 Introduction: Definition and Epidemiology

Breathlessness and dyspnea are common terms used to describe a conscious, unpleasant, intense, and frightening experience related to shortness of breath. Patients describe breathlessness as suffocating, choking, or tightness of breath. It can be described along three dimensions: (1) air hunger, a need to breathe while being unable to increase ventilation; (2) effort of breathing, physical tiredness associated with breathing; and (3) chest tightness, feeling of constriction and inability to breathe in and out [1, 2].

This is a frequent and distressing symptom in cancer patients; however, it is often overlooked [3]. In fact, for many people, breathlessness is tolerated and sublimated, and there is evidence of massive underreporting of the symptom [4].

Thus, epidemiological data is unlikely to reflect objectively much information. Although the case series are heterogeneous, depending on the baseline characteristics of patients and tumors, it may be present in around 20–40% of cancer patients at the diagnosis of advanced disease, with symptoms prevalence reaching 70% in the last 6 weeks of life. Therefore, breathlessness is the second most common reason for starting palliative sedation.

There is no correlation between objective measurements of dyspnea and the experience of breathlessness perceived by the patient. It is a personal subjective

M.S. Cánovas • A.C. Bayonas
Hematology and Medical Oncology Department, Hospital Universitario Morales Meseguer (Murcia), Calle Marqués de los Vélez s/n, Murcia, Spain

J. Gutiérrez Mejía, M.D., M.H.Sc. (Bioethics) (✉)
National Institute of Medical Sciences and Nutrition, Salvador Zubiran, Mexico City, Mexico
e-mail: jgtzm@hotmail.com

P. Jiménez-Fonseca
Medical Oncology Department, Hospital Universitario Central de Asturias (Oviedo), Oviedo, Spain

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experience colored by social and physiological unique characteristics and shaped under cognitive, sensory, behavioral, and emotional components from each patient. This explains why breathlessness can only be correctly interpreted by sufferers.

On the other hand, the experience of caregivers who are looking after a patient with dyspnea is in general negative, exhausting, and abundant in extreme tension that gives place to poor sleep and anxiety. Thus, appropriate care of advanced cancer patients should also take into account carers' needs and well-being. Recently the term "total dyspnea" has being proposed in consideration of the complexity of the symptom and its multiple dimensions affecting all domains of quality of life (e.g., emotional, functional, social, spiritual, etc.) because of their deep consequences [1, 5].

2.2 Etiology and Pathogenesis

Breathing is autonomously regulated at the respiratory centers located in the medulla and pons, triggered by specialized neuron networks under the major influence of the partial pressure of carbon dioxide (PCO_2) concentration and pH at the surrounding cerebrospinal fluid. Higher level of control is found at the motor cortex, which allows for transient voluntary changes of breathing patterns. The motor cortex interacts with the sensory cortex, integrating information of afferent receptors via the glossopharyngeal and the vagus nerve. Normally this information should be complementary and similar.

The origin of breathlessness experience is still matter of research. It is a consequence of a complex integration from multiple receptors along the respiratory and cardiovascular system at different neurologic levels [6]. There are several theories on the origin of dyspnea:

1. According to the corollary discharge theory, a copy of the respiratory commands is sent from the motor to the sensory cortex, informing other regions of the brain of the respiratory pattern and producing conscious awareness of the respiratory effort.
2. Dyspnea may also arise by the existence of mismatch between the output of the respiratory controllers, in the motor cortex and afferent signals arriving from the lungs and chest wall receptors that gauge the response of the effector ventilator pump, which is mediated through the phenomenon called efferent-reafferent dissociation.
3. The experience may also be directly provoked by mechanoreceptors and chemoreceptors, centrally and peripherally, that influence the perception of "chest tightness and air hunger" [3], as follows:
   (a) Peripheral chemoreceptors located in the carotid and aortic bodies respond to the partial pressure of O_2 in arterial blood (PaO_2), PCO_2, and pH serum changes. Carotid chemoreceptors are more sensitive than aortic bodies to variations of these parameters.

(b) Skeletal muscles also have metaboreceptors that respond to increasing levels of tissue metabolites like lactate, produced during anaerobic metabolism. Exercise-induced dyspnea in normal individuals may be explained by this mechanism, independently of the occurrence of hypoxemia or hypercapnia.
(c) Receptors in the oral mucosa, nasal airway, and facial receptors at the sensitive territory of trigeminal nerves can be stimulated with airflow, so that their stimuli decrease breathlessness experiences and improve exercise tolerance in patients with chronic dyspnea.
(d) Other mechanoreceptors and chemical receptors have been detected at the lower airway, some represented by unmyelinated nerve endings (C-fibers) responding to irritant signals and bronchoconstriction, while others as stretch receptors from parenchymal zones sensitive to distention, and finally pressure receptors from the airway walls and alveolar walls (J receptors) combined with pulmonary vascular receptors responding to high vascular pressures have also been related to breathlessness.
(e) Chest wall receptors located in joints, tendons, and intercostal muscles decrease breathlessness when stimulated.

Functional brain image has shown the activation of neurologic areas in the anterior insula and posterior cingulate gyrus induced by breathlessness; these areas have been related with pain perception which may explain why opioids have an effect in the palliative treatment of dyspnea [7–9]. The most frequent cause of dyspnea in cancer patients would be the existence of a primary lung tumors or the existence of pulmonary metastases. However, the origin of this symptom may be varied:

1. Direct effect of cancer; this section encompass several pathogenic mechanisms:
   (a) Obstruction of the airway: it can be the result of a primary tumor, lymph nodes, or metastatic disease. However, breathlessness can also have its origin in the excess of secretions associated to some tumor subtypes or the infiltration of vocal cords.
   (b) Injuries of the lung parenchyma (tumor, infections, radiotherapy, etc.).
   (c) Vascular syndromes, such as symptomatic pulmonary embolism in immobilized patients or thrombogenic tumors, superior vena cava syndrome (especially in small-cell lung cancer or lymphoma), etc.
   (d) Pleural effusions (malignant mesothelioma or metastases from other sites).
   (e) Weakness of the respiratory muscles; secondary to cachexia, electrolytic alterations, or neuromuscular disease or paraneoplastic syndromes (e.g., Guillain-Barre, Eaton-Lambert syndrome, etc.).
   (f) Decrease in the chest wall distensibility, which could be secondary to massive ascites or visceromegaly. This is typical of hepatocellular carcinomas, peritoneal metastases (e.g., gastric tumors), or ovarian cancer.
   (g) Other possible causes that could be included within this group would be systemic alterations such as anemia, acidosis, and neuropsychiatric disorders (depression, anxiety disorders, etc.), which are very common in cancer patients.

2. Effect of antineoplastic therapy (iatrogenic adverse events):

   (a) Cancer therapy constitutes a potential cause for dyspnea; specifically, both radiotherapy and chemotherapy (e.g., bleomycin, gemcitabine, everolimus, anti-PD1, etc.) can provoke pneumonitis, pulmonary fibrosis, cardiopulmonary toxicities, anemia, venous thromboembolic disease, cachexia, etc. Serious adverse events can contribute to the onset of dyspnea or the worsening of the previous health status.
   (b) It is expected that novel, emerging antitumor strategies such as immunotherapy or other targeted therapies may become a sources of respiratory distress in the cancer population. Therefore, it will be a challenge to develop effective management algorithms for these new modalities. Further research in this field is required to unveil the underlying physiopathological mechanisms, in order to prevent and manage these complications efficiently.
   (c) Finally, aggressive surgical approaches for lung primary tumors and metastases (e.g., lobectomy, pneumonectomy, etc.) can be a source of residual breathlessness, particularly in patients with prior vulnerabilities or chronic respiratory comorbidities.

3. Other contributing factors:

Chronic comorbidities (e.g., chronic obstructive pulmonary disease, cardiovascular disorders, bronchial hyperresponsiveness associated with asthma, etc.) are common in oncologic patients due the coexistence of multiple risk etiologic factors and increases in average life expectancy. In certain groups of patients, they may constitute the main causes for the onset or exacerbation of dyspnea.

2.3 Breathlessness Management in Oncological Patient: Diagnosis and Treatment

Concerning the palliative management of dyspnea, two basic fronts should be addressed:

(a) The etiologic approach: dyspnea has many causes involving either the breathing airways and lungs or the cardiocirculatory system. If we can identify them, they could be tackled with a targeted treatment (e.g., anticoagulants for pulmonary embolism, antibiotics, corticoids, etc.).
(b) The symptomatic strategy: dyspnea is per se a very disabling symptom for all patients, calling for an immediate therapeutic attitude regardless of the underlying etiology.

Obviously these dichotomies are two sides of the same coin, so both therapeutics should be resolved and approached at the same time. The key to distinguish which one should constitute our starting focus of attention should be given by the patient, taking into account that a number of severity criteria exist that need to be identified in patients with respiratory distress: tachypnea, altered mental status, tachycardia, hemodynamic

instability, and use of accessory muscles. Patients' prognosis and the potential reversibility of the respiratory syndrome should also be promptly elucidated.

The presence of severity criteria would force us to begin supportive care rapidly and should not lead to a delay in the establishment of palliative care management in these patients. This will not only impact on quality of life and anxiety, but it will also subsequently facilitate the realization of the necessary etiological studies.

In contrast, a patient who is apparently out of danger, and in situation of no severity, will mainly benefit from the identification of a causative factor to better target his treatment, without exempting us from controlling the symptoms that might present.

2.3.1 Etiologic Approach to Management

In general, the idiosyncrasy of cancer should not constitute an obstacle for the correct assessment in dyspneic patients. It is true that the differential diagnosis covers a wider range of possibilities in comparison with the general population, but the algorithm to follow does not include significant differences.

It will be crucial to evaluate the origin of our patient's dyspnea properly, since it will impact the management and outcomes in reversible conditions. Conducting a good anamnesis and thorough clinical examination will be the first step to identify the etiology and guide the subsequent workup. We show some examples in Table 2.1.

Table 2.1 Suggested workup in acute respiratory failure

Clinical findings	Diagnostic suspicion	Workup
Fever	Pneumonia	Chest X-ray
Sudden onset in immobilized subjects	Pulmonary embolism[a]	Computed tomography angiography
Abdomen distension	Ascites	Abdominal ultrasound
Unilateral auscultatory silence	Pleural effusions—pneumothorax	Chest X-ray
Facial and neck swelling	Superior vena cava syndrome	Chest CT scan
Normal oxygen saturation	Anxiety states	Not required
Neurological symptoms	Brain metastases	TC cerebral
Laryngeal stridor	Upper airway obstruction	Laryngoscopy
Wheezing	Bronchospasm	Chest X-ray (to discard associated complications)
Chemotherapy/radiotherapy	Pneumonitis	Chest X-ray
Lower extremity edema	Acute heart failure	Chest X-ray
Cachexia, other gastrointestinal complaints	Anemia, electrolytic alterations	Blood tests

[a]The risk of venus thromboembolism (VTE) is estimated to be fourfold higher in cancer patients compared with noncancer patients. VTE has been found to be an adverse prognosis factor in all stages of cancer [10]. In fact, it has been described as the second cause of death in cancer patients

Once we confirm each one of these diagnoses, management will be the specific for each entity. We would like to conclude this paragraph recalling that regardless the etiology and the requested workup, it could be essential for some patients to carry out an arterial gasometry in order to:

(a) Determine the severity of the event which has prognostic and therapeutic implications.
(b) Support the causative diagnosis of acute respiratory failure.

Of note, criteria for diagnosis of acute respiratory failure are based on laboratory and clinical findings. It is confirmed when the pressure of oxygen in arterial blood (PaO_2) is less than 60 mmHg, which is approximately equivalent to an arterial oxygen saturation of 90%, as measured by pulse oximetry.

Despite this approximate equivalence, pulse oximetry has a lower reliability in certain contexts in which it should not substitute an arterial blood gas analysis (serious anemia, jaundice, peripheral hypoperfusion, hypothermia, etc.) the former do not provide pH values or the partial pressure of carbon dioxide ($PaCO_2$), which is helpful in determining the origin of dyspnea, as displayed in Fig. 2.1.

There are some particular oncological fields whose management is essential to know in order to get better results in our patients:

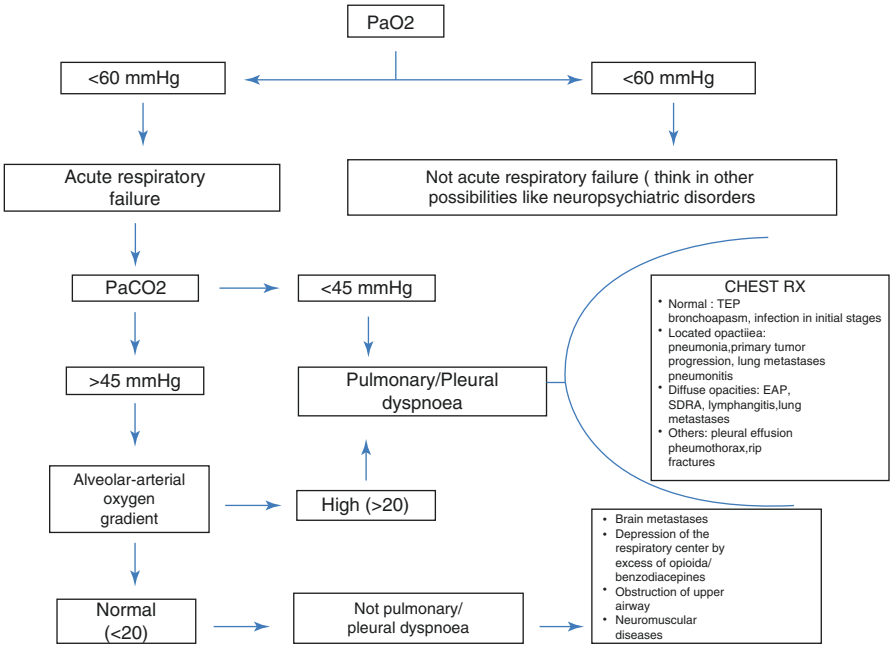

Fig. 2.1 Diagnostic algorithm for acute \ failure in cancer patients

2.3.1.1 Immunological Checkpoint Inhibition Agents (Targeting CTLA-4 and PD-1)

They are new therapeutic strategies whose use is increasing at different malignancies. This new group of medication is associated with immune-related adverse events. Examples related with breathlessness, have been described in sarcoidosis, organizing inflammatory pneumonia, or pneumonitis. The treatment of moderate (grade 2) or severe (grades 3–4) immune-related adverse events requires [11]:

- For patients with grade 2 toxicities, treatment with the checkpoint inhibitor should be withheld and should not be resumed until symptoms or toxicity is grade 1 or less. Corticosteroids (prednisone 0.5 mg/kg/day) should be started if symptoms do not resolve within a week.
- For patients experiencing grade 3–4 immune-mediated toxicities, treatment with the checkpoint inhibitor should be permanently discontinued. High doses of corticosteroids (prednisone 1–2 mg/kg/day) should be given. When symptoms subside to grade 1 or less, steroids can be gradually tapered over at least 1 month.

2.3.1.2 Bleomycin [12]

Bleomycin is associated with the four main types of pulmonary toxicities: subacute progressive pulmonary fibrosis, hypersensitivity pneumonitis, organizing pneumonia, and acute chest pain syndrome during rapid infusion. The risk appears to be higher in older patients and those with renal insufficiency.

Thoracic irradiation and concurrent administration of cisplatin at high doses may increase the risk. For patients with symptomatic pulmonary toxicity and evidence of impairment on pulmonary functions tests, the management consists in administration of systemic glucocorticoids (prednisone 0.75–1 mg/kg) and discontinuing bleomycin therapy.

2.3.2 Symptomatic Management

In patients with severe symptomatology or the aforementioned severity criteria, the control of the dyspnea becomes a fundamental objective. Before moving toward any etiologic management, the stabilization of our patient will be the priority. Cancer patients can decompensate for various reasons, similar to subjects with other chronic conditions.

Certain types of advanced cancer are not necessarily a synonymous of imminent death, and novel therapies are rapidly changing the landscape of tumors that were previously considered incurable. It is very easy to fall into the mistake of evaluating patients' health status and prognosis superficially which may consequently entail a definitive sedation or limitation of therapeutical effort.

There is also a debate on whether cancer patients are subsidiary to intensive care unit (ICU) admission or not. For a long time, an ICU admission has been denied to most patients with advanced tumors. Fortunately, this perception is beginning to change, and the label of a cancer diagnosis should not preclude the objective and accurate perception of the disease we are confronting.

It is mandatory to carry out a comprehensive assessment of the oncologic antecedents, including the evolution cancer, prognosis, possibilities of tumor control, etc., which should also entail the necessity of updating medical records with anticipated recommendations in case of acute respiratory failure. These anticipated orders as well as the presence of other chronic comorbidities and the acute baseline situation will help us to estimate medium-term prognosis and therefore to decide, in conjunction with the intensivists, whether an ICU admission is advisable. The basic clinical and laboratory criteria that would require an assessment by the ICU specialists include the following:

1. Shock or arterial blood pressure <90 mmHg
2. Severe dysfunction of two or more systems (including the respiratory)
3. Severe acidosis: pH < 7.25
4. PaO_2/FiO_2 ratio <200
5. Serious hypercapnia encephalopathy (Glasgow < 12)

Within the symptomatic management, we have three branches: the ventilatory support, non-pharmacological management, and pharmacological support.

2.3.2.1 Ventilatory Support

Oxygen therapy is recommended in hypoxemic patients with dyspnea [13]. There is no benefit of adding oxygen for cancer patients if they are not hypoxic. Hypoxemia is in general a weak stimulus for dyspnea. It is possible to obtain relief in symptoms associated with breathlessness by facilitating a flow through nasal prongs using room air, maybe as consequence of sensory stimulation. Because of the burdens in oxygen therapy and impact on patients and carers, initiation of this therapy should be clearly identified [14].

The venous blood gas and the patient's history will determine which type of oxygen therapy technique will be the most appropriate. It will be indicated always that hypoxemia is objectified by arterial blood gases:

(a) Nonspecific technique of oxygen therapy is a contraindication for patients who are not chronic CO_2 retainers (e.g., COPD), despite the existence of $PaCO_2$ elevations due to the acute respiratory disorder.
(b) Chronic CO_2 retainers that maintain high basal $PaCO_2$ must be ventilated with noninvasive mechanical ventilation (NIV), such as bi-level positive airway pressure (BiPAP) or even orotracheal intubation if the patients meet the criteria for ICU admission, because of the high risk of hypercapnic encephalopathy syndrome. Only consider intubation at the assumption of poor tolerance to BiPAP, high-flow nasal cannula oxygen therapy (4 L/min) or venturi masks (Ventimask) at (e.g., fraction of inspired oxygen (FiO_2) set at 35% and 6 L/min)

The increment on the complexity of devices for ventilatory support (nasal prongs, Ventimask, large-reservoir venturi masks, BiPAP, orotracheal intubation, etc.),

increasing the FiO_2, will rely on the SaO_2, as per the pulse oximetry (useful for monitoring and tracking).

High flow nasal cannula is suggested to be used early in patient's refractory to standard oxygen therapy with hypoxemia. Usually it is very well tolerated and allows patient to talk, eat, and avoid tight masks associated with NIV [13]. Noninvasive positive pressure ventilation such as BiPAP is indicated in patients with hypoxemia and hypercapnia, in which a substantial improvement is usually seen in the first hours. The success of this treatment is related with the "early" use and experience of the involved staff [15].

The clinical benefit of the BiPAP has been strongly demonstrated in different situations of dyspnea/acute respiratory failure, such as respiratory acidosis, advanced neuromuscular disease, immunocompromised patients, severe acute cardiogenic pulmonary edema, etc. Actually NIV has also a place in the palliation of patients at the end of life situations, by the following reasons:

(a) It reduces the ventilatory work facilitating breathing movements, by which the dyspneic sensation diminishes.
(b) NIV decreases the needs for opioids, which promotes a higher level of consciousness, which is usually regarded by palliative care teams as prerequisite for a good death, since it allows saying goodbye to loved ones.

2.3.2.2 Non-pharmacological Treatment

Non-pharmacological treatment is focused on cognitive, sensitive, emotional, and behavioral areas. This approach is based on models of symptom perception that establish stages of appraisal, from the interpretation of symptoms through patients' lens to the asignment of meaning according to their values, beliefs, previous experiences, expectations, motivations, and personality.

This type of treatment should be started early, if possible before the pharmacological options, and continued even when that medication has started. It is very important for the patient to have certain control over symptoms. Patient's experience is affected by the social context and behavior of others; this is the reason why relatives and other caregivers should be involved in the same educating process. Several interventions have been suggested, like:

(a) Sitting and using good posture; especially in this last point, patients should always acquire whatever position is more comfortable for them even against of what carers believe is a "better position." Pacing movements in a slower execution and dividing the job in several steps will help in symptoms control.
(b) Learning breathing strategies is very useful; one of the best techniques is pursed lip breathing that allows patients to increase tidal volume and vital capacity, improving the removal of CO_2, decreasing respiratory rate, and reducing hyperinflation, while improving dyspnea as a consequence [3, 16].
(c) Using a fan or opening a window, in order to produce a cold airflow that stimulates facial receptors in trigeminal territories.

2.3.2.3 Pharmacologic Support

Opioids are the main treatment of breathlessness in advanced cancer patients. They are usually used by oral or intravenous routes as the first option. However, studies looking for other possible routes of administration have been conducted. It should be noted the lack of efficacy observed for nebulized opioids. However the sublingual application seems to constitute an efficacious therapeutic option effective with fewer side effects in comparison with other systemic alternatives.

The mechanism of how opioids decrease breathlessness is not well known. Opioid receptors are localized at different levels of the cardiovascular, respiratory and central nervous systems. Opioids are safe when prescribed under a stepped incremental-reassessed dose guideline; their use helps to reduce the unpleasantness of dyspnea. Recommendations should be evaluated in an individual case-by-case approach and adjusted according to patient response; clinical judgment should always precede any treatment decision. Patients with prior chronic opioid treatment for pain may need different doses from that of opioid-naïve patients.

The adverse effects associated with opioid treatment include drowsiness, nausea, vomiting, and constipation compared with the placebo. Morphine is recommended over all other types of opioids, by oral or parenteral administration as the first option for symptom control. It should be used carefully in patients with severe renal insufficiency (Table 2.2).

Benzodiazepines have classically been considered as a therapeutic option for the control of dyspnea at the same level of opioids. Different clinical trials have made clear that this single-drug group is superior to opioid when the cause of dyspnea is neuropsychiatric, for example, in anxiety disorders [18]. Benzodiazepines cause more drowsiness in comparison with placebo, but less than with morphine. These results justify the consideration of benzodiazepines as a second line for refractory

Table 2.2 Opioid doses and administration in cancer patients with dyspnea

Clinical setting		
Naïve patients with mild dyspnea	Naïve patients with severe dyspnea	Patients with severe COPD (start at 50% of the above doses and titrate 25% every 24 h as needed)
Hydrocodone 5 mg orally every 4 h	Morphine sulfate 5 mg orally every 4 h	Increase baseline dose by 25–50% and reassess every 24 h [17]
Codeine 30 mg orally every 4 h	Oxycodone 5 mg orally every 4 h	Morphine regular opioid dose +1/6 of daily opioid intake
Morphine 2.5–5 mg/4 h orally and 1–2.5 mg /4 h subcutaneous	Breakthrough management considers an equivalent dose every 1–2 h	Hydromorphone regular opioid dose +1/6 of the daily opioid intake
Hydromorphone 1.3 mg/4 h orally or 0.2–0.5 mg/4 h subcutaneous	Titrate in increments of 50–100% every 24 h as needed	
Breakthrough management consider an equivalent dose every 1–2 h		

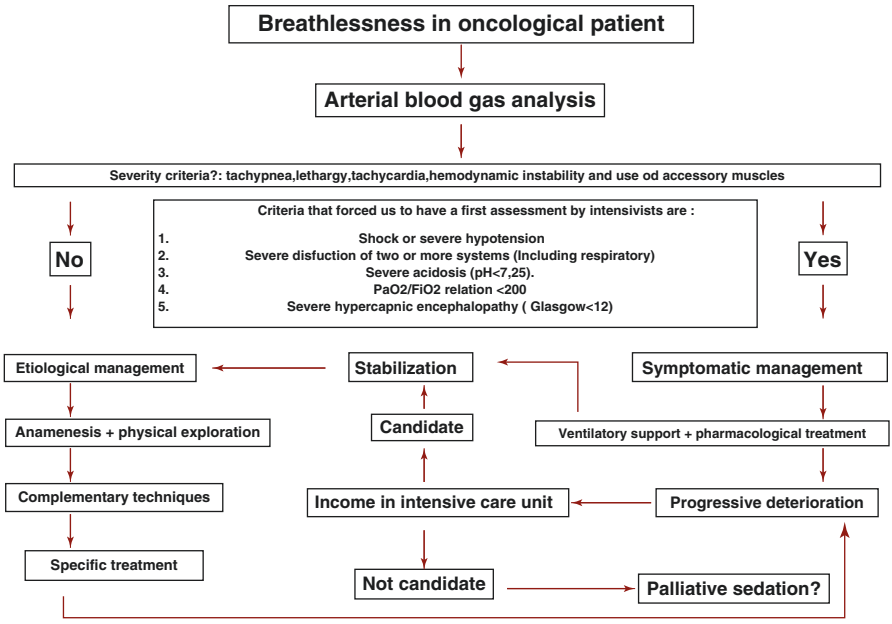

Fig. 2.2 Algorithm of management of dyspnea in oncological patient

symptoms, when opioids or other non-pharmacological measures have failed to control dyspnea. In fact, the combination of morphine with midazolam has shown good results in terminally ill patients.

Occasionally, it is erroneously believed that certain pharmacologic groups, such as bronchodilators, glucocorticoids, and diuretics, can be useful with regard to the control of dyspnea. This is only true in certain clinical scenarios (e.g., diuretics for pulmonary edema, corticoids in bronchospasm, etc.). For patients in the end of life that are not expected to benefit from any of these therapies, the use of palliative sedation provides relief of dyspnea; before considering a sedation, it is fundamental to ensure that the patient has a true indication, since this is an irreversible therapeutic intervention. Finally and to close this chapter, we show an algorithm that tries to summarize the management of dyspnea in this population (Fig. 2.2).

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Acute Respiratory Failure in Patients with Hematologic and Solid Malignancies: Global Approach

3

Sakshi Sethi and Stephen M. Pastores

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BAL	Bronchoalveolar lavage
BMT	Bone marrow transplant
CMV	Cytomegalovirus
CT	Computerized tomography
DAH	Diffuse alveolar hemorrhage
EMG	Electromyography
FB-BAL	Fiber-optic bronchoscopy with bronchoalveolar lavage
HSCT	Hematopoietic stem cell transplantation
ICU	Intensive care unit
IVIg	Intravenous immunoglobulin
NIPPV	Noninvasive positive pressure ventilation
MV	Mechanical ventilation
PCP	*Pneumocystis jiroveci* pneumonia
PCR	Polymerase chain reaction
PE	Pulmonary embolism

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S. Sethi, M.D.
Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

S.M. Pastores, M.D., F.A.C.P., F.C.C.P., F.C.C. (✉)
Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Professor of Medicine and Anesthesiology, Weill Cornell Medical College, New York, NY, USA
e-mail: pastores@mskcc.org

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RSV	Respiratory syncytial virus
TRALI	Transfusion-related acute lung injury
VTE	Venous thromboembolism

3.1 Introduction

The incidence of all types of cancer is predicted to rise from 12.7 million new cases in 2008 to 22.2 million by 2030 [1]. Concomitantly, the last two decades have witnessed notable advances in the diagnosis and management of cancer patients including the use of high-dose chemotherapy, stem cell transplantation, targeted therapies, and immunotherapy. Although these strategies have significantly improved the overall and disease-free survival rates of patients with cancer, they have also resulted in increasing numbers of patients being admitted to the intensive care unit (ICU) for life-threatening toxic and infectious complications which are either cancer related or treatment associated.

Acute respiratory failure (ARF) is the leading cause for ICU admission in cancer patients and usually associated with high mortality rates especially in those requiring mechanical ventilation [2–4]. The incidence of ARF is about 5% in patients with solid tumors and up to 50% in those with hematological malignancies. Among hematopoietic stem cell transplant (HSCT) recipients requiring MV and ICU admission, the incidence of ARF ranges from 42 to 88% with an overall survival rate of approximately only 15% in those receiving MV [5].

The various causes of ARF in critically ill cancer patients are shown in Fig. 3.1. The most common causes include infections, cardiogenic and non-cardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]), antineoplastic therapy (chemotherapy, radiation therapy)-induced lung injury, malignancy-related medical disorders, and progression of underlying cancer.

3.2 Pulmonary Infections

Pulmonary infections are the leading cause of ARF, and the spectrum of possible responsible organisms depends on the underlying comorbidities (such as chronic lung disease, smoking history, cardiac failure, prolonged corticosteroid therapy), type of underlying malignancy, type of antineoplastic therapy, presence of neutropenia or defects in both cell-mediated and humoral immunity, frequent antibiotic exposure, and prophylactic treatments (Table 3.1).

3.2.1 Bacterial Pneumonia

Cancer patients with bacterial pneumonia tend to have atypical clinical features where fever is common but cough and sputum production are not. The chest radiograph may be normal or demonstrate diffuse interstitial infiltrates; the classic lobar

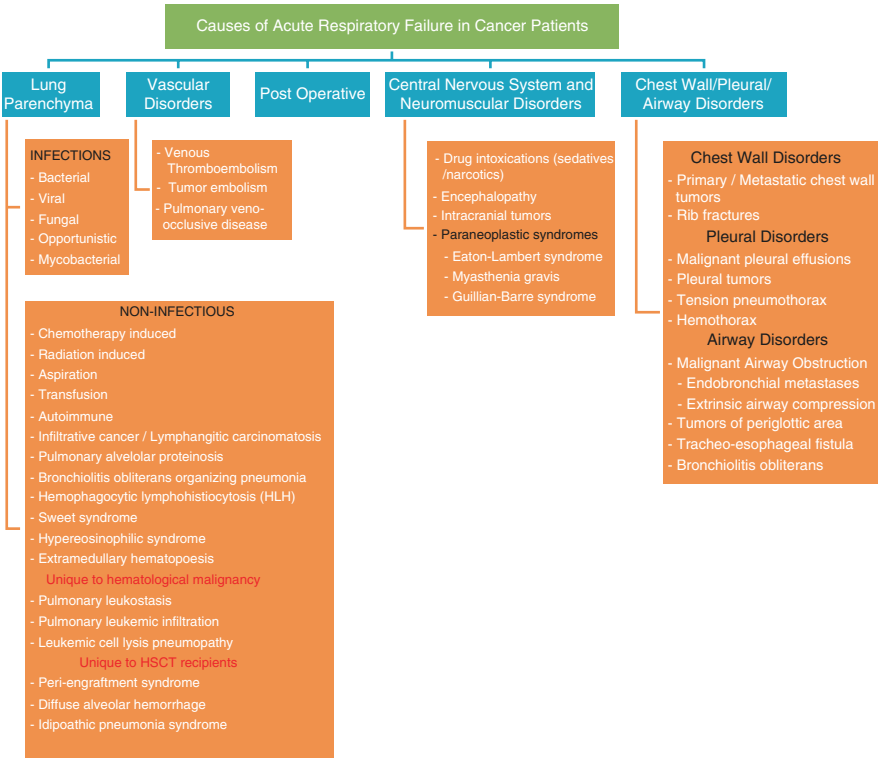

Fig. 3.1 Causes of acute respiratory failure in cancer patients

Table 3.1 Causative organisms depending upon the underlying immune deficiency

Immune deficiency	Cancers/conditions	Common organisms
Impaired humoral (B cell) immunity	CLL, multiple myeloma, BMT	Encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*)
Impaired cell mediated (T cell) immunity	Lymphomas, AML, ALL, high-dose corticosteroids, BMT	*Pneumocystis jiroveci* pneumonia, mycobacteria, *Cryptococcus* and other pathogenic fungi, *Legionella pneumophila*, *Nocardia asteroides*, *Rhodococcus equi* and other bacteria, herpes virus (esp. cytomegalovirus)
Chemotherapy-induced neutropenia		*Staphylococcus aureus*, *Streptococcus pneumoniae*, gram-negative enteric bacilli (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*), opportunistic fungi (especially *Aspergillus*)
Compression, obstruction, ulceration	Solid cancers	*Bacteria*, *Stenotrophomonas maltophilia* (frequent antibiotic exposure, prolonged mechanical ventilation)

CLL chronic lymphocytic leukemia, *BMT* bone marrow transplantation, *AML* acute myelogenous leukemia, *ALL* acute lymphoblastic leukemia

consolidation however is usually absent. Aspiration pneumonia is common in patients who have head and neck or esophageal cancers, poor cough and difficulty clearing secretions, upper airway dysfunction due to laryngeal nerve involvement, and cancer patients who require a tracheostomy. Cancer patients who are debilitated and received enteral feedings in the supine position, those who received high-dose narcotics, and those who have central nervous system metastases are also high risk for aspiration.

3.2.2 Fungal Pneumonia

Aspergillus pneumonia can be a life-threatening lung infection associated with dyspnea, chest pain, and hemoptysis. The chest radiograph may show patchy bronchopneumonia or multiple nodular lesions. Computerized tomography (CT) scans may reveal peripheral wedge-shaped infarcts or a characteristic halo or air crescent sign. Recovering *Aspergillus* spp. from a respiratory culture (sputum or bronchoalveolar lavage [BAL]) in the appropriate clinical setting suggests a high probability of invasive pulmonary aspergillosis necessitating antifungal therapy. Voriconazole is the antifungal agent of choice.

3.2.3 *Pneumocystis jiroveci* Pneumonia (PCP)

Patients usually have a subacute presentation with fevers, dyspnea, and hypoxia and bilateral ground-glass opacities on chest imaging. Detection of *P. jiroveci* by conventional staining methods or polymerase chain reaction (PCR) in samples of induced sputum, BAL fluid, or lung biopsies is diagnostic. Trimethoprim-sulfamethoxazole or pentamidine with adjunctive corticosteroid therapy remains the preferred treatment for severe cases.

3.2.4 Viral Pneumonia

The most common viruses responsible for pneumonia in cancer patients include cytomegalovirus (CMV), respiratory syncytial virus (RSV), influenza viruses A and B, parainfluenza virus, human adenoviruses, human parainfluenza viruses 1–3, human enteroviruses, human rhinoviruses, and human metapneumoviruses. CMV pneumonia clinically presents with fever, nonproductive cough, and dyspnea. Radiographically, it can present as lobar consolidation, focal parenchymal infiltrates, ground-glass opacities, or bilateral reticulonodular infiltrates. Viral shell vial culture and conventional culture of BAL samples, fluoroscopic antibody testing, and PCR testing of respiratory secretions are used for diagnosis of CMV. Therapeutic options include ganciclovir or foscarnet for CMV pneumonia and aerosolized ribavirin for RSV pneumonia either used alone or in combination with IV immunoglobulin (IVIg).

3.3 Noninfectious Causes

3.3.1 Antineoplastic Agent-Induced Lung Injury

Various chemotherapeutic agents can cause pulmonary toxicity resulting in ARF in cancer patients. A myriad of clinical syndromes may be associated with antineoplastic-induced lung injury including interstitial pneumonitis/fibrosis, ARDS, capillary leak syndrome, hypersensitivity pneumonitis, diffuse alveolar hemorrhage (DAH), organizing pneumonia, and bronchospasm. Diagnosis should be considered in any patient who develops cough, exertional dyspnea, and low-grade fever during or several months after chemotherapy. Pulmonary function tests usually reveal a restrictive defect with reduced diffusing capacity. Chest imaging shows patchy or diffuse ground-glass opacities or consolidations. Radiation recall pneumonitis can occur in patients with history of prior radiation to the chest. Chest imaging reveals pulmonary infiltrates in the same field as in the previous radiation therapy. Drugs commonly associated with radiation recall pneumonitis include doxorubicin, etoposide, paclitaxel, gemcitabine, and trastuzumab [6]. Diagnostic procedures are performed to exclude other likely etiologies especially infections or recurrence or progression of tumor. Definitive diagnosis usually requires transbronchial or open lung biopsy in conjunction with appropriate history. Management includes cessation of the implicated chemotherapeutic drug and use of systemic corticosteroids.

3.3.2 Radiation-Induced Lung Injury

Radiation-induced lung injury can occur in patients who receive chest radiotherapy for intrathoracic or chest wall malignancies. Factors influencing the severity of injury include the volume of lung irradiated, the total dose, dose per fraction used, concomitant chemotherapy, and steroid withdrawal. Pathogenesis involves production of local inflammatory and fibrotic cytokines and activation of cell adhesion molecules. The lung injury can manifest either as early acute phase (radiation pneumonitis) or a late phase (pulmonary fibrosis). Radiation pneumonitis occurs 1–3 months after radiotherapy and commonly presents with insidious onset of dyspnea, cough, and fever. Interstitial or alveolar infiltrates within the irradiated field are found on chest radiograph. It is mostly self-limiting, but severe respiratory failure requiring systemic corticosteroids can also occur. Radiation fibrosis occurs 6–12 months after irradiation and is irreversible, and use of corticosteroids is not recommended.

3.3.3 Transfusion-Related Acute Lung Injury (TRALI)

Cancer patients who require frequent transfusions of blood and its products (including granulocyte transfusion in neutropenic patients) are most susceptible to TRALI. This syndrome presents as ARF in association with fever, hypotension, and non-cardiogenic pulmonary edema with bilateral infiltrates on chest x-ray. Pathogenesis is

multifactorial and includes the passive transfer of donor antibodies directed against histocompatibility antigens or granulocyte-specific antigens in the recipient resulting in complement activation, blood products from alloimmunized female donors, and transfusion of donor serum with normal serum IgA concentrations to a recipient with anti-IgA antibodies. Diagnosis is supported by the presence of granulocyte, leukoagglutinating, or lymphocytotoxic antibodies from either donor or recipient serum. Treatment is mainly supportive and most cases resolve within a few days.

3.3.4 Diffuse Alveolar Hemorrhage (DAH)

DAH is a life-threatening cause of respiratory failure in patients with thrombocytopenia, patients with hematologic malignancies, and those undergoing hematopoietic stem cell transplantation (HSCT). Common risk factors for HSCT recipients include pretransplant intensive chemotherapy, total body irradiation, thoracic irradiation, and old age. Signs and symptoms include dyspnea, cough, fever, and hemoptysis (present in one-third of cases). Chest radiograph shows diffuse interstitial and alveolar infiltrates, predominantly in the middle and lower lung zones. The diagnosis is confirmed by demonstration of progressively bloodier BAL fluid and the presence of greater than 20% hemosiderin-laden macrophages in BAL fluid. Management includes supportive measures with corticosteroids, platelet transfusions, epsilon-aminocaproic acid or recombinant factor VIIa (rFVIIa), and mechanical ventilatory support. Prognosis is usually guarded with mortality exceeding 50% in most studies.

3.3.5 Pulmonary Leukostasis

Pulmonary leukostasis is an uncommon cause of severe hypoxemic respiratory failure in patients with acute leukemia who present with extremely high leukocyte or blast counts (>100,000/μL) and is associated with high mortality rates. In this syndrome, the leukocytes aggregate and form thrombi in the pulmonary vasculature. Another syndrome, *leukemic cell lysis pneumopathy*, can present within 48 hours of initiating chemotherapy. It manifests with severe hypoxemia and diffuse infiltrates secondary to leukostasis in the pulmonary vasculature and is associated with perivascular hemorrhage and interstitial edema. Management includes leukapheresis, hydroxyurea, adequate hydration, supplemental oxygen, and ventilator support in severe cases.

3.3.6 Venous Thromboembolism (VTE)

Thrombotic events are most commonly associated with malignancies of the pancreas, ovary, and brain. Cancer patients are more susceptible to deep venous thrombosis and pulmonary embolism (PE) due to various factors including intrinsic tumor procoagulant activity, antineoplastic drugs, hormonal therapies, surgery, immobilization, and indwelling central venous catheters. Clinical features include sudden-onset dyspnea,

pleuritic chest pain, hemoptysis, and hypoxemia. CT scan remains the gold standard imaging modality for the diagnosis of PE.

Anticoagulation and thrombolytic therapy are more challenging in cancer patients, because they have a higher risk of recurrent VTE than noncancer patients on one hand and a larger risk for bleeding complication on the other, especially in those with brain tumors or metastatic disease. Thus, treatment has to be individualized and based on overall goals of care. Low-molecular-weight heparins are preferred over unfractionated heparin for treating cancer patients with PE. Inferior vena cava filters are recommended to prevent or treat PE in high-risk patients with contraindications or failure of anticoagulation therapy.

3.3.7 Postoperative Respiratory Failure

The incidence of postoperative respiratory complications resulting in ARF in cancer patients can range from 6 to 76%, depending upon the type of surgery and underlying comorbidities. It is most commonly seen after thoracic and upper abdominal surgeries such as intrapericardial or extrapleural pneumonectomy and esophagectomy. Common etiologies include atelectasis, pneumonia, pulmonary edema, and bronchopleural fistula, and mortality rates are generally high.

3.4 Paraneoplastic Syndromes

3.4.1 Myasthenia Gravis

Myasthenia gravis is commonly associated with thymomas and can result in respiratory failure requiring prolonged mechanical ventilation. Diagnostic tests include edrophonium (Tensilon) test showing improvement in muscle strength after administration of the drug and electromyogram (EMG) studies showing decremental response of the muscle action potential to repetitive stimuli. Management includes cholinesterase inhibitors, thymectomy, plasmapheresis, corticosteroids, immunosuppressive therapy, and IVIg.

3.4.2 Lambert-Eaton Myasthenic Syndrome

This is a rare syndrome strongly associated with small cell lung cancer that presents with slowly progressive muscle weakness and late respiratory failure due to impaired neuromuscular junction transmission from decreased acetylcholine release. Confirmatory tests include the presence of antibodies directed against voltage-gated calcium channels and EMG showing increase in muscle action potential amplitude of at least 100% compared with pre-exercise baseline value. Therapeutic options include treatment of the underlying malignancy, drugs to increase the available acetylcholine at the postsynaptic membrane, cholinesterase inhibitors, plasma exchange, IVIg, corticosteroids, and immunosuppressive therapy.

3.4.3 Guillain-Barré Syndrome

This syndrome is a form of acute sensorimotor neuropathy that is associated with malignancies like Hodgkin's lymphoma and chemotherapeutic agents such as vincristine, oxaliplatin, and sunitinib. Lumbar puncture reveals albuminocytologic dissociation. Management involves plasma exchange and IVIg. ARF results from progressive upper airway and respiratory muscle weakness. Close monitoring of vital capacity and inspiratory/expiratory pressures is required to prevent emergency intubation and cardiopulmonary arrest.

3.5 Airway Obstruction

Upper airway obstruction can result from tumors of hypopharynx, larynx, thyroid, esophagus, and lung causing ARF. Signs and symptoms include dyspnea, wheezing, hoarseness, and stridor. These patients usually require emergent airway management including cricothyroidotomy or tracheostomy. Central airway obstruction can be endoluminal, extraluminal, or a combination of both. Endoluminal lesions can be treated with laser, electrocautery, or brachytherapy, whereas extraluminal compression requires airway stent placement.

3.6 Diagnostic Strategy and Management of ARF in Cancer Patients

A detailed clinical history and thorough physical examination are the first step to identify the cause of ARF in cancer patients. Azoulay and colleagues suggested six criteria to help identify the etiology of ARF which can be listed using the mnemonic DIRECT: *d*elay since malignancy onset or BMT, pattern of *i*mmune deficiency, *r*adiographic appearance, clinical *e*xperience and knowledge of the literature, *c*linical picture, and findings by HRCT. This strategy provides guidance for selecting empirical antimicrobial drugs and life-supporting interventions as well as other treatments and diagnostic investigations [7]. Rapid investigations and early identification of the cause of ARF have been shown to improve patient survival.

Fiber-optic bronchoscopy with bronchoalveolar lavage (FB-BAL) is the diagnostic strategy of choice for cancer patients whose respiratory symptoms are not severe enough to warrant ICU admission. However, the procedure can be associated with many complications with decline in respiratory status requiring mechanical ventilation being the most dreaded. Moreover, the diagnostic yield with FB-BAL is only about 50% prompting interest in noninvasive strategies for identifying the cause of ARF [8]. The recent expansion of new noninvasive diagnostic tools as listed in Table 3.2 requires reconsideration of the role of semi-invasive or invasive tests such as FB-BAL and lung biopsy.

Finally, the diagnosis of noninfectious causes of ARF also requires a careful approach as most of these patients require a significant change in their management,

Table 3.2 Noninvasive diagnostic testing for cancer patients with ARF

Radiography Chest radiography Thin-section high-resolution computed tomography Echocardiography or pleural ultrasonography
Sputum Bacteria, mycobacteria, and fungi (*Aspergillus*)
Tests for *Pneumocystis jiroveci* (MGG staining and immunofluorescence)
PCR for *Pneumocystis jiroveci*
Blood cultures
Serum tests Serology: *Chlamydia*, *Mycoplasma*, *Legionella* Herpes consensus PCR test Circulating *Aspergillus* antigen, beta-D-glucans, *Aspergillus galactomannan* Circulating cytomegalovirus antigen
Nasopharyngeal aspiration Tests for viruses (PCR and immunofluorescence)
Urine tests Cytology, bacteriology *Legionella*, *Streptococcus*, and *Histoplasma* antigens
Biological markers B-type natriuretic peptide (BNP) or pro-BNP C-reactive protein Procalcitonin

such as initiation of corticosteroid therapy, addition or change in chemotherapy, or discontinuation of a seemingly toxic chemotherapeutic agent. Noninfectious causes of ARF mostly fall into one of the following three categories: (a) acute or subacute nonspecific pulmonary infiltrates with severe hypoxemia in the initial phase of malignancies, especially hematological. Chest CT and other noninvasive tests can be helpful, but management entails rapid initiation of chemotherapy and broad-spectrum antibiotics against community-acquired organisms. FB-BAL is necessary only if initial treatment fails. (b) Progressive, subacute, lung infiltrates in patients with recurrence of underlying cancer. Radiographic findings can reveal peribronchial and perivascular nodules suggestive of specific lesions or interlobular septal thickening resulting in prominent secondary pulmonary lobules manifesting as tessellating polygons suggestive of carcinomatosis. Transbronchial biopsy is really helpful in this situation. (c) Acute respiratory failure in patients receiving consolidation therapy for hematological malignancies. Chest imaging reveals diffuse interstitial infiltrates characterized by a diffuse ground-glass appearance. FB-BAL is essential to rule out opportunistic infections before chemotherapy-associated lung toxicity is considered. Lung biopsy has a role to play in this group of patients.

Basic management principles include supplemental oxygen to correct hypoxemia, early initiation of appropriate empiric antimicrobial therapy in patients with suspected pneumonia, diuretics to decrease pulmonary congestion, and ventilator support including early use of noninvasive positive pressure ventilation (NIPPV) as well as invasive mechanical ventilation (MV), if necessary [9].

3.7 Prognosis and Outcome

ARF in cancer patients portends dismal outcomes despite aggressive management. Various studies report survival rates close to 50% for cancer patients admitted to the ICU with ARF, which further declines to about 20% for those requiring MV. Factors associated with higher mortality include, but not limited to, documented invasive aspergillosis, lack of definitive diagnosis, use of vasopressors, first-line conventional MV, conventional MV after NIPPV failure, and late NIPPV.

Physicians should assist all cancer patients and their families to make informed decisions regarding the use of MV and other life-sustaining treatments in the ICU and to complete advance directives. End-of-life discussions have been shown to be associated with increased family satisfaction, less aggressive medical care near death, and earlier hospice referrals. In contrast, aggressive care is associated with worse patient quality of life and worse bereavement adjustment. Ethics and palliative care consultations also greatly benefit end-of-life discussions with family members of cancer patients dying in the ICU [10].

3.8 Key Major Recommendations

1. The most common causes of ARF in cancer patients include infections, cardiogenic and non-cardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]), antineoplastic therapy (chemotherapy, radiation therapy)-induced lung injury, malignancy-related medical disorders, and progression of underlying cancer.
2. A detailed clinical history and thorough physical examination are the first step to identify the cause of ARF in cancer patients.
3. Fiber-optic bronchoscopy with bronchoalveolar lavage has a diagnostic yield of only about 50% in cancer patients with ARF. Noninvasive strategies such as respiratory virus PCR testing, sputum and blood cultures, urine and serum tests, echocardiography, and chest imaging are often useful.
4. Corticosteroids are often used for patients with chemotherapy-induced lung injury and radiation pneumonitis.
5. Management of ARF includes supplemental oxygen to correct hypoxemia, early initiation of appropriate empiric antimicrobial therapy for pneumonia, diuretics to decrease pulmonary congestion, early use of noninvasive positive pressure ventilation (NIPPV) in selected cases, and lung-protective ventilatory support for ARDS.

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Radiation Therapy: Impact on Lung Function and Acute Respiratory Failure

4

Athanasia Proklou, Eleni Diamantaki, Emmanouil Pediaditis, and Eumorfia Kondili

4.1 Introduction

Chest wall radiotherapy (RT) is a well-established part of early breast cancer management, as well as of lung and neck cancer [1, 2]. Currently, ACCP Lung Cancer Guidelines published in 2013 suggest the use of postoperative radiotherapy (PORT) for patients with stages I and II non-small cell lung cancer (NSCLC) and a positive bronchial margin. In patients with NSCLC, who cannot tolerate a lobectomy or segmentectomy, stereotactic body radiation therapy (SBRT) and surgical wedge resection are suggested over no therapy. Also, SBRT is favored in compromised patients and in those for whom an adequate margin is unlikely with a surgical wedge resection. The RT should involve once-daily therapy and a total dose of 60–66 Gy. In patients with infiltrative stage III (N2,3), NSCLC radiotherapy is recommended, either as palliative care or as complementary to chemotherapy. In patients with extensive-stage small cell lung cancer (ES-SCLC) who have completed chemotherapy, a course of consolidative thoracic radiotherapy (TRT) is suggested [3].

The use of SBRT is increasing over time, both due to the increasing cancer burden worldwide and the efficacy, low toxicity profile, cost-effectiveness, and ease of compliance with SBRT. An average incidence of 9–28% of radiation pneumonitis (RP) after SBRT is estimated, while 5–15% of patients irradiated for breast cancer may develop a form of lung toxicity [4–9].

The lung is a radiosensitive organ, and the reaction to radiation is a complex process. In humans, a lethal dose (LD50) of 10 Gy (single fraction) has been described [10]. The absorption of ionizing radiation causes immediate chemical,

A. Proklou, M.D., Ph.D. • E. Diamantaki, M.D. • E. Pediaditis, M.D.
Department of ICU, University Hospital of Heraklion, Crete, Greece

E. Kondili, M.D., Ph.D. (✉)
Department of ICU, University Hospital of Heraklion, Crete, Greece

School of Medicine, University of Crete, Heraklion, Crete, Greece
e-mail: konde@med.uoc.gr

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subcellular, and cellular interactions, while its morphological expression regarding gross tissue injury and organ dysfunction is often considerably delayed. The latent period between the exposure and the manifestation of damage is critically dependent on how efficiently the normal cells can repopulate the tissue [11].

Numerous factors are altering the risk of developing pulmonary radiation damage. These include radiation treatment factors, prior irradiation, use of chemotherapy, and coexisting lung disease, mainly the presence of interstitial lung disease and chronic obstructive lung disorders. Thus, the extent of lung damage arises as a result of physical and biological factors. The size of the radiation dose, its quality, and whether the exposure is single, fractionated, or protracted are the main physiological factors influencing subsequent tissue changes. Meantime, the presence or absence of repair and repopulation processes of the different tissue cells, their radiosensitivity and population kinetics, their state of oxygenation, and the differential sensitivity of the mitotic cycle phases play a crucial biological role in the extension of radiation damage [12].

The most important of the factors determining the extent of injury in a tissue is its ability to repopulate after radiation damage. The diving stem cells begin to die when they attempt their first or second postirradiation divisions, while the nondividing, differentiated cells, relatively unaffected by radiation, will continue to function. The injury will not become apparent until the number of functional cells falls below a critical level. The time of damage onset is more dependent on the cell kinetics of the tissue and less reliant on the size of the dose [13].

The lung's response to radiation therapy is clinically expressed into two syndromes that are not necessarily related: the so-called radiation pneumonitis (RP) that develops within 6 months after exposure and radiation pulmonary fibrosis (RPF), which is a delayed or late reaction, that develops from about 6 months to years after exposure.

4.2 Radiation Pneumonitis

RP consists of acute lung toxicity during or between 1 and 6 months after completion of a thoracic irradiation course. There is typically a latent period between radiation exposure and the development of acute pulmonary reactions, due to the low mitotic index of the pulmonary parenchymal cells.

The risk of radiation-induced injury is related to several factors. There is a direct relation to the incidence of RP and the volume of the lung irradiated within the tangential fields, as well as the use of additional supraclavicular (SC) fields [14]. Other factors that may increase the incidence and severity of radiation-induced lung disease are prior exposure to chemotherapy, mainly paclitaxel-based regimens, high-dose chemotherapy, and hormone replacement therapy in breast cancer patients [15, 16].

Symptoms may develop before radiographs changes. The most common manifestations are dyspnea, which can vary from mild to severe, and nonproductive cough, typically prominent. Fever occasionally occurs, either high spiking or low

grade but, nonetheless, transient. Hemoptysis is rare, though in the late phase of the disease, pink (blood-colored) sputum may be expectorated [17, 18].

Routine chest examination may reveal moist rales, a pleural friction rub, or evidence of consolidation over the area of irradiation. Skin changes secondary to radiation exposure can be present, but do not correlate well with the extent of pulmonary radiation damage. A polymorphonuclear leukocytosis and elevated erythrocyte sedimentation rate are neither common nor specific laboratory findings.

There is impaired pulmonary lung function, with a predominantly restrictive pattern. The measurement of carbon monoxide diffusion capacity (DLCO) is the most accurate predictive component for pulmonary radiation damage. The DLCO falls by 20–60% during the first 3–5 months after irradiation and then usually returns to its previous level 12 months later. The change in DLCO correlates with the volume loss of tissue for gas transfer, reflecting the alveolar-capillary block in affected tissues. Peak oxygen consumption significantly decreases in some patients, mainly affecting patients with coexisting lung diseases [18].

The CT severity score of RP ranges from grades 1 to 5, according to the National Cancer Institute Common Toxicity Criteria version 3.0 (CTCAE version 3) [19] (Table 4.1). Grade 2 severity is defined when diffuse consolidation or patchy consolidations with ground-glass opacities are present in the irradiated field. The extensive RP beyond the irradiated field, including the contralateral lung, upgrades the severity index from grade 3 to grade 5.

The onset and course of the disease can be either fulminant with severe respiratory insufficiency and cyanosis progressing to acute cor pulmonale in a matter of days, or subtle if the affected area of the lung is small. Overall, the early onset of symptoms implies a more severe and more extensive clinical course [17]. Radiation pneumonitis is considered as a form of acute or subacute lung injury corresponding to the site that is irradiated. It occurs more often when the dose exceeds 20 Gy and always leads to lung fibrosis [20].

4.2.1 Pathogenesis of Radiation Pneumonitis

The initiating arranger of RP is the inflammatory cascade. The main cells involved are the endothelial cells interacting with inflammatory leukocytes, the macrophages, and, at the late fibrosis phase, the fibroblasts [21]. Specific T-lymphocyte

Table 4.1 CT severity score of radiation pneumonitis

Grade 1	Minimal radiographic findings (or patchy or bibasal changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%
Grade 2	Patchy or bibasal changes with estimated radiographic proportion of total lung volume that is fibrotic of 25–50%
Grade 3	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50–75%
Grade 4	Estimated radiographic proportion of total lung volume that is fibrotic of >75%
Grade 5	Death

subsets are activated and participate in the repair process acting protectively against radiation-induced lung fibrosis. T helper type 1 (Th1) and T helper type 2 (Th2) lymphocyte polarization in the context of the immune response plays a crucial role. Th1 lymphocytes facilitate generation of IL-2 and IFN-γ resulting in enhanced cellular immune responses, while Th2 lymphocytes are associated with the production of IL-4 and IL-10, thus facilitating immunoglobulin production. Th2 responses prevail in progressive lung inflammation, with further development of pulmonary fibrosis, while Th1 response resolve without a disabling outcome [22–24].

There is a vicious cycle of inflammation, angiogenesis-hypoxia, cell death-proliferation, maintained by cytokines, growth factors, and fibroblasts that promote collagen accumulation [22, 25].

The key cytokine involved in the early stages of RP is TNF-a with pro-inflammatory and immunoregulatory effects, while TGF-β cytokine holds a mandatory role in the later stage of fibrosis. TNF-a expression is impaired under the action of anti-inflammatory interleukins, such as IL-4, IL-10, and IL-13. Also, macrophage colony-stimulating factor (M-CSF) and macrophage chemoattractant protein-1 (MCP-1) may promote the attraction of macrophages into the irradiated lungs [10, 26].

Recent studies based on the development of the human genome project and pharmacogenomics suggest that single-nucleotide polymorphisms (SNPs) in inflammation-related, DNA repair-related, stress response-related, and angiogenesis-related genes may be used as biomarkers to predict the development of RP. The implication of TGF-β, lineage protein 28 (Lin28), and numerous DNA repair-related genes is demonstrated by preliminary reports, though accurate evaluation and risk stratification for the occurrence of RP are not completely elucidated yet [27].

4.2.2 Treatment of Radiation Pneumonitis

The treatment of RP remains challenging, though symptomatic. Several agents have been experimentally tested for the prevention or treatment of RP and RPF. However, corticosteroids remain the mainstay for radiation pneumonitis. Antibiotics can be used, especially in the case that atypical chest infection cannot be ruled out. Previous trials with inhibitors of TNF-a, such as infliximab, and TGF-β inhibitors, such as naringenin, pentoxifylline, and relaxin that block, downregulate, and inhibit TGF-β, respectively, have shown some promising results, but none of them have been established in the clinical practice [22, 28]. Serious pulmonary toxicity (grades 3 and 4) always requires hospitalization with oxygen supplementation or mechanical ventilation if needed, fluids, empirical antibiotics, and intravenous steroids [29, 30]. The recommended dose of steroids is for oral prednisone 0.75–1 mg/kg/day and for intravenous methylprednisolone 2–5 mg/kg/day for at least 3 days or dexamethasone 8 mg twice per day [29, 31].

4.3 Radiation Fibrosis

Radiation fibrosis applies to the clinical syndrome resulting from chronic pulmonary lung damage. Typically it occurs 6–12 months after radiation therapy completion but usually remains stable after 2 years. Occasionally patients may present radiation fibrosis without a history of acute radiation pneumonitis. Symptoms range from minimal to varying degrees of dyspnea and radiographic signs of pneumonia with pulmonary infiltrates ipsilateral to the radiated site [29]. In some cases, chronic pulmonary insufficiency may develop and progress to chronic cor pulmonale from the resultant pulmonary hypertension, with associated cyanosis, hepatomegaly, or liver tenderness [18].

Radiation fibrosis is a more difficult radiographic diagnosis to make since the fibrosis distorts the outline of the radiotherapy ports. The delayed changes of fibrosis usually appear 6–9 months after the end of an RT course and become stable after 2 years. If the fibrosis is mild, subtle changes are present, such as the elevation of the hemidiaphragm, apical thickening, widening of the mediastinum, and paramediastinal fibrosis. The fibrosis can be severe enough to shift the trachea and cause stenosis. The fibrotic lung is prone to infection, affecting overall the survival of these patients. Late in the course of RF, the diaphragm can scar and become immobile [18].

From pathophysiological aspect, the gas-exchange interface is reduced by fibrosis, with thickening of alveolar-capillary barriers, resulting in impaired gas transfer. Both static and dynamic lung compliance are impaired and may be accompanied by a reduction in vital capacity [32].

4.3.1 Pathogenesis of Radiation Fibrosis

The exact mechanism of RF is not yet elucidated completely. Different pathophysiological mechanisms of lung fibrosis have been proposed. One suggests the presence of a tolerance threshold for the normal lung tissue that is not reached by the delivery of RT alone. Thus, any adjuvant treatment with a systemic anticancer agent may overpass the host's lung tolerance threshold. Another theory suggests that the repair capacity of the pneumocytes has been impaired by previous RT and any subsequent therapy will promote further lung injury and permanent fibrotic changes. The most commonly reported antineoplastic drugs that have been implicated in the development of RF are anthracyclines, gemcitabine, paclitaxel, trastuzumab, and everolimus [29, 33–36].

4.3.2 Treatment of Radiation Fibrosis

The treatment of both radiation fibrosis and radiation pneumonitis remains empiric and mainly supportive and is escalated depending on the severity of the symptoms. Although evidence exists for effective treatment, there is no therapeutic strategy of

proven benefit for the treatment of radiation pulmonary fibrosis. The supportive strategy includes supplementary O_2, bronchodilators, and antibiotics if needed. New anti-fibrotic drugs targeting connective tissue growth factor (CTGF) are in the initial stages of development and may be implicated as therapeutic agents for radiation fibrosis [37].

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Radiation Pneumonitis and Noninvasive Ventilation

5

Erica Altschul, Shalin Patel, and Bushra Mina

Radiation therapy is a major treatment modality for cancer as an intent to cure as well as palliative therapy. While its efficacy has been well proven, the complications of therapy can limit its effectiveness which ultimately affects morbidity and mortality posttreatment. Radiation exposure to the lung, in particular, can have acute and chronic toxicities manifested as radiation pneumonitis and pulmonary fibrosis, respectively.

Radiation is a form of energy that inhibits cell growth and division. After multiple exposures to radiation, the cells that make up a tumor shrink in size. Radiation targets cells that are actively dividing in specific areas of the cell cycle (Table 5.1); those in phase G0 are less responsive to radiation therapy. Since cancer cells are known for rapid cellular division and growth, they are most susceptible to radiation. The exact mechanism of cell death is unknown, but most evidence dictates that double-stranded DNA breaks are the main contributors, though single-stranded breaks, base damage, and cross-link damage between DNA-DNA and DNA protein are factors as well [1, 2]. The double-stranded DNA breaks lead to irreparable damage and cell death [2]. While tumor destruction is the ultimate goal, normal tissue cells can also be affected. Those that grow quickly will be acutely affected, while tissue that is slow growing may not show signs of toxicity until years after treatment have completed [1].

Thoracic radiotherapy is a common treatment modality for breast cancer, pleuropulmonary cancer, and mediastinal lymphomas. The most common structures at risk are the lungs, heart, esophagus, brachial plexus, and mammary glands [3]. Radiation pneumopathy is the direct lung-induced injury due to radiation therapy. The severity of toxicity depends on a variety of factors including the dose, length of

E. Altschul • S. Patel • B. Mina (✉)
Pulmonary Medicine and Critical Care Medicine Divisions, Lenox Hill Hospital, Northwell Health, New York, NY, USA
e-mail: bmina@mindspring.com

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Table 5.1 Cell Cycle Phase

Cell cycle phase	Description
G0	Cell rest, carry out day-to-day body functions
G1	RNA and protein synthesis made for cell division
S	Synthesis of DNA made for new cells as the chromosomes are copied
G2	Apparatus for mitosis is built
M	Mitosis

Adapted from [1]

treatment, and volume of body exposed to radiation as well as patient-specific factors, such as genetic predisposition, pretreatment functional status, underlying lung injury, and smoking [4]. The two main radiation-induced pulmonary toxicities as stated previously include acute radiation pneumonitis and radiation fibrosis.

Acute radiation pneumonitis occurs 6–12 weeks after completion of thoracic radiotherapy [3], but the damage begins immediately. Within the first few hours of radiation, type I and type II pneumocytes are affected. Type I pneumocytes, found on 90% of the alveolar epithelium surface, are deleted. The type II pneumocytes, the cells that synthesize and secrete surfactant and regulate surface tension, rapidly proliferate leading to hyperplasia and increased surfactant production [4]. The next site of damage is the basement membrane; in normal physiology, the basement membrane fuses the capillaries to alveoli providing a thin membrane for gas exchange from intra-alveolar air into the vasculature. After exposure to radiation, there is separation of the basement membrane and proliferation of fibroblasts in the extracellular membrane (ECM). In addition to poor gas exchange, the change in ECM causes an increased vascular permeability and ultimately perivascular congestion [4]. Macrophages become activated to release cytokines and chemokines within in the interstitium leading to the activation of fibroblasts and collagen buildup, an effect which is worsened by radiation interference of gene expression causing an overabundance of cytokine and growth factor [4]. Lastly, there is thrombosis of the capillaries and degeneration of the small arterioles with areas of necrosis in the regions targeted by radiation therapy [3], and these acute changes are usually reversible after 3–4 weeks [1].

The workup of acute pneumonitis involves a combination of history of thoracic radiation exposure, clinical picture, imaging studies, and PFTs. Clinically, the acute phase is usually asymptomatic with the earliest evidence of damage seen on imaging. The most common presenting symptoms are dyspnea and nonproductive cough [3]. Patients tend to develop nonspecific symptoms, such as low-grade fever or cough, more commonly after receiving higher doses (>50 Gy) of radiation [4], and those who receive radiation therapy to more than 75% of lung tissue have the highest risk of developing severe pneumonitis [3]. Laboratory workup does not contribute much to diagnosis as it is nonspecific, mainly with an elevation of inflammatory markers [3]. Chest x-ray and chest CT may show diffuse interstitial infiltrates that can coalesce and be associated with effusions—both pleural and interlobular [1]. Acute radiation pneumonitis can cause a restrictive disease, evident by changes in

the pulmonary function tests with mainly a decreased DLCO, decreased compliance, and decreased lung volumes due to alveolar degeneration and interstitial fibrosis [1]. An obstructive pattern can exist if the patient has underlying obstructive lung disease [4].

Treatment of acute radiation pneumonitis focuses mainly on symptomatic improvement. Corticosteroids have shown the quickest and effective improvement; however, prior to administering corticosteroids, the clinician must rule out all infectious etiology first. The prognosis of acute radiation pneumonitis varies. The majority of patients recover with no lasting effects. Rarely, patients can develop bronchiolitis obliterans with organizing pneumonia (BOOP) which manifests as what clinically appears to be an infectious pneumonia immediately following radiation therapy [3]. There is an association between the development of BOOP and patients receiving radiation therapy for breast cancer with tamoxifen therapy, and this condition also responds to steroids [3]. ARDS, while a significant and severe complication, is extremely rare. If the acute pneumonitis does not regress, patients may ultimately develop pulmonary fibrosis [4].

Pulmonary fibrosis occurs approximately 6 months after completion of radiation therapy and stabilizes over the next 1–2 years [3]. The pathophysiology of pulmonary fibrosis is similar to that of acute pneumonitis, dominated by fibroblast and collagen accumulation and disruption of capillaries leading to focal necrosis which becomes chronic and irreversible. However, these changes persist and the constant release of cytokines leads to fibrosis [3].

The clinical picture is highly dependent on the amount of lung affected by fibrosis development (Fig. 5.1). Patients again may be asymptomatic as it depends on the volume of lung affected by radiation toxicity. Small volumes of lung irradiation usually do not produce clinically active symptomatology [3]. With the destruction of pulmonary vasculature comes intrapulmonary shunting of unoxygenated blood into the systemic system. The larger the area of shunting, the greater the amount of unoxygenated blood and hypoxia [4], leading to increased dyspnea on exertion, cyanosis, cor pulmonale, and

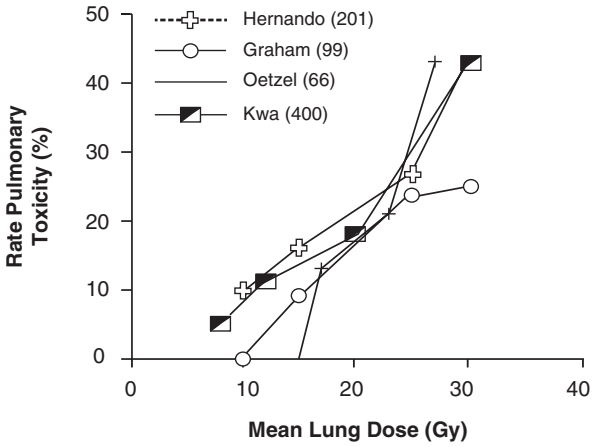

Fig. 5.1 Rate of pulmonary toxicity compared to mean lung dose of radiation therapy [1]

ultimately restrictive respiratory failure. Imaging modalities are similar to acute pneumonitis with high-resolution CT used as the image of choice. A ventilation perfusion scan, while nonspecific, can support the diagnosis by showing areas of decreased perfusion [4]. PFTs again demonstrate a restrictive pattern, and the severity of pneumonitis is determined by the degree of diffusion capacity impairment [4]. PFTs have been shown to continuously decline even 1 year after cessation of radiation [4].

Multiple grading systems have been developed to determine the severity of radiation-induced lung injury. The two most commonly used are the NCI CTC for acute pneumonitis and RTOG for pulmonary fibrosis [5], illustrated in Tables 5.2 and 5.3. Treatment with corticosteroids depends on the severity of symptoms and is usually prescribed as 40–60 mg daily with a very slow taper [6]. Oxygen therapy can be guided by the grade of pneumonitis, and ventilatory support may ultimately be required. As chronic radiation-induced lung injury presents as pulmonary fibrosis, one can make the assumption that ventilation support guidelines should follow those of the more well-known pulmonary fibrosis spectrum.

There is limited data to guide physicians on optimal oxygen therapy during radiation pneumonitis. Some patients may not require oxygen therapy, some require low-flow oxygen modalities, and others may require high-flow modalities depending on the severity of the pneumonitis. The use of noninvasive ventilation (NIV) specifically in radiation pneumonitis is limited. One small study included 19 patients receiving NIV for acute radiation pneumonitis. Seventy-nine percent of the patients had significant improvements in their respiratory parameters and gas exchange with decrease in heart rate, and respiratory rate, with improvement in SpO_2, and PaO_2 allowing for adequate oxygenation and ventilation to be maintained without the need for invasive mechanical ventilation [8]. Acute radiation pneumonitis is similar in physiology and treatment to lupus pneumonitis which manifests as ALI/

Table 5.2 NCI/CTC grading system for acute radiation pneumonitis [3]

Grade	0	1	2	3	4	5
Description	No change from baseline	Asymptomatic, radiographic findings only	Symptomatic but not interfering with ADL	Symptomatic and interfering with ADL with O_2 indicated	Life threatening requiring ventilatory support	Death

Table 5.3 RTOG late radiation morbidity scoring schema for lung tissue [7]

Grade	Description
0	No change from baseline
1	Asymptomatic or mild symptoms (i.e., dry cough) with slight radiographic appearances
2	Moderate symptomatic fibrosis or pneumonitis (severe cough) with low-grade fever, patchy radiographic appearances
3	Severe symptomatic fibrosis or pneumonitis with dense radiographic changes
4	Severe respiratory insufficiency requiring continuous O_2 or assisted ventilation
5	Death directly related to radiation late effects