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Pulmonary Toxicities and Treatment of Radiation Therapy

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Abstract

Radiotherapy (RT), used for the treatment of cancers, such as lung cancer, lymphoma, breast cancer, bone marrow transplantation, and esophageal cancer, causes the exposure of lungs to radiation. Since the lungs are very sensitive to ionizing radiation, radiation-induced lung diseases due to radiation therapy are usually common. In this article, lung diseases secondary to RT and the diagnosis and treatment of these diseases were evaluated in light of the literature.

Keywords: Cancer, lung, radiotherapy, toxicity

INTRODUCTION

The exposure of normal tissues, besides cancerous tissues, to radiation from the first days of radiotherapy (RT) application has been an important limiting factor. Although the incidence of radiation-induced normal tissue injury has diminished with the development of radiation oncology technology in recent years, it still goes on. In this review, general information about RT is given, and RT-induced toxicity types that develop in the lungs and therapies are explained.

GENERAL INFORMATION

RT is used for palliative, curative, adjuvant, and prophylactic purposes in cancer treatment. The aim during radiotherapy application is to reduce or remove tumor load while protecting normal tissue. The injury of normal tissue always poses the main obstacle to RT. In time, strategies, such as dose-volume modulation, image-guided RT applications, involved-field radiotherapy, and the use of lung disease-preventive agents, have been developed to overcome this problem

Thoracic RT may be conducted in cases, such as lung cancer, bone marrow transplantation, and esophageal cancer. Lungs are among the most sensitive organs to ionizing radiation, and this sensitivity is one of the most important dose-limiting obstacles of thoracic RT. Temporary sequential inflammatory events are seen in the lung tissue as a response to radiation exposure. Here, individual differences, by affecting the outcome, bring about the occurrence of normal or pathological responses. Radiation-induced lung injury is a progressive process, including inflammation and repair. The development of injury may be prevented and the development of new strategies for treatment may be possible by understanding the underlying mechanisms of the basic molecular damage caused by radiotherapy (1, 2).

Today, external RT (EBRT), brachytherapy, intraoperative RT (IORT), stereotactic RT (SRT), three-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), image-guided RT (IGRT), tomotherapy, cyberknife (robotic radiosurgery), boron neutron capture therapy, and hyperthermia are among RT applications. Location of the tumor, its histopathological feature, sensitivity to RT, the patient's undergoing surgical intervention, and his receiving chemotherapy are important for the preference of the appropriate technique (3).

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Table 1. RTOG traditional scoring system for lung injury secondary to radiation

EARLY (<90 days)	LATE (>90 days)	Grade
Mild symptoms; dry cough or exercise dyspnea	Asymptomatic or mild symptoms (like dry cough) Mild radiological changes	1
Persistent cough requiring narcotic, antitussive agents Dyspnea with minimal exercise	Moderate symptomatic fibrosis or pneumonitis (severe cough) Sub-febrile fever Patched radiological change	2
Cough not responding to narcotic, antitussive agents Clinical or radiological symptoms of acute pneumonia Intermittent oxygen need	Fibrosis or pneumonitis presenting with severe symptoms Intense radiological changesr	3
RI requiring oxygen or MV continuously	Severe RI, need for oxygen therapy, or MV continuously Death	4 5

MV: Mechanical ventilation; RI: respiratory insufficiency; RTOG: Radiation Therapy Oncology Group

Radiation has an impact on the alveolocapillary unit of the lung according to the proliferation of cells. Endothelial, epithelial (particularly, type 2 pneumocytes producing surfactant), and reticuloendothelial system cells are more sensitive to radiation. Radiation gives damage to these cells by apoptosis and stimulation of stress response genes. Reactive oxygen (ROS) and nitrogen (RNS) production primarily causes the breakdown of DNA, lipid, and proteins and necrosis as a result (4-7). The DNA damage caused by ionizing radiation leads to apoptosis of type 1 and type 2 pneumocytes. Moreover, radiation-induced damage in the lung disrupts the epithelial and endothelial barrier. As a result of this damage, various inflammatory cells move to the damaged region. RT applied to the lung may cause hypoxia by reducing vascular density and lung perfusion. Additionally, activation transcription of some early and late response genes may be seen as a response to ionizing radiation in cells (8-10).

Transforming growth factor beta 1 (TGF-β1) is a multifunctional peptide, playing a role in the pathogenesis of fibrosis, and has an important place in radiation-induced pneumopathy (5-7). Plasma TGF-β1 level was first detected by Anscher et al. (11) as a predictor in normal tissue injury. Although serum interleukin (IL) 1, 6, 8, and 10 levels were correlated with radiation-induced lung damage, the very correlation could not be found in some studies (12-14).

Radiation damage in many cases is restricted to the radiation-applied region; it may develop in regions apart from the RT-applied region in some instances, and the best example of it is cryptogenic organizing pneumonia (KOP/BOOP) (7, 8). Partial lung irradiation sometimes may cause acute respiratory distress syndrome in spite of corticosteroid therapy (15). Other lung regions' being affected by the application of RT on the lungs locally is thought to be associated with a lymphocyte-mediated hypersensitivity reaction (16).

Radiation-induced lung damage causes respiratory disorders. The most common radiological finding is interstitial infiltrates in the RT-applied region. Furthermore, consolidation, nodullary, and pleural effusion may be also seen. This may lead to difficulty, especially in the progression of tumor progression and the differential diagnosis of the infection. Positron emission tomography (PET) may help in the differential diagnosis (18).

The most important factor influencing the development of radiation-induced lung damage is the lung volume exposed to radiation (19-21). Radiation application to both lungs is very rare. Total body irradiation may be conducted for bone marrow transplantation. Radiation pneumonia developing after low volumes of RT is milder and heals spontaneously. Understanding the real incidence of radiation pneumonia is difficult due to the change of the standards used for the identification and grading of the disease (22).

Radiotherapy-induced effects and the traditional scoring system developed by the Radiation Therapy Oncology Group (RTOG) are displayed in Table 2. Furthermore, the late effects in normal tissue subjective, objective, management criteria (LENTSOMA) toxicity criteria were identified by RTOG and the European Organization for Research on Treatment of Cancer (EORTC) (23-26). The Radiation Therapy Oncology Group determined the early and late toxicity period according to 90 days. However, there was difficulty in evaluating some radiation-induced pneumonias with this determination. The National Cancer Institute (NCI) rearranged these side effects as common terminology criteria (CTCv3.0). The new CTCv3.0 was adopted in evaluating side effects for existing and future studies (Table 2) (27).

Most of the clinical studies of radiation oncology have focused on the dose-volume histogram (DVH) concept, which is one of the most important parameters to assess the three-dimensional conformal plan. The volume of tissue is divided into equal rates, and doses corresponding to these rates are calculated. Thus, the proportional dose distribution of tumor and normal tissue volume can be seen graphically. The dose-volume histogram is divided into two: differential and cumulative (28). One of the parameters assessed in lung DVH is the evaluation of the irradiated lung volume and the development of pneumopathy risk. The lower the volume, the smaller the risk of pneumopathy development. Hodgkin reported that radiation pneumonia risk decreased from 29% to 17% with involved-field radiotherapy for lymphoma (29). The use of DVH for predicting radiation pneumopathy was just based on anatomic data. Lung physiology or

Table 2. CTC v3.0 criteria in the evaluation of side effects in radiation pneumonia (27)

Side effect	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis/pulmonary infiltration	Asymptomatic; there are only radiological findings	Symptomatic, daily life is not affected	Symptomatic, daily life is affected. O_2 is required.	There are life-threatening threatening symptoms Ventilator support is required	Mortality

CTC: Common Terminology Criteria

the underlying disease of the patient was not considered. This may make the prediction difficult, especially in old and smoking patients with lung or esophagus cancer. The risk of radiation pneumopathy development is higher, since the perfusion rate of lower lobes in lower lobe lung cancer treatment is higher (30).

Dosimetric factors are used in tomography-based treatment planning. Therefore, before planning, lung volume is calculated mathematically by introduction of organs to the treatment device with the tomography conducted in the treatment position. Oetzel et al. (31) indicated by using mean lung disease (MLD) and normal tissue complication possibility (NTCP) that there was a correlation between radiation dose and the risk of lung damage. In another study, it was found that the quantity of lung volume, taking a dose of 20 Gy, was the most important factor in determining the incidence rate of radiation-induced lung injury (31, 32). Normal tissue complication possibility is used to predict the dose-volume relationship in low-dose-taking regions of tissue. Mean lung dose and NTCP are the best markers used to predict lung injury. In a study carried out, when only dosimetric factors were considered, it was found that a lung volume taking 5 Gy (V5) of 50% or above was an important factor for symptomatic pneumonia development (33).

In the guideline prepared by the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS), by stating that lung physiology can not determine the acute and long-term risks associated with thoracic radiotherapy definitely, the cut-off value for FEV_1 was reported to be 2 liters in simultaneous RT KT studies for locally advanced disease. Moreover, it was reported that in patients with chronic obstructive pulmonary disease (COPD), radiotherapy should not be performed at values below 1.2 lt.

Apart from radiation dose-volume parameters, factors related with the treatment (daily radiation fraction size, simultaneous chemotherapy application) are also important in radiation pneumopathy development. Although neoadjuvant chemotherapy (CT) does not increase radiation pneumopathy risk much, the risk increases significantly with simultaneous CT. The maximum tolerated dose of localized RT is generally 60-66 Gy. Higher doses were tried, however quitted due to the increase in complication rate (36-38). Gemcitabine, a chemotherapeutic agent,highly increases RT toxicity (39, 40). Moreover, the use of anthracyclines (like doxorubicin), methotrexate, and bleomycin during thoracic radiotherapy is contraindicated. It was reported that simultaneous chemoradiotherapy, when applied with taxanes (paclitaxel or docetaxel), was safer with regard to radiation pneumopathy development (41).

In a study, other factors apart from treatment were evaluated in radiation-induced lung damage development, and it was found that performance was associated with damage development. In another study, no relationship was found between age, gender, smoking history, diabetes, induction chemotherapy, simultaneous chemotherapy regimen, and damage. It was suggested that lung functions before treatment were important in lung damage development, and it was indicated that RT-associated damage development risk increased in cases with COPD and low FEV_1 (35, 42).

Radiation Pneumonia

Radiation pneumonia (RP) is characterized by high interstitial inflammation and alveolar exudates. It occurs 1-6 months after radiotherapy and generally recovers within 6-12 months. Age, localization of lesion, application of simultaneous or sequential chemotherapy, and smoking are known as risk factors for radiation pneumonia development. Chest radiography is not sufficient to evaluate changes that may develop with modern RT methods. RT-applied patients with pulmonary complaints should be evaluated with thorax computerized tomography (CT). When interstitial infiltrate and/or ground-glass opacity is imaged, a differential diagnosis with infection diseases may be difficult. If fever accompanies in the presence of suspected moderate or severe pneumopathy, it may be necessary to make an examination to exclude possible infection (22, 44). The oxygen requirement of the patient should be evaluated with pulse oximetry or arterial blood gas. Measurement of diffusion capacity is among the diagnostic tests for evaluating the severity of impaired gas exchange. Although spirometric parameters in radiation pneumopathy are usually reversible, the probability of diffusion abnormalities reversing is low (45). Measurable changes in spirometry occur 2-3 months later, and after reaching the maximum level, they usually revert within 8-12 months. A decrease is observed in lung volumes, compliance, and DLCO. There may be an increase after radiotherapy in lung volumes of patients whose tumors shrank apparently (46, 47). The response to corticosteroid in radiation pneumonia treatment is generally positive, and a dramatic response to the treatment is important in the differential diagnosis.

The corticosteroid treatment decision may be made if the clinical findings and test results are compatible with grade 2 or higher radiation pneumonia and the patient is symptomatic. Since there are no randomized controlled studies for radiation pneumonia developing in humans, the effectiveness of corticosteroids has been displayed with nonrandomized clinical studies (14, 48). There is no standard dose scheme for radiation pneumopathy. Usually, a daily dose of 1 mg/kg prednisolone should be used for 2 weeks in severe radiation pneumonia (grade 3/4). Short-term hospitalization may be necessary for intravenous application of corticosteroids. Since early-onset radiation pneumonia occurring in a short time following completion of radiotherapy may have a serious course, more aggressive treatment approaches may be necessary (14).

Moderate radiation pneumonia (grade 2) may be treated with a lower dose of corticosteroid (0.5-0.75 mg/kg/day prednisolone); however,

the patient should be followed closely to evaluate whether there is progress to a more severe picture (grade 3). After a couple of weeks, the dose should be gradually reduced to 10 mg in 2 weeks. There may be symptomatic recurrences while reducing the corticosteroid dose. It is important to exclude concurrent infections when recurrence is observed. If it is a recurrence of RT pneumonia, the corticosteroid dose should be increased again (14, 48). Corticosteroid treatment should be given for a period of 2-4 months in grade 3 or grade 2 severe radiation-induced lung damage. Even though the effect of corticosteroids after 6 months is disputable, it may be necessary to give them for a longer period in some cases. The use of low-dose prophylactic antibiotic with corticosteroid is controversial.

Excluding an accompanying infection completely in all patients developing interstitial pneumonia after thoracic RT is difficult without applying bronchoscopy or other invasive diagnostic procedures (1). In high-dose corticosteroid-initiated cases after chemoradiotherapy, trimethoprim-sulfamethoxazole prophylaxis should also be initiated in the presence of deep lymphopenia (49). If there are findings in thoracic BT supporting concurrent infection, the use of broader-spectrum antibiotics is necessary. The prognosis of grade 1 and 2 RP is relatively better with careful supportive care and corticosteroid use (50). It is not known how the treatment will be in cases that are resistant to corticosteroid or if the use of corticosteroid is nonapplicable. Immunosuppressive therapy was tried in some similar cases (51, 52).

Radiation Fibrosis

Radiation fibrosis (RF) is chronic lung damage. TGF-β1 discretion in tissue exposed to radiation leads to stimulation of fibroblasts and changes the lung structure by converting tissues to myofibroblasts. An inflammatory response follows this, and macrophage accumulation and activation occur. Increased oxygen consumption and vascular changes contribute to the development of hypoxia. Hypoxia formation further stimulates production of ROS and proinflammatory, profibrogenic, and proangiogenic cytokines. Consequently, the persistent nonhealing tissue response leads to the occurrence of chronic lung damage. Radiation fibrosis begins after a few months and progresses gradually over the years. It usually takes place 6-24 months after radiotherapy. RF can happen without an underlying acute pneumonia history. As patients may be asymptomatic, there may be a complaint of dyspnea to varying degrees (2). The radiological findings may be in the form of fibrotic changes in the RT field, scar-associated withdrawals in the lung parenchyma, traction bronchiectasis, volume loss, pleural thickening, and replacement in the trachea and mediastinum (1).

The treatment of radiation-induced pulmonary fibrosis is a supportive treatment, and it includes oxygen support, antibiotics in the presence of infection, and a bronchodilator and diuretics when necessary. In order to provide sufficient oxygen for the tissue, if required, it is necessary to prescribe cardiac and blood pressure drugs and heal anemia if present. It is not clearly known whether pulmonary rehabilitation programs are useful or not. If the patient remains immobile because of respiratory insufficiency, deep-vein thrombosis prophylaxis should be applied. Smoking should be definitely avoided (1).

Bronchiolitis Obliterans Organizing Pneumonia

It is a rare pulmonary disease and infection, and toxic agent inhalation and exposure to radiation are among the causes of it. In the connective tissue reaching from the alveoli to bronchia a patchy distribution with intraluminal plugs is observed. The development mechanism of organized pneumonia after radiotherapy is not known completely (53). The first radiological changes in the lung receiving radiotherapy are in the forms of diffuse patchy ground-glass appearance in general and consolidation fields, including air bronchograms. Ambulant featuring of radiological findings is important in the differential diagnosis for OP. Increased sedimentation with polymorphonuclear leukocytosis is found as the laboratory findings. Positron emission tomography can be useful in the differential diagnosis. Transbronchial biopsy or open lung biopsy can be performed for the final diagnosis (54). The bronchoalveoler lavage (BAL) finding is often in the form of lymphocytic alveolitis (55). It may be confused with RP in the differential diagnosis. Organized pneumonia tends to occur a few months after RT is completed. It often takes longer than RP and usually gets better within 1 year. Although radiation pneumonia is restricted in the RT-applied region, ambulant alveolar opacities are seen in OP.

In the treatment, 1 mg/kg corticosteroid is used for 1-3 months at the beginning; then, 40 mg/day corticosteroid is used for 3 months; and finally, 10-20 mg/day corticosteroid is used for a year. The response to corticosteroid therapy is good. Recovery is observed clinically in 1 week and radiologically in 2-4 weeks. Recurrence can occur in treatments lasting shorter than 1 year (53, 54).

Eosinophilic Pneumonia

Almost all patients developing eosinophilic pneumonia after radiotherapy have a history of asthma or allergy. Symptoms in eosinophilic pneumonia are non-specific. Peripheral alveolar opacities are observed in the chest radiography. The clinical and radiological symptoms of eosinophilic pneumonia and OP are similar, and both respond to corticosteroid very well. The presence of eosinophils in the peripheral blood and alveoli is evaluated on behalf of eosinophilic pneumonia in the differential diagnosis (57). In eosinophilic pneumonia, there are CD4+ T helper cells (Th2) activated in the lung, and these are held responsible for antigenic stimulation (58).

Radiation "Recall Phenomenon"

Radiation "recall phenomenon" (RRF) is a rare inflammatory reaction that occurs as a response to trigger agents in the previous radiotherapy site. However, its etiology and pathogenesis are not well known. It is mainly seen with chemotherapeutic agents (59), the most common ones of which are taxanes, anthracyclines, gemcitabine, and erlotinib. However, it has been reported that it is also observed with tuberculosis drugs, antibiotics, tamoxifen, and simvastatin (60-63). Radiation "recall phenomenon" is generally seen in skin exposed to radiotherapy, but it has been also found in the lung, gastrointestinal system, muscle, central nervous system, and supraglottic region (64).

There are some hypotheses on the development mechanism of RRF. One of them is the development of a reaction associated with recall in cells going on to live in the previous RT site, after cytotoxic therapy is given following RT. An alternative hypothesis is that a permanent mutation secondary to radiation can develop in cells continuing to live in the RT site.

In the diagnosis of radiation "recall phenomenon," the presence of a history of chemotherapy after thoracic radiotherapy, radiological findings, and clinical condition are important. Typical radiological

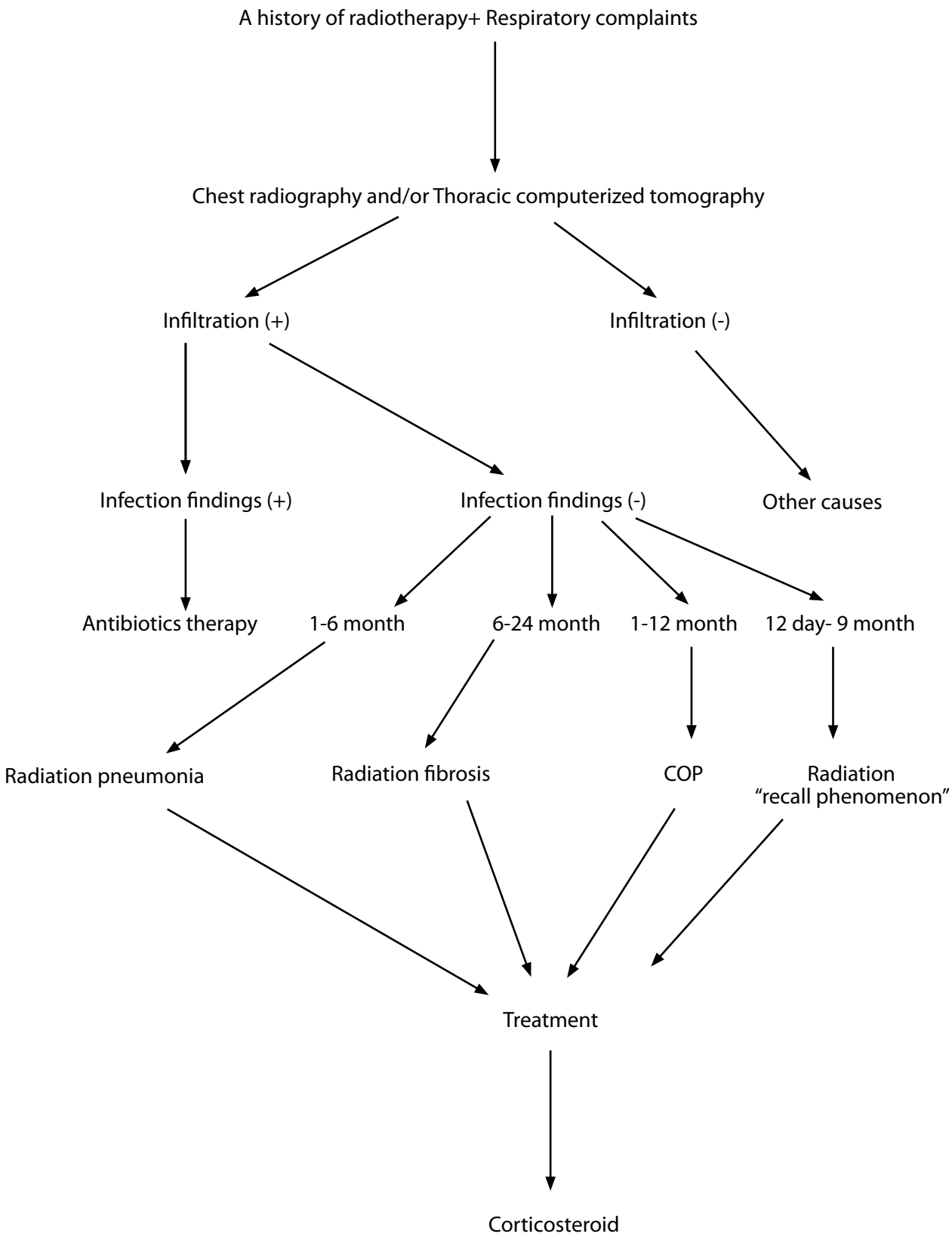

Figure 1. General approach for pulmonary toxicity secondary to RT

findings are a glassy appearance of the lung region being exposed to RT, diffuse infiltration, or consolidation. Patients have complaints of dry cough, mild fever, chest pain, and shortness of breath. Typically, RRF occurs following the first use of the trigger agent, but RRF developing after a couple of days has also been reported. In the literature, the time between the completion of RT and the occurrence of RRF was reported to be ranging from 12 days to 9 months. Treatment includes discontinuation of the trigger agent, the use of corticosteroid, and supportive care (64, 66).

Other types of lung injury induced by radiation

There is an increasing awareness that high-dose radiation can contribute to severe problems in the lung. One of the most scary complications is bronchopleural fistula, which is mostly seen in the postoperative period and is found at a significantly higher rate in patients having a history of RT or CT. In patients receiving neoadjuvant chemotherapy, the application of some methods, like intercostal flap, in order to improve bronchial stump decreases the risk for fistula (67).

In mediastinal malignancies (lung, esophagus, lymphoma, etc.), bronchoesophageal fistula (BEF) can occur secondary to RT. It is a life-threatening complication. The treatment approach is determined, depending on the severity of symptoms, localization of BEF, and general state of the patient. Self-expanding metallic stents, silicone esophageal prostheses, percutaneous gastrostomy, and surgical esophageal bypass can be administered in the treatment (68-71).

The risk rate for the development of pulmonary complications (massive hemoptysis, bronchial stenosis) is approximately 10% with endobronchial brachytherapy applied for the palliation of endobronchial obstructive malignant tumors (72). It can be difficult to distinguish the contribution of radiation from the effects of cancer in severe cases. In the final stage, similar side effects can be observed without the administration of brachytherapy because of the increased doses of external RT (73).

RT dose and concurrent CT can lead to unexpected complications. For instance, the increased traction due to radiation fibrosis can lead to the development of a cavity or pneumothorax (74).

Prevention of lung injury associated with radiation

In some studies, it was found that the administration of prophylactic amifostine during thoracic radiotherapy prevented radiation pneumonia (75, 76). However, these are preclinical data, and the use of amifostine is not a standard treatment that is recommended. Negative results have been obtained in some studies, including large series. Additionally, there are logistic and financial difficulties in the supply of amifostine. Moreover, amifostine has some side effects, such as nausea, exhaustion, and skin rashes (77).

Although it was specified that angiotensin-converting enzyme (ACE) inhibitors were effective in preventing radiation-induced lung injury in some animal studies, this result was confirmed clinically by a few studies. Its mechanism of action is not clear, but it was suggested that this result could result from their vasodilator effect on the vessel wall or antioxidant activity (33, 78-80).

It was reported in randomized controlled trials that the combination of pentoxifylline and vitamin E decreased radiation-induced toxicity at the molecular level in normal tissue. In a study including cases with lung cancer, it was observed that radiation-induced toxicity decreased significantly in the group receiving a combination of pentoxifylline and vitamin E compared to the control group. Moreover, in another study, it was revealed that the use of only pentoxifylline decreased lung toxicity secondary to radiation in both the early stage and late stage. Especially in cases simultaneously exposed to chemoradiotherapy, which increases the risk for toxicity, it is specified that vitamin E and pentoxifylline can be used (81, 82). It is thought that understanding the mechanism based on cytokine in radiation-induced lung injury can be solution options for treatment. TGF-beta is accepted to be the dominant profibrotic cytokine, and it can even be the cause of RP. Therefore, the interventions are for developing molecules with anti-TGF beta activity (83-85). The use of keratinocyte growth factor in mucositis developing in bone marrow transplantation is approved by the American Food and Drug Administration (FDA), and its preclinical trials have been continuing for RF (86).

In conclusion, various lung injury types, the radiation-related mechanism of which is still unclear, occur, and it is difficult to predict the risk factors for toxicity. Toxicities developing during radiotherapy administration are serious obstacles in applying the effective dose. The number of side effects can be reduced through dose control with modern RT techniques. However, there are insufficient data on this issue. Therefore, understanding the toxicities that are associated with RT will increase early diagnosis and treatment success.

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