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2022 Selasi Abla Heletsi

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Radiation–induced lung injuries after modern radiotherapy methods

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V Pardubicích dne 14. března 2022

AUTHOR'S DECLARATION

I declare:

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ANOTACE

Tato bakalářská práce představuje moderní metody používané v radioterapii zhoubných nádorů hrudníku. Teoretická část je věnována popisu náchylnosti plic k radiačnímu poškození při radioterapii s využitím moderních radioterapeutických metody a popisu těchto poškození. Praktická část hodnotí účinky konformní metody radioterapie ve srovnání s konvenčními metodami radioterapie u pacientů s rakovinou hrudníku, jejich účinky na zdravé tkáně a prevalenci plicních poranění.

KLÍČOVÁ SLOVA

Plíce, poškození plic, radioterapie, radiosensitivita, radiační fibróza, radiační pneumonitida.

RADIATION–INDUCED LUNG INJURIES AFTER MODERN RADIOTHERAPY METHODS.

ABSTRACT

This bachelor's thesis introduces the modern techniques used in radiation therapy of thoracic malignancies. The theoretical part is devoted to describing the susceptibility of the lungs to radiation injury during radiotherapy with the use of modern radiotherapy techniques, and describing these injuries. The practical part assesses the effects of conformal radiotherapy techniques compared to conventional radiotherapy techniques in thoracic cancer patients, their effects on healthy tissues, and the prevalence of lung injuries.

KEYWORDS

Lungs, lung injury, radiotherapy, radiosensitivity, radiation fibrosis, radiation pneumonitis.

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LIST OF ABBREVIATIONS AND SYMBOLS

3D-CRT	Three- dimensional conformal radiotherapy
ACB	Alveolar-capillary barrier
AECI	Type I pneumocytes
AECII	Type II pneumocytes
CT	Computed tomography
DNA	Deoxyribonucleic acid
EBRT	External beam radiation therapy
IMRT	Intensity-modulated radiation therapy
IR	Ionizing radiation
MLC	Multi- leaf collimator
NSCLC	Non- small cell lung cancer
OS	Overall survival
PTV	Planning target volume
RF	Radiation fibrosis
RILI	Radiation- induced lung injury
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RP	Radiation pneumonitis
RR	Relative risk
RT	Radiotherapy
SBRT	Stereotactic body radiation therapy
TGF- β1	Transforming growth factor-beta 1
VMAT	Volumetric arc radiation therapy

INTRODUCTION

The occurrence of cancerous malignity is widespread in our world today. It is a leading cause of death worldwide. Even though improvements in cancer therapies increase their success rate, some long-term treatment results are still unsatisfactory due to the after-effects, radiation-relative injuries. Treatment methods, including radiotherapy, give many patients hope for an overall cure, thereby enabling the patient to live a longer and to some extent, a much better life. For many years, radiotherapy (RT) has played an essential role in cancer treatments.

Thoracic Cancer, on which this thesis will be based, is treated with curative intent with the help of radiation therapy. Most patients with thoracic malignancies are expected to undergo RT during their treatment strategy, thereby putting a significant population at risk. This therapy facilitates the occurrence of a common complication: Radiation-Induced Lung Injury (RILI). RILI is a common complication in patients undergoing local thoracic irradiation for thoracic, breast, esophageal, or hematologic malignancies.

Understanding the pathophysiological sequence of radiation-induced lung injury (RILI) is crucial. This could help develop effective strategies for the prevention and better management of potential damage to the lungs. Studying RILI also enables a more durable therapeutic tumor response.

This bachelor's thesis will consist of two parts. The first part will be theoretical, centered on the anatomy and physiology of the lungs as an organ, radiation therapy, and the modern techniques used in radiation therapy. The theoretical part will be concluded with the oncological problem and epidemiology, its classifications, radiation therapy, and the techniques used in radiation therapy of the thorax. The second part of this thesis will be the practical part, which will be based on a literature review to assess the effects of conformal radiotherapy techniques compared to conventional radiotherapy techniques in thoracic cancer patients, and their effects on healthy tissues and the prevalence of lung injuries.

1 AIMS AND METHODOLOGY

1.1 Aims

The main objective of my bachelor's thesis is to outline the prevalence of lung injuries as a result of modern radiotherapeutic treatment techniques of thoracic malignancies and describe these injuries.

The sub-objective of my bachelor's thesis, which the practical part would cover, is to assess the effects of conformal radiotherapy techniques compared to conventional radiotherapy techniques in thoracic cancer patients, the effects they have on healthy tissues, and the prevalence of lung injuries.

1.2 Methods used to achieve aims

The methods used to achieve the objective of my thesis will be through a literature review. The review will be centered on a review/research question that answers the clinical problem. Databases used for my research were Pubmed and ScienceDirect, intending to create a more comprehensive outcome to the given problem. According to the JBI protocol, the PICO formula will be used to compile an answerable research question and compare the development of the effects conformal and conventional radiotherapy techniques have on healthy tissues and how they influence the formation of RILI.

THEORETICAL PART

2 ANATOMY AND PHYSIOLOGY OF THE LUNGS

2.1 Anatomical structure of the lungs

The lungs are a paired organ located in the thoracic cavity (Figure 1). They are a vital organ in which the exchange of gases between air and blood takes place during respiration. Humans have two lungs, right lung and left lung, situated in the mediastinum (thoracic cavity) (Čihák, 2013, p. 223). The right lung forms the right pleural cavity, consisting of 3 lobes; upper, middle, and lower lobes, and is larger than the left lung. The left lung forms the left pleural cavity and is divided into the upper and lower lobe. The lobes of the lungs are further divided into segments that are considered the basic building and functional units of the lungs (Naňka et al., 2009, p. 182-185).

The place of entry and exit of blood vessels and bronchi is known as the pulmonary hilum (hilus pulmonis). The bronchi recede into the lungs. In the pulmonary hilum, they gradually branch out and form a bronchial tree. The walls of the bronchi consist of a large number of smooth muscles. Smaller bronchi are called bronchioles and do not have cartilaginous reinforcement. The wall is composed of mucus, ligaments, and smooth muscles. It is easily damaged by inflammation. Bronchioles have finite twigs, which are called alveoli. There are about 300 to 400 million alveoli located in both lungs, with a total surface area of 80 – 150 m^2. They are covered with a network of capillaries and due to their thin walls, exchange of respiratory gases between the air and blood is allowed (Čihák, 2013, p. 223).

The alveoli are millions of hollow, distensible, cup-shaped cavities in the lungs, about 0.1 – 0.2 mm in diameter. The alveoli consist of an epithelial layer of simple, fragile, flattened cells surrounded by capillaries. These flattened cells are known as Type I (AECI) and type II (AECII) pneumocytes. Alveolar epithelial cells (pneumocytes) play a vital role in lung homeostasis. Type I pneumocytes cover 90 – 95 % of the alveolus, are responsible for the facilitation of gaseous exchange between the airspace and the underlying capillaries, and the transport of protein that maintains fluid homeostasis. On the other hand, AECII cover just 7% of the total alveolar surface. They also reside in the alveolar lining, and this type of pneumocytes produce surfactant. Each alveolus has 4 to 12 capillary loops. Some have blood flowing through them constantly, while some have blood flow only when there is an increased need for oxygen. The inner surface of the alveoli consists of alveolar macrophages, which can be located individually

or in groups. Alveolar macrophages function as a defense against infections (Ghafoori et al., 2008; Lierová et al., 2018).

The lungs are covered on the surface with a fine shiny, fibrous membrane called the pulmonary pleurae (pleura visceralis*)*. The enclosed space between the pleurae is filled with 10 to 15 ml of clear liquid. This fluid reduces the friction between the two pleurae during respiratory movements (Rokyta, Marešová a Turková, 2016, p. 108).

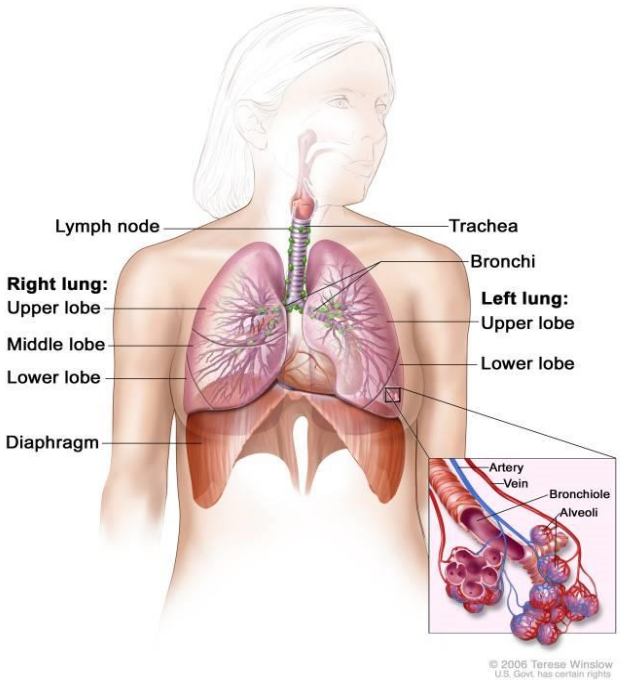

Figure 1 – Anatomy of the respiratory system (Winslow, 2006).

2.2 Respiratory physiology

The lungs are organs that ensure the exchange of gases. Human breathing is, to some extent, dependent on consciousness. The center of respiration is located in the medulla oblongata (Čihák, 2002, p. 233-235). The basis of inspiration is the enlargement of the thoracic cavity. There is a lower pressure in the pleural cavity compared to atmospheric pressure. Due to the connection of the airways to the external environment, the atmospheric pressure in the lungs is higher than it is in the pleural cavity. This higher pressure causes the lungs to dilate and press it against the pleural cavities' walls. During inhalation, the volume of the chest increases, and thus, the increasing vacuum in the pleural cavity allows for more dilation of the lungs. During exhalation, when the chest cavity is reduced, the lungs remain in contact with the wall of the pleural cavity and thanks to its flexible apparatus contract in the direction of the hilum (Čihák, 2013, p. 252-254).

2.3 Radio sensitivity of the lungs

The lungs are one of the most sensitive tissues to ionizing radiation (IR). Its vulnerability to radiation damage limits the success of radiotherapy for lung cancer treatment. The radiation causes inflammation of the alveoli, making it harder for oxygen to pass through the alveoli into the bloodstream (Figure 2) (Hanania, 2019).

The alveolar-capillary barrier (ACB) is the most radiosensitive subunit of the lungs to ionizing radiation. This frequently describes radiation-induced lung injury as diffuse alveolar damage (Ghafoori et al., 2008). The alveolar-capillary barrier is the gas-exchanging region of the lungs. It is formed by AECI and the endothelial cells of capillaries. The flat nature of both epithelial and endothelial cells causes them to have a large surface area, but minimal cytoplasm, and compose the ACB. The ACB's ability to resist the movements of proteins is dependent on the formation of tight junctions between alveolar epithelial cells. Resident fibroblasts are the most populated cells in the alveolar interstitium as they make up more than 95 % of the interstitial cells. These are highly adaptable cells that constantly adjust the support they provide to growth, regeneration, and cytokine production capability. Resident fibroblasts have the ability to activate and transform into myofibroblasts under certain pathological conditions. These myofibroblasts constitute the key effector cell type in tissue fibrosis (Lierová et al., 2018).

The energy of ionizing radiation passing through lung tissue has ample strength to cause direct double-strand breaks in DNA molecules, as well as the hydrolysis of water and other molecules. The result of this hydrolysis is the generation of reactive radicals ROS and NOS, which may lead to secondary interaction with DNA, and other components of the cell (Lierová et al., 2018).

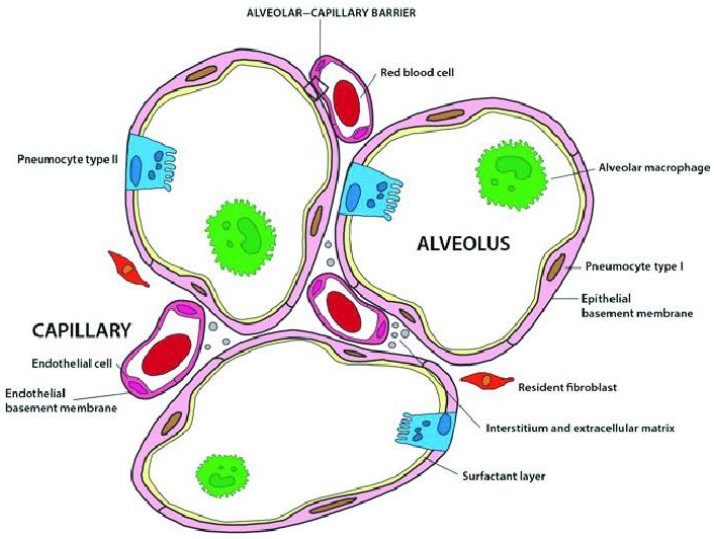

Figure 2 – Structural scheme of an alveolus in the lung under physiological conditions (Lierová et al., 2018).

3 RADIATION–INDUCED LUNG INJURIES

Radiation-induced lung injury (RILI) is a general term for damage to the lungs as a result of exposure to IR. This injury more than often occurs in the area of the lung exposed to radiation. It is a common complication in patients with thoracic malignancies receiving local thoracic irradiation and occurs in 5 – 20 % of patients. The lungs are one of the most sensitive tissues to ionizing radiation. Its susceptibility to injury makes irradiation unavoidable and dose-limiting, and this, in turn, limits the success of radiotherapy for lung cancer treatments (Giuranno, 2019).

3.1 Classification

Radiation-induced lung injury is stratified into two phases. The early phase, radiation pneumonitis (RP), manifests as acute lung tissue inflammation. This inflammatory reaction is a consequence of exposure to radiation. The late phase of RILI, radiation fibrosis (RF), is progressive chronic dyspnea that presents itself as chronic pulmonary tissue damage. RP usually occurs one to three months after the patient has undergone radiation treatment but can manifest as late as six months after treatment. While early lung injury occurs as early as one to three months after exposure to radiation, late lung injury may occur even years following radiation treatment. Late injury, the manifestation of RF, can be detected radiographically six months post radiation exposure. By twelve to twenty-four months following exposure, the majority of patients have radiologic evidence of lung fibrosis. Patients with radiation pneumonitis are more prone to developing fibrosis. However, not all patients who develop fibrosis have a history of pneumonitis. The severity of lung injury varies widely among patients ranging from asymptomatic to severe respiratory failure and death (Giuranno, 2019, Hotchkin, 2019).

3.2 Pathophysiology of radiation-induced pneumonitis

Exposure of the lungs to radiation instigates the destruction of epithelial and endothelial cells, which leads to a loss of the function of the alveolar barrier. This dysfunction induces increased inflammation, vascular permeability, and cytokine release within days or weeks. The aggregation and accumulation of macrophages facilitate the development of hypoxia and invigorates the generation of reactive oxygen / nitrogen species (ROS / RNS) and proinflammatory, profibrogenic and proangiogenic cytokines that preserve non-healing tissue response that leads to chronic radiation injury. The changes induced by radiation can be classified into five phases according to the exposure time:

- **Early phase** begins within hours or days of RT and comprises vascular congestion that induces leukocyte infiltration, pneumocytes type I apoptosis, and intra-alveolar edema. Discharge of the first cytokines takes place within two weeks post-radiotherapy. It consists of the following: tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), high-molecular-weight mucin-like antigen KL-6, platelet-derived growth factor-β (PDGF-β), and basic fibroblastic growth factor (bFGF). 6 – 8 weeks post-radiation, a second wave is activated. This wave is characterized by increased oxidative damage to the deoxyribonucleic acid (DNA), hypoxia, decreased lung perfusion, and increased expression of transforming growth factor-beta 1 (TGF-β1).
- **Latent phase,** characterized by augmented secretions due to the rapid increase in the number of respiratory goblet cells and ciliary cell malfunction. It is followed by tracheal-bronchial hypersecretion and degenerative changes within the alveolar epithelium and endothelium.
- **Exudative phase** (clinical RP phase) occurs 3 – 12 weeks after RT exposure. It comprises epithelial and endothelial detachment that causes alveolar collapse followed by a narrowing of the pulmonary capillaries and microvascular thrombosis. The desquamation of pneumocytes and the alveolar discharge of a fibrin-rich exudate contribute to the formation of hyaline membranes.
- **Intermediate phase** alludes to the disintegration of hyaline membranes, which occurs after fibroblasts that migrate and proliferate in the alveolar walls induce the synthesis of collagen. The significance of TGF-β1 expression is based on the influx of fibroblasts and their conversion to myofibroblasts, which produces lung fibrosis. This condition, in turn, leads to hypoxia, which induces the release of both profibrogenic and proangiogenic factors, so this cycle proceeds until it reaches the ultimate stage of chronic lung disease.
- **Fibrotic phase** can present itself after six months of radiation exposure. It advanced biologically for several years and is characterized by hyperplastic pneumocytes, increased myofibroblasts, and extensive collagen depositions in the pulmonary interstitium and alveoli. These deposits lead to the collapse of alveolar spaces, eventually decreasing pulmonary volume (Arroyo- Hernández et al., 2021).

3.3 Pathophysiology of radiation fibrosis

The pathophysiology of RF consists of a complex event. The most crucial player in this complex event is the product of radiation stimulated inflammatory, epithelial, and mesenchymal cells

referred to as the transforming growth factor-β (TGF-β). This growth factor is responsible for the conversion of fibroblasts into matrix-synthesizing myofibroblasts. The myofibroblasts, on their part, secrete excess matrix-forming substances such as collagen, proteoglycans, and fibronectin that result in subsequent and progressive avascularity, thickening, stiffness, scarring, atrophy, and non-functionality of the affected tissue. TGF-β reduces the activity of matrix metalloproteinase (MMP)-2 and MMP-9 and therefore results in excess matrix deposits (Purkayastha et al., 2019).

TGF-β is also responsible for the regulation of the production of fibroblast growth factor, tumor necrosis factor, epidermal growth factor, and interleukin-1 that act in various cell lines such as the fibroblasts, smooth muscle cells, and endothelial cells, hence contributing to the process of the development of fibrosis. Ionizing radiation may directly result in RF by causing vascular endothelial injury and indirectly by activating the inflammatory, epithelial regeneration, tissue remodeling pathways and the coagulation cascade. The two mechanisms involved in radiation injury to both tumor and normal cells are the direct and indirect DNA damage through the generation of reactive oxygen species and FRs that destroy protein, lipid, and nucleic acid molecules, thus causing ischemia and thrombosis through the secretion of cytokines and chemokines (Figure 3) (Purkayastha et al., 2019).

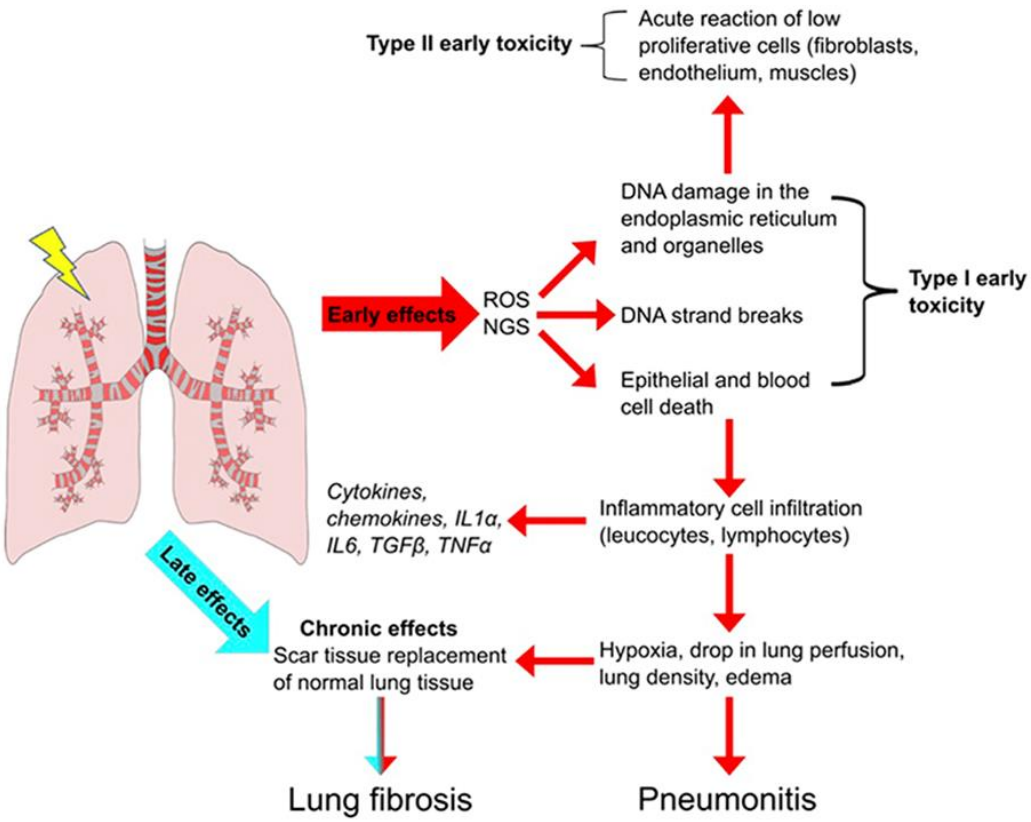

Figure 3 – Radiation induced lung injures RILI). Schematic overview of the steps leading to pulmonary toxicity after radiotherapy (Giuranno et al., 2019).

3.4 Predisposing factors

Radiotherapeutic treatments are affected by many factors. The probability of adverse lung effects after radiotherapy and the severity of these effects is mainly associated with patient characteristics and dosimetric parameters. The total dose of radiation delivered is one of the primary risk factors for the development of radiation-induced lung injury. Other factors that influence the development of RILI include fractionation, tumor location, tumor volume, smoking, comorbid conditions, age, and sex. In addition, patients who are treated with chemotherapy, especially those treated with actinomycin D, adriamycin, bleomycin, and busulfan, are at greater risk of injury. These agents are known to potentiate the effects of radiation on the lungs (Hotchkin, 2019).

Ionizing radiation during radiation therapy is the primary treatment-related risk factor of radiation fibrosis. Parameters such as the total dose of radiotherapy, dose per fraction, the volume of tissue treated, and the time course of treatment delivery also influence the occurrence of RF. More specifically, the degree of radiation-induced fibrosis directly correlates with increased radiation dose and hypofractionation (fewer fractions require greater doses),

increased field size, and prolongation of therapy. (Purkayastha et al., 2019). Patients with pre-existing diseases such as connective tissue disease, systematic scleroderma, and systematic lupus erythematosus (SLE) are more prone to developing radiation fibrosis (Suarez et al., 2014).

3.4.1 Risk factors predisposing to radiation pneumonitis

Lung dose

The total lung radiation dose is the main factor that predisposes to radiation pneumonitis. Radiation pneumonitis rarely presents among patients treated with a dose of less than 20 Gy, while it almost always presents among patients who are treated with doses of 40 Gy or more. The radiation dose delivered to the percentage of healthy lung tissue receiving at least 20 Gy (V20) links to the development of lung injury (Hotchkin, 2019).

Fractionation

Radiation therapy makes use of certain basic fraction regimes. The probability of the occurrence of lung injury is dependent on the values of these fraction regimes. Normofractionation (conventional fractionation) applies 5 fractions per week; 2.0 (1.8) Gy per fraction (10 Gy per week). Hypofractionation makes use of the application of a higher single dose at longer intervals while reducing the total focal dose. Hyperfractionation uses a smaller single dose of radiation several times a day. The minimum required interval between fractions is 6 hours. However, 8 hours is more suitable (Binarová, 2012).

Tumor location and volume

Tumor location is one of the main factors that vaticinate the development of radiation pneumonitis. Tumors (neoplasms) located primarily in the lower lobes of the lungs are more strongly associated with the development of RP due to the better oxygenation, perfusion, and ventilation of the lower pulmonary region (Guiranno, 2019).

Patients with a higher tumor volume usually have a more significant lung and surrounding radiated volume. The most crucial factor that influences the development of RP is thus related to the percentage of lung-radiated volume (Arroyo- Hernández et al., 2021).

Comorbid conditions, age and sex

The most common pre-existing conditions in lung cancer patients are chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Pre-existing subclinical interstitial lung disease is a significant risk factor for both the development of radiation pneumonitis and the increased severity of the disease (Arroyo- Hernández et al., 2021).

Older patients are at increased risk of radiation injury. Age is one of the main factors that influence the development of radiation-induced lung injury. Older patients (>65 years old) have less tolerance to RT and are at a significant risk of developing adverse effects. This is primarily due to the fact that older patients have two or more diseases co-existing at once (comorbidities). The impact of gender on RILI is still unclear. Women have smaller lung volumes and more often develop an autoimmune disease, which increases their risk of RILI as compared to men, whose lungs have larger volumes. Despite age being a strong risk factor, additional risk factors such as the patient's smoking status and pulmonary function also influence the development of RP (Hotchkin, 2019).

3.4.2 Risk factors predisposing to radiation fibrosis

The increase in the risk of development of radiation fibrosis is a result of a number of factors. These risk factors are either treatment-related or patient-related. The primary treatment-related factors are the total dose received by the patient during radiotherapy and dose per fraction, the volume of tissue area that is treated, and the time course of treatment delivery. More specifically, the degree or increased risk of radiation fibrosis is directly proportional to increased radiation dose and hypofractionation; fewer fractions require greater doses. The degree of RF also directly correlates with increased field size and prolongation of the therapy period (Straub et al., 2015).

The simultaneous use of chemotherapy, as well as the incorporation of surgical management pre or post-radiotherapy are also treatment-related factors that are known to play a role in the development of RF. In particular patients with systematic scleroderma, systemic lupus erythematosus (SLE), or Marfan syndrome, the susceptibility to developing severe RF increases. Preexisting connective tissue disease may also contribute to the development of RF, and these are classified as patient-related factors. Other factors that have been recently found to play a part in the predisposition to RF include genetics and epigenetic modifications to DNA and histones (Straub at al., 2015).

3.5 Symptomatology of radiation pneumonitis and radiation fibrosis

Radiation pneumonitis typically presents 1 to 6 months after the patient is exposed to radiotherapy treatment, with symptoms of chest congestion, chest pain, shortness of breath, cough, and occasionally a mild fever. The radiographic findings are variable and often unrevealing. A chest x-ray should be obtained but is usually unrevealing. Differentiating radiation pneumonitis from other processes (e.g., tumor progression, infection, pulmonary

emboli, heart disease) can be challenging. Acute pneumonitis is therefore a clinical diagnosis after considering other disorders that cause similar symptoms.

Radiation Fibrosis is generally a late complication of radiation that has the ability to remain dormant and not manifest clinically for years after treatment. This form is described as delayed RF. Chronic RF manifests within a year after radiotherapeutic treatment. A few cases, known as acute RF, manifest as early as during treatment. Acute RF usually may start during or right after treatment and last for several weeks after it ends, and then they get better. Acute RF may manifest as skin darkening, scarring, dermatitis, decreased salivation, hair loss, and ultimately pain (Purkayastha et al., 2019).

After relatively high doses of RT, unusual pulmonary complications, such as bronchial stenosis, bronchomalacia, and mediastinal fibrosis, are reported. More regionally specific chronic manifestations of RF include trismus, xerostomia, reduced voice quality, skin induration, osteoradionecrosis, dysphagia, and aspiration in patients with muscle atrophy, soft-tissue edema, lymphedema, restricted joint mobility, mucosal thickening, ulceration, fistula, and stenosis of hollow organs. Long-term complications occurring due to RF may include progressive thickening and skin fibrosis; subcutaneous tissue; muscle fibers, ligaments, tendons, bones, nerves, and lymphatic system; progressive ischemia; and adherence to underlying subcutaneous and fibro-fatty tissues. RF causes easy fatigability, weakness, myopathy, and painful spasms in the skeletal muscles (Purkayastha et al., 2019).

3.6 Diagnosis of radiation-induced lung injuries

Diagnosis of lung injury can be determined with the help of high-resolution imaging techniques of the thorax and is best visualized with a computed tomography (CT) scan. A chest X-ray is the first tool used in approaches to RP. A CT scan is more sensitive than chest radiography for detecting slight lung injury following radiation treatment. Frequently, radiographic evidence presents before or even in the absence of symptoms of lung injury. A lung biopsy is rarely needed to establish a diagnosis of radiation pneumonitis or fibrosis. However, in early radiation pneumonitis, if a lung biopsy is performed, there could be visible evidence of acute inflammation with interstitial inflammation and neutrophils with evidence of organizing pneumonia seen slightly later in the acute phase (Hotchkin, 2019).

3.7 Patient management after diagnosis

Because of the common nature of radiation-induced lung injury, more attention has been directed toward preventing the injury. The most frequently used approach is modulating the

dose of radiation in patients at the highest risk of developing radiation pneumonitis. However, while a decrease in radiation dose is associated with a decreased risk of lung injury, it is also associated with decreased control of the primary malignancy. For high-risk patients, the dose can be adjusted. With the advent of new forms of radiotherapy techniques, such as stereotactic body radiation therapy, intensity-modulated RT, and volume modulated arc therapy, delivery of beam arrays to the tumor and surrounding tissues is more precise, reducing the incidence of lung toxicity (Hotchkin, 2019).

4 RADIOTHERAPY AND THE USE OF MODERN RADIOTHERAPY TECHNIQUES

Radiotherapy (RT) is an indispensable method that utilizes IR for the treatment of both cancerous and non-cancerous diseases (Hynková et al., 2012). This ionizing radiation can cause the death of cancer cells or engender genetic changes, resulting in the death of cancer cells. High-energy radiation damages the genetic material (DNA) of cells thus blocking their potential to separate and multiply further. In spite of the damage caused by radiation to both normal and cancer cells, the objective of radiotherapy is to maximize the radiation dose abnormal cancer cells receive while simultaneously minimizing the radiation dose normal cells that are near the tumor focus or in the direction of the radiation beam are exposed to (Baskar et al., 2012).

RT plays a significant role in the treatment procedure for oncological patients. Significantly, large groups of oncological patients, up to 50 – 70 %, undergo radiotherapy during the period of their illness (Hynková et al., 2012). RT is not only applied with curative intent but also as a very effective palliative treatment method to relieve patients from pain. Other indications for radiotherapy include its combination with other treatment strategies such as surgery, chemotherapy, or immunotherapy. The goal of radiotherapy before surgery (neoadjuvant therapy) is to shrink the tumor before the main treatment, while radiotherapy after surgery (adjuvant therapy) has the purpose of destroying the microscopic tumor cells that may have remained after the surgical procedure (Baskar et al.,2012).

After the discovery of computed tomography in 1973 and advanced computer technology, there have been significant developments and advancements in radiotherapy planning and irradiation. With the development of highly conformal radiotherapy techniques such as Three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, image-guided radiotherapy, or volumetric modulated arc therapy, dose distribution is optimized while preserving healthy tissues (Hynková et al., 2012).

At present, the possibilities for planning radiotherapy and irradiation itself are significantly advanced. Conformal irradiation techniques have been involved in the practice to help the target radiation while examining healthy tissue. Three-dimensional conformal radiotherapy (3D-CRT) is an irradiation technique in which a beam of radiation is adapted to an asymmetrical shape three-dimensional target volume (Hynková et al., 2012). 3D-CRT is based on CT imaging, thanks to which the exact location of the tumor and surrounding organ structures is possible for optimal beam placement and shielding. The aim is to deliver radiation to the gross

volume of the tumor, with a margin for microscopic tumor spread and for additional organ edge uncertainties caused, for example, by organ movement (Baskar et al., 2012). Using CT scans or magnetic resonance imaging (MRI), which are three-dimensional imaging methods, is the basis for 3D planning (Hynková et al., 2012). Magnetic Resonance imaging is increasingly used in radiotherapy planning due to its excellent contrast of soft tissue compared to CT. MR images are formed from small induced signals and atomic magnetic dipoles when coherently preceded by a strong magnetic dipole field. Most MR clinical systems use superconducting magnets with a field strength of 1.5 or 3 T. MR images are primarily used to outline tumor volume and endangered organs, but also, they are often used to assess the extent of tumor movement, so MR examination is ideally performed in a patient in an RT treatment position (Schmidt et al., 2015)

4.1 Three-Dimensional Conformal Radiotherapy

Conventional RT for lung cancer, developed in the 1970s before the adoption of computed tomography (CT) for treatment planning, was supplanted by 3D-CRT, which uses 3D patient-specific geometry in treatment planning. Despite this progression from conventional RT, limited beam arrangements and uniform dose in each beam in 3D-CRT can lead to high doses to organs at risk (OARs) (i.e., normal lungs, heart, spinal cord, and esophagus) because of the simple and relatively large fields. Several pioneers of the early 3D-CRT era published predictors of complications. This high risk of complications translated to poor outcomes from increased morbidity and mortality in patients whose disease was controlled. A significant risk of local failures, suggesting a possible utility to dose escalation, was also noted; however, the already high rates of toxicity meant that newer techniques would be required that could change the therapeutic ratio. For these reasons, considerable interest focused on developing and applying treatment planning and delivery techniques that could improve dose conformality (e.g., IMRT) (Diwanji et al., 2017).

Three-dimensional conformal radiotherapy (3D-CRT) is a technique where irradiated fields try to adapt to the irregular shape of the planned target volume (PTV). Two-dimensional conventional RT, which uses rectangular fields based on plain X-ray imaging, has been generally replaced by 3D conformal radiotherapy (Hynková et al., 2012). It was developed and proven in the late 90s as an advantageous method for the treatment of cancer because it allows the irradiation of the target volume with a safety margin called the Clinical Target Volume (CTV), and thus putting less strain on the healthy surrounding tissues. 3D-CRT allows for a high level of precision and accuracy. Thus, it is used in the delivery of radiation treatment to

tumors that are close to vital organs like the lungs during the treatment of chest tumors, and the spinal cord, optic nerve, and salivary glands, during the treatment of head and neck tumors (Baskar, et al., 2012).

4.2 Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is a more advanced form of 3D-CRT (Figure 4). IMRT was introduced into clinical practice in the mid-1990s. In this technique, in addition to the adaptation of the radiation beam to the shape of the target volume, the intensity (fluence) of the beam also makes some adaptation. Beam modulation can be performed in several ways. Using a multi-Leaf Collimator (MLC) in the head of the device and a unique SW system is the most used method in clinical practice. The MLC perpetually change its position at a certain speed so that the shape of the irradiated field changes perpetually. They deliver radiation directly into the target area from multiple angles. During beam modulation, either the arm of the irradiator could be immobile, and the patient is irradiated by individual static fields from multiple angles, or the irradiator head rotates with a simultaneous movement of the treatment couch. The beams are precisely sculpted to match the shape of the tumor so that they treat it while minimizing exposure to surrounding healthy tissue (Hynková et al., 2012).

The dosimetric benefits of dose distribution modulation by IMRT are particularly evident in radiotherapy of nasal, paranasal, and basal tumors, sites that were previously very difficult to cover homogeneously in a dose-free manner without simultaneously irradiating surrounding organs that are potentially at risk. This technique is also used advantageously for irradiation of gynecological tumors or the rectum, where the intestines and bladder are spared (Šlampa et al., 2022).

IMRT is also used medically as a treatment technique for breast cancer, usually in patients with large breast volume, patients receiving treatment to the whole left breast, and patients with previously irradiated tumors that recur. It may also be considered a technique for partial breast irradiation. IMRT is a technique which is also often used in patients with lung cancer, thoracic esophageal cancer, thoracic lymphoma, or sarcoma to deliver radiation therapy (Sura et al., 2008). IMRT can deliver a higher dose to the targets and spare more critical organs in lung cancer than can 3D-CRT when used to treat lung cancer. However, tumor-motion management and radiotherapy planning on the basis of four-dimensional computed tomography (4D CT) scanning are pivotal to achieving the maximum benefit of IMRT and eliminating or minimizing potential uncertainties of this treatment technique. Several unmodulated fields in 3D-CRT

(typically 3–4) are designed to deliver the dose directly to the targets, while with IMRT, optimized modulated fields (normally 6–12) are designed to deliver the dose to the targets. The shapes and intensities of each field in IMRT are optimized by means of computer algorithms to conform the dose to the targets and spare the critical structures and organs in proximity. Consequently, radiation plans formulated for IMRT can deliver a higher dose to the targets and spare more critical structures than with 3D-CRT (Chang, 2016).

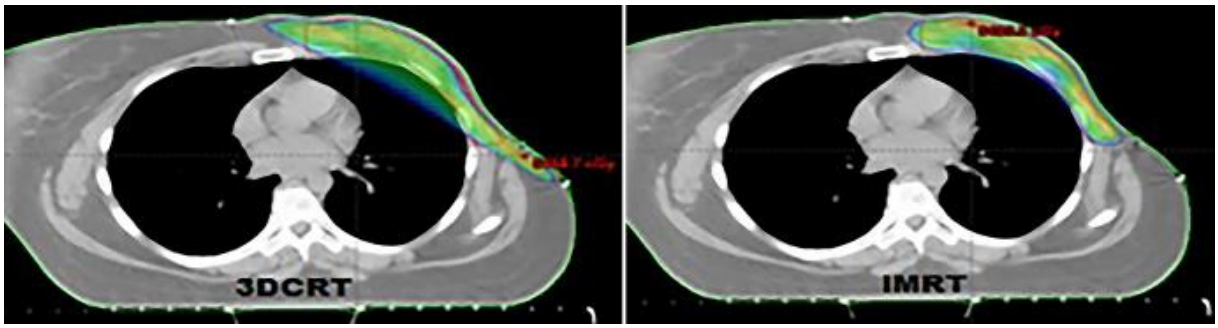

Figure 4 – Dose distribution patterns in IMRT and 3D-CRT radiotherapy methods (Serhat et al., 2019).

4.3 Volume modulated arc therapy

Volume Modulated Arc Therapy (VMAT), in comparison with conventional radiotherapy techniques, is a radiation technique that can obtain a high conformal distribution of doses with improved coverage of the target volume and spares healthy tissues. In 2007, a practical algorithm for arc optimization was published, which supported rapid commercial development and clinical adoption of volumetric modulated arc therapy. It was a technique based on the Intensity-modulated arc therapy (IMAT) principle, where other variable factors such as the speed of the gantry, dose rate, and MLC orientation affect modulation and thus reduce the number of swings needed. This shortens the irradiation time. VMAT is a widely used radiation treatment technique for therapy due to its significantly higher delivery efficiency while maintaining relative dosimetry in comparison to conventional IMRT (Hynková, 2012).

The basic concept of arc therapy is the delivery of radiation from the continuous rotation of the source, where the patient is treated at an angle of 360°. The advantage VMAT has is the potential to offer an effective treatment administration as a result of a reduced treatment delivery time compared to IMRT (Teoh et al., 2011). VMAT has a significant potential benefit for cancer patients in the situation where the tumor comes in close approximation to the chest

wall region. It can accommodate the multiple sloping surfaces of the chest wall and the dynamic nature of the simultaneous dual motion of both the gantry and the multileaf collimators. It permits potentially more optimal radiation therapy treatment planning and therapy execution. Recently, for the treatment of esophageal and gastroesophageal junction tumors, parasternal nodes in breast tumor irradiation, and irradiation after bilateral partial or total mastectomy, the VMAT technique is used most often (Šlampa et al., 2022).

4.4 Stereotactic body radiation therapy

Stereotactic body radiation therapy (SBRT) has emerged as a new radiotherapy delivery technology that allows for potential treatment in many patients who have stage I Non- Small-Cell Lung Cancer (NSCLC) and was set aside as candidates who are not worthy of surgical resection. These treatment methods have curative intent. The basis of SBRT is the delivery of extremely high doses of radiation in small fractions while minimizing the amount of high-dose radiotherapy to other organs with an accurate definition of the goals of the treatment (Donovan et al., 2018). The administered dose for SBRT ranges from 25 to 70 Gy, according to the type and size of the tumor. This technique has the potential to achieve similar results as a surgical procedure in many patients where resection is not possible. The SBRT method allows treatment with meager rates of morbidity and mortality. It is performed on an outpatient basis in 1– 5 fractions for 1 hour within a week) (Blasco et al., 2017). Tumors situated close to vital body organs or in areas that are prone to body movement such as the chest and the abdomen, are difficult to reach. SBRT is used to address these tumors (Ding et al., 2013).

The challenges of SBRT treatment planning are emphasized by the high dose per fraction and a low number of fractions. Dose calculations for SBRT must also be very precise and, therefore, should include a heterogeneity correction, due to the fact that lung density can vary up to 0.1 times that of surrounding tissue (Diwanji et al., 2017).

REVIEW PART

5 METHODOLOGY OF RESEARCH PART

A search of articles in professional magazines and published studies were used in order to compile an overview and write this theoretical work. I followed a well-defined procedure methodology of the Joanna Briggs Institute (JBI), which is currently the leader in the creation of systematic reviews. Systematic reviews have become very popular in the last few years. Creating systematic reviews allows for an accurate response as possible to different species of clinical issues. A systematic review starts with a thorough, well-thought-out review/research question, which is clearly and narrowly focused in order to be able to answer a clinical problem. Following the formulation of a review question, inclusion and exclusion criteria need to be defined and studies located through searching. According to the criteria, studies are then selected for inclusion and assessed. Extracting data, analyzing, and synthesizing the relevant studies is carried out after assessing and selecting studies to be included in the review. Finally, presenting and interpreting the results of the selected studies brings the systematic review to a conclusion (Klugar, 2015; JBI.Global, 2021). These standards will be used in my methodology and research.

Before the actual search for the studies, it was necessary to define the topic and determine the selection criteria. I, therefore, compiled an answerable question according to the PICO formula, i.e., (P) - patient/population, (I) - the type of intervention used, (C) - comparison with another type of intervention, (O) – outcome (Table 1). Therefore, if I wanted to assess the effects of conformal radiotherapy techniques compared to conventional radiotherapy methods in thoracic cancer patients and their effects on healthy tissues and the prevalence of lung injuries, it was necessary to define and concretize the individual concepts (Table 1).

Each patient who was the subject of the sought-after studies had to be an adult, that is, over the age of 18, who has undergone radiation therapy of the thoracic region. Conformal or conventional techniques of radiation therapy were used during the treatment process.

Table 1 – Criteria according to the PICO formula

Population	Adults (18 years and older), patients with thoracic malignancies
Intervention	Radiation therapy using conventional radiotherapy techniques
Comparison	Radiation therapy using conformal radiotherapy techniques
Outcome	Occurrence of Radiation-induced lung injuries

5.1 Review question

In patients with thoracic malignancies, is the development of radiation-induced lung injuries minimal with the use of conformal radiotherapy techniques as compared to the use of conventional radiotherapy techniques?

5.2 Database search

For the search of publications, I used the internet databases PubMed and Science Direct. Based on the keywords I entered (see Tables 2 and 3) the system generated a number of articles and studies. PubMed is a free search engine and resource that supports the search and retrieval of biomedical and life sciences literature, granting access to references and abstracts. This database contains only bibliographic citations and abstracts. Links to full-text variants are available for most articles. The National Library of Medicine of the United States and the National Institute for Health operates PubMed https://pubmed.ncbi.nlm.nih.gov/ (database 1). Science Direct, likewise, is a large database that provides access to perform research scholarly in various scientific areas. It is one of the world's leading source for scientific, technical and medical research. Link to full-text variants are also available for most articles https://www.sciencedirect.com/ (database 2).

Table 2 – PICO keywords

Population	Adult, lung cancer patients, non-small-cell lung cancer.
Intervention	IMRT, intensity-modulated radiation therapy, VMAT, volumetric modulated Arc therapy, SBRT, stereotactic body radiation therapy.
Comparison	3D-CRT, three- dimensional conformal radiation therapy, radiotherapy.
Outcome	Toxicity, radiation pneumonitis, radiation fibrosis, lung toxicity.

For the selection of my articles for this review, I used a set of criteria to aid in the choosing of suitable articles, which would provide answers to my research question. I included an inclusion and exclusion criteria for the results of my database research, where articles that fell under the exclusion criteria were eliminated from my review. My inclusion criteria comprised of publications published in English, research studies that involved patients, respondent sample with lung cancer, comparative publications that compared two or more techniques, publications that were relevant to my research question, among others (see Table 3).

Table 3 – Criteria for literature search

	Criteria	EC= Exclusion Criteria	IC= Inclusion Criteria
1	Population	Respondent sample without lung cancer or tumors within the lung area.	Respondent sample with lung cancer or tumors around the lung area.
2	Context	Publications published in languages other than English.	Publications published in English.
3	Context	Publications that are not comparative.	Publications comparing two or more radiation techniques.

4	Methodology	Insufficiently described methodology.	Sufficiently described methodology.
5	Methodology	Research studies out of context of the research question.	Research studies in context with the research question.
6	Publication	Publications not published in peer-reviewed journals.	Publications published in peer-reviewed journals.
7	Topic	The content of the publication is not relevant to the research question.	Publications relevant to the research question.

I entered individual words into each database. PubMed and ScienceDirect database search results for individual keywords and variations using the Boolean operators AND and OR (see Table 4).

Table 4 – Database search

	Keywords	**Pubmed**	**Sciencedirect**
1	lung cancer patient	191,923	42,485
2	adult	8,455,137	433,422
3	non-small cell lung cancer	92,396	34,467
4	**1 OR 2 OR 3**	**8,562,210**	**489,977**
5	Intensity-modulated radiation therapy	18,827	4,418
6	IMRT	10,956	8,323
7	Volumetric modulated arc therapy	18,463	1,530
8	VMAT	19,004	2,863
9	Stereotactic body radiation therapy	7,011	3,423

10	SBRT	5,633	4,640
11	Three-dimensional conformal radiation therapy	3,491	728
12	3D-CRT	23,320	948
13	Radiotherapy	401,236	79,645
14	**5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13**	**403,997**	**92,655**
15	Toxicity	994,631	306,339
16	Radiation pneumonitis	3,740	1,617
17	Radiation fibrosis	6,631	1,795
18	Lung toxicity	66,948	15,210
19	**15 OR 16 OR 17 OR 18**	**1,001,781**	**308, 619**
20	**4 AND 14 AND 19**	**38**	**41**

From a total of 79 studies, I found 16 duplicates that were found on both databases. Based on titles and abstracts, I eliminated 38 studies because they were not suitable according to my criteria. The eliminated studies did not match my inclusion criteria, where their titles and abstracts were either not related to lung cancer and toxicity or were not comparative studies.

The titles and abstracts of the first group of eliminated studies were neither suitable to provide an answer to the PICO question nor did they have the full article text accessible for screening and, eventually a review. Eliminated studies were based on esophageal, breast, and other types of malignancies, rather than lung malignancies, which is the focus of my research. Several of the eliminated articles were also geared towards chemoradiotherapy. From the remaining 25 studies, I studied the entire text and further eliminated 15 studies based on the context and content, and how well they answered the PICO question. The whole process of included studies are displayed in the flow chart below (see Figure 5). Thus, I included a total of 10 studies in my

literature review after these eliminations (see Table 5). The studies are ranked according to the year of publication, from the oldest to the newest.

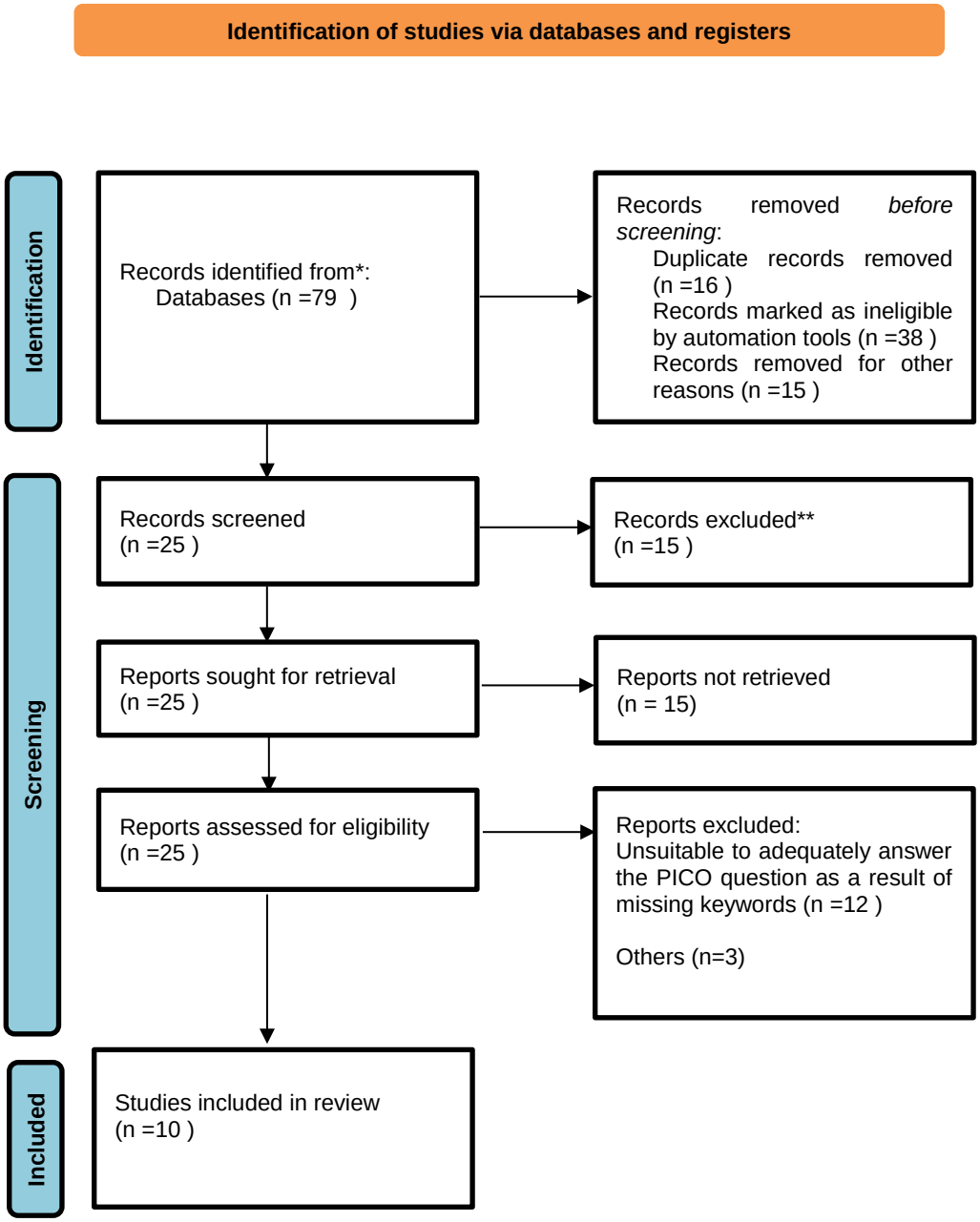

Figure 5 – Database Flow chart

Table 5 – Included publications in review

Number	Title	Author (year)
1.	Dose and volume reduction for normal lung using Intensity-modulated radiotherapy for advanced-stage non-small-cell lung cancer.	Murshed et al. (2004)
2.	Comparison of inverse-planned Three-dimensional conformal radiotherapy and Intensity-modulated radiotherapy for non-small-cell lung cancer.	Christian et al. (2007)
3.	Volumetric modulated arc therapy for Stereotactic body radiotherapy of lung tumors: A comparison with 2 other delivery techniques (IMRT and 3D-CRT).	Khodri et al. (2011)
4.	Prediction of chest wall toxicity from lung Stereotactic body radiotherapy (SBRT).	Stephans et al. (2012)
5.	Is IMRT superior of inferior to 3D-CRT in radiotherapy for NSCLC? A meta-analysis.	Hu et al. (2016)
6.	Intensity-modulated radiation therapy may improve local-regional tumor control for locally advanced non-small-cell lung cancer compared with Three-dimensional conformal radiation therapy.	Wang et al. (2016)
7.	Comparative effectiveness of Intensity-modulated radiation therapy to 3-dimensional conformal radiation in locally advanced lung cancer: pathological and clinical outcomes.	Appel et al. (2019)

8.	Retrospective comparison of Stereotactic body radiotherapy versus Intensity-modulated radiotherapy for stage III ultra-central squamous non-small-cell lung cancer.	Cong et al. (2019)
9.	Outcomes following Stereotactic body radiotherapy with Intensity-modulated therapy versus Three-dimensional conformal radiotherapy in early stage non-small-cell lung cancer.	Mix et al. (2019)
10.	Dosimetric and toxicity comparison of IMRT and 3D-CRT of non-small-cell lung cancer.	Guillemin et al. (2021)

6 EVALUATION OF SELECTED STUDIES

1. Dose and volume reduction for normal lung using Intensity-modulated radiotherapy for advanced-stage non-small-cell lung cancer.

This retrospective study is the oldest on my list of compiled studies. It is a comparative study from the year 2004, written by Hasan Murshed and others, performed in the United States. The purpose of this study was the investigation of dosimetric improvements in regards to the tumor-dose conformity and normal tissue sparing using IMRT compared with 3D-CRT for advanced-stage non-small-cell lung cancer.

Methods: In this study, patients with Stage III-IV and recurrent NSCLC who previously underwent 3D-CRT were included (n = 41). The use of the IMRT technique was planned such that they delivered a dose of 63 Gy to 95% of the planning target volume utilizing nine equidistant coplanar 6-MV beams. To minimize the volumes of normal lung, heart, esophagus, and spinal cord irradiated above their tolerance doses, inverse planning was carried out. Dose distributions and dosimetric indexes for the tumors and critical structures in both plans were computed and compared.

Results: There was a decrease of > 2 Gy in the total lung mean dose and of 10% in the risk of radiation pneumonitis using the IMRT technique. The volumes of the heart and esophagus irradiated to > 40 – 50 Gy and normal thoracic tissue volume irradiated to > 10 – 40 Gy were reduced using the IMRT plans (see Table 6).

Conclusion: Target coverage and the volume of normal lung irradiated above low doses improved significantly with IMRT planning. The risk of normal tissues receiving low doses can be controlled in IMRT with the appropriate selection of planning parameters.

Table 6 – Summary of Murshed et al., 2004 – Study no. 1

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the cohort description?	Yes				The study compared the RT techniques patients underwent and the risk of exposure.

2. Are the inclusion criteria clearly defined in the research?	Yes				
3. Are there misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?		No			The results of the comparison were centered on IMRT.
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out.
7. Are there outputs of participants who were not described and excluded from the analysis?		No			The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

2. Comparison of inverse-planned three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for non-small-cell lung cancer.

This study is a prospective study that was published in the year 2007, written by Judith A. Christian and others. This study was performed in the United States, and it had the objective of studying and comparing IMRT with 3D-CRT in reducing the dose to the lungs.

Methods: In this study, ten patients with localized non-small-cell lung cancer underwent CT. The planning target volume (PTV) was defined, and the organs that were to be at risk during the procedure were outlined. AutoPlan, an inverse-planning program, was used to design 3D-CRT plans. Each of the patients had their 3D-CRT plans compared with a series of five IMRT plans. The planning objectives were to maintain the dose the PTV was meant to receive while minimizing the lung dose.

Results: The PTV90/20 ratio, with V20 being the lung receiving volume, and PTV90 being the percentage of the PTV covered by the 90% isodose, were used as a parameter accountable for both the reduction in lung volume treated and the PTV coverage. Except for the three-field coplanar plans, all IMRT plans improved the PTV ratio significantly compared with the optimized 3D-CRT plan (see Table 7).

Conclusion: By improving the conformity of the plan, the results of this study showed that **IMRT could reduce the dose the lungs receive compared with the dose they receive during 3D-CRT**.

Table 7 – Summary of Christian et al., 2007 – Study no. 2

Criteria	Yes	No	Unclear	Not applicable3	Comments
1. Do the patients in the study match the Cohort description?	Yes				The study compared two techniques of RT in patients and the minimization of potential risk.
2. Are the inclusion criteria clearly defined in the research?	Yes				

3. Are there misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?	Yes				
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out.
7. Are there outputs of participants who were not described and excluded from the analysis?		No			The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

3. Volumetric Modulated Arc Therapy for Stereotactic Body radiotherapy for lung tumors: A comparison with 2 other delivery techniques (IMRT and 3D-CRT)

This retrospective study, performed in France, had the purpose of demonstrating the potential of volumetric modulated arc therapy (VMAT) compared with intensity-modulated radiotherapy (IMRT) techniques and 3D-CRT for stereotactic body radiotherapy (SBRT) for small lung cancer, written by M. Khodri and others.

Methods: This study involved 5 patients who completed RapidArc SBRT for small tumors. New treatment plans were generated using co-planar intensity-modulated radiotherapy (IMRT) and 3D non-coplanar conformal field. PTV dose coverage and treatment delivery times for organs at risk doses were assessed.

Results: The mean dose to the healthy lung was 1.99 Gy for RapidArc, 2.25 Gy for co-planar IMRT and 2.48 Gy for 3D non-coplanar conformal field. RapidArc Plans achieved a superior conformal index (CI) and lower V30Gy to the chest wall compared to IMRT and 3D-RCT (see Table 8).

Conclusion: Volumetric modulated arc therapy (RapidArc) for SBRT for small lung cancer achieved plan quality and slightly better than those with coplanar IMRT and 3D-CRT.

Table 8 – Summary of Khodri et al., 2011 – Study no. 3

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the Cohort description?	Yes				
2. Are the inclusion criteria clearly defined in the research?		No			Number of patients involved in the study does not match the inclusion criteria.

3. Are there misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?	Yes				
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out.
7. Are there outputs of participants who were not described and excluded from the analysis?		No			The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

4. Prediction of chest wall toxicity from lung stereotactic body radiotherapy (SBRT)

This study was prospective. The purpose of this study was to determine patient, tumor, and treatment factors related to the development of late chest wall toxicity after lung stereotactic body radiotherapy (SBRT). It was performed in the department of Radiation Oncology, Cleveland, OH.

Methods: This study reviewed a registry of 134 patients treated with lung SBRT to 60 Gy in 3 fractions who had greater than 1 year of clinical follow-up and no history of multiple treatments to the same lobe (n = 48).

Results: With a median follow-up of 18.8 months, 10 patients had late symptomatic chest wall toxicity (4 Grade 1 and 6 Grade 2) at a median of 8.8 months after SBRT. No patient characteristics (age, diabetes, hypertension, peripheral vascular disease, or body mass index) were predictive for toxicity, whereas there was a trend for continued. Greatest single tumor dimension (p = 0.047; OR, 2.63) and planning target volume (p = 0.040; OR, 1.04) were correlated with toxicity, whereas distance from tumor edge to the chest wall and gross tumor volume did not reach statistical significance. Volumes of chest wall receiving 30 Gy (V30) through 70 Gy (V70) were all highly significant, although this correlation weakened for V65 and V70, and maximum chest wall point dose only trended to significance (p = 0.06). On multivariate analysis, tumor volume was no longer correlated with toxicity, and only V30 through V60 remained statistically significant (see Table 9).

Conclusion: Tumor size and chest wall dosimetry are correlated to late chest wall toxicity. Only chest wall V30 through V60 remained significant on multivariate analysis. Restricting V30 to 30 cm3 or less and V60 to 3 cm3 or less should result in a 10% to 15% risk of late chest wall toxicity or lower.

Table 9 – Summary of Stephans et al., 2012 – Study no.4

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the Cohort description?		No			The study does not involve a comparison.

2. Are the inclusion criteria clearly defined in the research?		No			
3. Are the misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?				Not applicable	The study is based on just one technique, therefore, uncomparative.
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out but the period within which their treatments took place.
7. Are there outputs of participants who were not described and excluded from the analysis?		No			The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?				Not applicable	
9. Is an appropriate statistical analysis used?				Not applicable	

5. Is IMRT superior or inferior to 3D-CRT in radiotherapy for NSCLC? A meta-analysis

This study was a retrospective meta-analysis written by Xingsheng Hu and others to compare the clinical outcomes of IMRT and 3D-CRT in the treatment of NSCLC as there are no adequate data to determine whether intensity-modulated radiotherapy is superior to three-dimensional conformal radiotherapy in the treatment of non-small-cell lung cancer (NSCLC). It was performed in the United States.

Methods: This study was based on a literature search in the databases PubMed, EMBASE, and the Cochrane Library database from their inception to April 30, 2015. The overall survival (OS) and relative risk (RR) of the development of radiation pneumonitis and radiation esophagitis were evaluated in this study. Two authors independently assessed the methodological quality, and data extraction was carried out from the search results. Egger's test results was used for the evaluation of publication bias by funnel plot.

Results: 10 retrospective studies were collected from the literature search and of those, 5 (12,896 patients) were selected for OS analysis, 4 (981 patients) were selected for radiation pneumonitis analysis, and 4 (1339 patients) were selected for radiation esophagitis analysis. Cox multivariate proportional hazards models revealed that 3D-CRT and IMRT had similar OS (HR = 0.96, P = 0.477) but that of IMRT reduced the incidence of grade 2 radiation pneumonitis (RR = 0.74, P = 0.009) and increased the incidence of grade 3 radiation esophagitis (RR = 2.47, P = 0.000) (see Table 10).

Conclusions: OS of IMRT for NSCLC is not inferior to that of 3D-CRT, but IMRT significantly reduces the risk of radiation pneumonitis and increases the risk of radiation esophagitis compared to 3D-CRT.

Table 10 – Summary of Hu et al., 2016 – Study no. 5

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the Cohort description?	Yes				

2. Are the inclusion criteria clearly defined in the research?	Yes				
3. Are there misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?	Yes				OS and RR OF 3D-CRT and IMRT were described.
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out.
7. Are there outputs of participants who were not described and excluded from the analysis?		No			The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

6. **Intensity-Modulated radiation therapy may improve local-regional tumor control for locally advanced non-small-cell lung cancer compared with three-dimensional conformal radiation therapy.**

This was a retrospective study written by Jingbo Wang and others as a result of the lack of consistent results in regards to the comparative effectiveness of intensity-modulated radiotherapy (IMRT) versus three-dimensional conformal radiotherapy (3D-CRT) in patients with locally advanced non-small-cell lung cancer. It was performed in England.

Methods: This study retrospectively reviewed patients treated with definitive radiotherapy (RT) between 2002 and 2010. Overall survival (OS), local-regional progression-free survival (LRPFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS) were compared among patients irradiated with different techniques. The association between the RT technique and survival indexes was assessed in a Cox proportional hazard regression model.

Results: A total of 652 patients were eligible for analysis, including 206 with 3D-CRT and 446 with IMRT. The median OS of the 3D-CRT and IMRT groups were 19.4 and 23.3 months, with a 5-year rate of 13% and 19%, respectively ($p = .043$). Multivariate analysis identified IMRT as an independent favorable factor associated with LRPFS and DMFS. PSM analysis further verified the beneficial effect of IMRT on LRPFS. No difference in OS or PFS was observed between the two techniques. Subgroup analysis revealed that IMRT might have been differentially more effective in both OS and LRPFS among female patients, nonsmokers, with adenocarcinoma, or without weight loss. There was a significant reduction in lung toxicity and similar esophagus toxicity in the IMRT group compared with the 3D-CRT group (see Table 11).

Conclusion: IMRT may confer superior LRPFS and comparable OS than can be achieved with 3D-CRT in LA-NSCLC, along with the reduction of pulmonary toxicity.

Table 11 – Summary of Wang et al., 2016 – Study no.6

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the Cohort description?	Yes				

2. Are the inclusion criteria clearly defined in the research?	Yes				
3. Are the misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?	Yes				
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out but the period within which their treatments took place.
7. Are there outputs of participants who were not described and excluded from the analysis?		No			The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

7. **Comparative effectiveness of intensity-modulated radiation therapy to 3-dimensional conformal radiation in locally advanced lung cancer: pathological and clinical outcomes.**

This was a retrospective study written by Sarit Appel and others, performed in England, and published in 2019. The objective of this study was to assess the impact of radiation techniques on pathological and clinical outcomes in locally advanced non-small-cell lung cancer.

Methods: This study retrospectively reviewed LANSCLC patients treated from August 2012 to August 2018 at Sheba Medical Center, Israel. The planning target volume (PTV) was defined by co-registered PET/CT. A comparison was carried out between the pathological regression, surgical margin status, local control rates (LC), disease-free (DFS), and overall survival (OS) between 3D-CRT and IMRT.

Results: The cohort of this study consisted of 74 patients with mean age of 62.9 years, 51 out of the 74 patients were male. 46 out of 74 patients were with adenocarcinoma, with 59 out of 74 in stage 3. 51 out of 74 of the patients were treated with the 3D-CRT technique, while 23/74 were treated with the IMRT technique. Other variables, including pathological response and local control rates, were similar between groups (see Table 12).

Conclusion: The results of this study showed that **when used to treat LANSCLC in the neoadjuvant setting, both IMRT and 3D-CRT produce comparable pathological and clinical outcomes. This study validated the real-world effectiveness of IMRT compared to 3D-CRT.**

Table 12 – Summary of Appel et al., 2019 – Study no. 7

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the Cohort description?	Yes				
2. Are the inclusion criteria clearly defined in the research?	Yes				

3. Are the misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?	Yes				
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out.
7. Are there outputs of participants who were not described and excluded from the analysis?	No				The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

8. **Retrospective comparison of stereotactic body radiotherapy versus intensity-modulated radiotherapy for stage III ultra-central squamous non-small-cell lung cancer.**

This retrospective study, performed in England and written by Yang Cong and others, aimed to analyze the efficacy and toxicity of stereotactic body radiotherapy (SBRT) versus intensity-modulated radiotherapy (IMRT) in stage III patients with ultra-central squamous non-small-cell lung cancer.

Methods: The study reviewed Forty-four stage III patients with ultra-central sqNSCLC. 15 patients received SBRT (n = 15) and 29 patients received IMRT (n = 29) between December 2014 and August 2017.

Results: At a median follow-up of 16.5 months, the 1-year local control rate of SBRT and IMRT was 60.8 and 37.5%, respectively (p = 0.23); the median overall survival was 17 versus 18 months (p = 0.48); ≥3 grade toxicity was 20 versus 24.1% (p = 0.83) (see Table 13).

Conclusion: Study results showed that **SBRT is effective and patient-friendly for stage III patients with ultra-central sqNSCLC. Toxicity might be tolerable with a moderate dose five to six fraction regimen.** However, more prospective studies are warranted.

Table 13 – Summary of Cong et al., 2019 – Study no. 8

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the Cohort description?	Yes				
2. Are the inclusion criteria clearly defined in the research?	Yes				
3. Are the misleading factors identified and are there established strategies for dealing with them?		No			

4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?	Yes				
6. Is the monitoring of patients carried out for a long period of time?	Yes				Monitoring was carried out for 16.5 months.
7. Are there outputs of participants who were not described and excluded from the analysis?	No				The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

9. Outcomes following stereotactic body radiotherapy with intensity-modulated therapy versus three-dimensional conformal radiotherapy in early stage non-small-cell lung cancer.

This retrospective study, performed in New Zealand and written by Michael Mix and others, evaluated the clinical outcomes following SBRT according to the use of either 3D conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT).

Methods: Patients with stage I NSCLC who received SBRT from 2007 to 2015 were retrospectively reviewed. Disease control and survival were assessed using Kaplan-Meier estimates. Dosimetric analyses for target dose heterogeneity and coverage were performed.

Results: A total of 297 patients with 351 lesions were included. 3D-CRT was used in 52% and IMRT in 48%. IMRT was utilized at a higher rate in more recent years. Local failure did not differ in patients treated with 3D-CRT and IMRT. Mean dose to gross tumor volume (GTV) as a percent of prescription dose was higher with 3D-CRT compared with IMRT. Tumor stage, histology, and SBRT regimen did not correlate with local tumor control. Overall survival for the entire population approximated 72% at 2 years. Treatment was well tolerated (see Table 14).

Conclusion: The results of this study showed that **there was no discernible difference in clinical outcomes between those treated with 3D-CRT and IMRT.**

Table 14 – Summary of Mix et al., 2019 – Study no. 9

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the Cohort description?	Yes				
2. Are the inclusion criteria clearly defined in the research?	Yes				

3. Are the misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?	Yes				
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out but the period within which their treatments took place.
7. Are there outputs of participants who were not described and excluded from the analysis?		No			The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

10. Dosimetric and toxicity comparison of IMRT and 3D-CRT of non-small-cell lung cancer

This retrospective study, written by F Guillemin and others, was purposed to assess the clinical (immediate toxicities) and dosimetric impact of IMRT compared to 3D-CRT in the treatment of locally advanced (stages IIIA to IIIC) non-small-cell lung cancer (NSCLC). These patients were treated with concurrent radiochemotherapy, while IMRT in lung cancer was implemented. The study was performed in the radiotherapy department of the Jean-Perrin Center, France.

Methods: Between March 2015 and October 2019, 64 patients treated with concomitant radiochemotherapy were retrospectively included. Thirty-two received 3D-CRT and 32 IMRT. The radiotherapy prescription was 66 Gy in 33 fractions of 2 Gy.

Results: IMRT has improved coverage of target volumes (V95 increased by 14.81% in IMRT; P<0.001) without increasing doses to OARs and reducing dysphagia (RR=0.67; P=0.027). Low doses to the lung were not significantly increased in IMRT (pulmonary V5 increased by 7.46% in IMRT) (see Table 15).

Conclusion: Intensity-modulated radiotherapy, compared with the standard 3D-CRT technique, improves the coverage of target volumes without increasing the dose to the OARs. It also improves the immediate tolerance of the treatment by reducing the number of dysphagia (Guillemin et al., 2021).

Table 15 – Summary of Guillemin et al., 2021 – Study no. 10

Criteria	Yes	No	Unclear	Not applicable	Comments
1. Do the patients in the study match the Cohort description?	Yes				
2. Are the inclusion criteria clearly defined in the research?	Yes				

3. Are the misleading factors identified and are there established strategies for dealing with them?		No			
4. Are the results evaluated using objective criteria?	Yes				
5. If a comparison was made, is there a sufficient description of both groups?		No			The description was geared more towards IMRT.
6. Is the monitoring of patients carried out for a long period of time?			Unclear		The study did not make mention of the period of time within which the monitoring was carried out but the period within which their treatments took place.
7. Are there outputs of participants who were not described and excluded from the analysis?		No			The number of patients excluded from the study are not included.
8. Are the results measured in a reliable way?	Yes				
9. Is an appropriate statistical analysis used?	Yes				

A complete summary of all included studies can be found below (see Table 16).

Table 16 – Complete summary of all studies

Criteria	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**
1. Do the patients in the study match the Cohort description?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the inclusion criteria clearly defined in the research?	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
3. Are the misleading factors identified and are there established strategies for dealing with them?	No	No	No	No	No	No	No	No	No	No
4. Are the results evaluated using objective criteria?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. If a comparison was made, is there a sufficient description of both groups?	No	Yes	Yes	Not appli-cable	Yes	Yes	Yes	Yes	Yes	No
6. Is the monitoring of patients carried out for a long period of time?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
7. Are there outputs of participants who were not described and excluded from the analysis?	No	No	No	No	No	No	No	No	No	No
8. Are the results measured in a reliable way?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
9. Is an appropriate statistical analysis used?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes

7 DISCUSSION

The lungs are the most vital organ in the oncological complication of RILI. They are one of the most sensitive tissues to IR, and their vulnerability to radiation damage places a limit on the success of RT for lung cancer treatment. The alveolar-capillary barrier, being the most radiosensitive subunit of the lungs to IR frequently describes RILI as diffuse alveolar damage (Hanania, 2019). RILI more than often occurs in the area of the lung exposed to radiation. It is stratified into two phases, the early phase, known as radiation pneumonitis, and the late phase, radiation fibrosis. Early toxicity results in DNA strand breaks and epithelial and blood cell death, which later results in the late phase, lung fibrosis. Predisposing factors, which are either treatment-related or patient-related, increase the probability of the occurrence of these adverse effects on the lungs. Some of these factors include lung dose, fractionation, tumor location and volume, comorbid conditions, age, and sex, among others (Hotchkin, 2019).

Significant large groups of oncological patients undergo RT during the period of their illness, causing RT to play a significant role in the treatment procedure for oncological patients. This treatment method eventually has some effects on the patients as a result of its use of ionizing radiation. Due to significant developments and advancements in radiotherapy planning and irradiation, there has been the development of highly conformal radiotherapy techniques such as three-dimensional conformal therapy, intensity-modulated radiation therapy, stereotactic body radiation therapy, and volumetric modulated arc therapy. These techniques allow for the optimization of dose distribution while preserving healthy tissues (Hynková et al., 2012). The review part of this thesis was focused on these radiation techniques and their abilities to preserve and spare normal healthy tissues during radiation therapy. The included articles in my review also covered factors contributing to the development of lung toxicity and the effects the various radiation techniques have on the individual stages of NSCLC in patients.

After my research, it was noted that some of my reviewed studies were observational while others were analytical, and so they did not carry the same strength of association. I would classify this finding as a weakness of my methodology. Most of the studies did not include monitoring of patients for a long period of time therefore, it is unclear how long patients were monitored to achieve the said results, as it was not stated in the results. The comparison of these studies was based on quality parameters and treatment efficiency. However, the study Hu et al. (study no. 5) sought to evaluate the overall survival and relative risk of the development of RP in patients undergoing treatment for NSCLC. Patient analysis revealed that both IMRT and 3D-CRT have similar OS. Despite the fact that the OS of IMRT for NSCLC is not inferior

to that of 3D-CRT, it was found that IMRT significantly reduces the risk of RP while increasing the risk of radiation esophagitis in comparison to 3D-CRT (Hu et al., 2016). Similar results were found in the study Wang et al. (study no. 6). Both studies attained a similar result; therefore there were no conflicts of interest. The study Wang et al. found no difference in OS between the two techniques, IMRT and 3D-CRT, and concluded the study with the fact that IMRT may confer superior due to its ability to reduce the development of pulmonary toxicity, even though it has comparable OS to 3D-CRT (Wang et al., 2016).

Based on the results of the other individual studies, I found that the study Stephans et al. (study no. 4) reviewed the factors related to the development of late chest wall toxicity after SBRT, which showed that tumor size and chest wall dosimetry influence the development of chest wall toxicity. Patient characteristics such as age, diabetes, body mass index, or hypertension were found not to be predictive factors for toxicity. There was said to be a tendency for prediction of chest wall toxicity in smokers (Stephans et al., 2012).

The study of Murshed et al. (study no. 1), which was focused on dosimetric parameters and the tissue sparing-ability of the compared techniques, IMRT and 3D-CRT, found that there was a decrease of >2Gy in the total lung mean dose and of 10% in the risk of RP using the IMRT technique. The study was concluded with the fact that target coverage and the volume of normal lung irradiated above low doses improved significantly with IMRT planning. With the selection of appropriate planning parameters, the risk of normal tissues receiving low doses can be controlled in IMRT (Murshed et al., 2004). Likewise, the study of Christian et al. (study no. 2) compared the dose-reducing properties of IMRT and 3D-CRT to the lungs. The PTV90/V20 ratio was used as a parameter for the reduction in lung volume and the PTV coverage, and it was found that IMRT planning could reduce the dose received by the lungs by 20% compared to 3D-CRT (Christian et al., 2007). The study of Guillemin et al. (study no. 10) achieved similar results. IMRT was found to have improved coverage of target volumes without increasing doses to OAR's. Low doses to the lungs were also found not to have significantly increased using the IMRT technique. These three studies came to a common conclusion. Therefore there were no conflicts of interest recorded (Guillemin et al., 2021).

The study of Appel et al. (study no. 7) assessed the pathological and clinical outcomes in NSCLC patients. The study found that both IMRT and 3D-CRT produced comparable pathological and clinical outcomes (Appel et al., 2019). This study's result is similar to that of

the study of Hu et al. (study no. 5) and Wang et al. (study no. 6). These three studies had a similar result and an absence of any conflicts of interest.

SBRT being effective and patient-friendly for stage III NSCLC patients was proven in the study of Cong et al. (study no. 8). The study found that toxicity that develops after the SBRT technique might be tolerable with a moderate dose five to sex fraction regimen. However more prospective studies are warranted (Cong et al., 2019). The Khodri et al. study (study no. 3) also found similar results to the Cong et al. study (study no. 8). It found that SBRT plans for small cell lung cancer were of slightly better quality than those for IMRT and 3D-CRT (Khodri et al., 2011).

Eventually, the OS of IMRT for NSCLC is not inferior to that of 3D-CRT, despite the fact that IMRT significantly reduces the risk of radiation pneumonitis but at the same time increases the risk of radiation esophagitis compared to 3D-CRT. IMRT is just an advanced form of 3D-CRT, as it uses multiple intensity-modulated beams to deliver a high dose of radiation to the target and a low dose to the surrounding structures. IMRT, however puts forward potential problems such as target volume, target definition, target motion, and potential toxicity of low-dose RT to larger amounts of lung tissue, while 3D-CRT is not usually as sensitive to target motion, compared to IMRT.

The clinical outcomes between patients with stage I NSCLC, were not any different with the use of the IMRT and 3D-CRT techniques. By improving the conformity of treatment plans, the study results also showed that IMRT could reduce the dose the lungs receive compared with the dose they receive during 3D-CRT. According to current research and data results, IMRT can be said to be more tissue sparing as compared to 3D-CRT.

VMAT, on the other hand, according to the study by Khodri et al. (study no. 3), achieved a slightly better plan quality than those with IMRT and 3D-CRT. Treatment accuracy, improvement in patient comfort, and patient outcomes are to be expected. Analyzing the efficacy and toxicity of SBRT compared to IMRT, SBRT is more effective and patient-friendly for stage III NSCLC patients, according to Cong et al. (study no. 8). Toxicity might be more tolerable for patients (Khodri et al., 2011; Cong et al., 2019).

After a comparison of studies, IMRT has been proven to be a more effective treatment technique with regard to healthy tissue sparing. The improvement of a patient's quality of life is dependent on the choice of technique for treatment. The dosimetric benefits of dose distribution in the IMRT radiation technique are particularly evident in these research studies however; more

studies are warranted to prove if, indeed, IMRT is a superior radiation technique as compared to other radiation techniques.

8 CONCLUSION

The development of radiation-induced lung injury, a common complication in patients undergoing thoracic radiation, cannot be entirely circumvented. However, understanding its pathophysiological sequence could help in developing strategies for the prevention and better management of this potential damage to the lungs. This bachelor's thesis, titled radiation-induced lung injuries after modern radiotherapy methods, was devoted to describing the susceptibility of the lungs to radiation injury during radiotherapy with the use of modern radiotherapy techniques and describing these injuries. This was achieved through the theoretical part. The theoretical part covered the anatomy and physiology of the lungs as an organ, describing and characterizing the individual structures and components of the lungs, as they were essential for the eventual description and classification of lung injuries. I further went on to conclude the theory with the oncological problem itself, its classifications, radiation therapy, and finally, the techniques used in radiation therapy of the thorax. This helped me to fulfill my aims for the theoretical part fully.

My aim for the review part of this thesis was to assess the effects of conformal radiotherapy techniques compared to conventional radiotherapy methods in thoracic cancer patients, the effects these techniques have on healthy tissues, and the prevalence of lung injuries. This aim was fulfilled with the help of a publication search and the compilation of a literary review from the databases PubMed and Science Direct. The results of the included studies were consistent and geared towards one conclusion. The comparison between conformal and conventional radiotherapy techniques deduces that the conventional techniques such as IMRT and SBRT are more effective during the treatment of lung cancers as they have a better ability to spare normal healthy tissues and reduce the risk of radiation-related injuries during or after the radiation treatment process, as compared to the conformal techniques, 3D-CRT. With adequate planning and selection of a suitable technique, taking into account patient characteristics before the therapeutic intervention of thoracic cancer, the development of RILI could be adequately managed. For further studies, I would recommend a randomized control study or a meta-analysis to assess further if indeed, IMRT is a superior radiation technique as compared to other radiation techniques.

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