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The Role of Radiotherapy in the Treatment of Lung Cancer: A Review of Therapeutic Methods and Effects

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Abstract

Introduction

Lung cancer is a leading cause of cancer-related deaths worldwide, with rising cases and mortality. In 2022, there were 2.48 million new cases and 1.8 million deaths globally. The primary risk factor is tobacco smoking, though genetic factors, pollution, and other exposures also contribute. Lung cancer is divided into Non-Small Cell Lung Cancer (NSCLC), which includes adenocarcinoma, squamous cell carcinoma, large-cell carcinoma; and Small Cell Lung Cancer (SCLC), characterized by rapid growth, early metastatic spread and greater chemosensitivity in comparison to NSCLC. Treatment depends on the cancer type and stage, with surgery and radiotherapy being treatment of choice for NSCLC and chemoradiotherapy for SCLC.

Materials and methods

This article is the result of the review of the scientific literature available in PubMed database using keywords: “Lung Cancer”, “Radiotherapy”, “Non-Small Cell Lung Cancer”; “Small Cell Lung Cancer”

Aim of study

The aim of the study is to summarize available knowledge about various methods of treatment of lung cancer by means of radiation therapy and its diverse techniques. The epidemiology, etiology, staging and methods of treatment were summarized and described. Modern radiotherapy techniques for treating lung cancer have also been included.

Conclusions

For NSCLC, modern techniques like stereotactic radiotherapy (SBRT/SABR) provide surgical-level effectiveness in early stages with reduced toxicity, while concurrent chemoradiotherapy is optimal for inoperable stage III disease. Palliative radiotherapy remains vital for symptom relief in advanced stages. For SCLC, concurrent chemoradiotherapy is the standard for limited-stage disease, while prophylactic cranial irradiation (PCI) and thoracic radiotherapy improve survival in extensive-stage cases responding to chemotherapy.

Keywords

Lung cancer; Radiotherapy; Non-Small Cell Lung Cancer; Small Cell Lung Cancer

1. Introduction

Lung cancer is one of the most common cancer worldwide in both of incidence and mortality, remaining the leading cause of cancer-related deaths [1] in 2020, despite female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer in that year [2]. Globally, lung cancer cases and deaths continue to rise. In 2022, GLOBOCAN estimated 2.480 million new cases (12.4% of total cancer cases) and 1.817 million deaths (18.7% of total cancer deaths) [3], exceeding reported rates in GLOBOCAN 2020 (2.206 million new cases and 1.796 million deaths), making it back the most frequent cancer in men and women combined.

In Poland, according to Polish National Cancer Registry's "Cancer in Poland 2021" report [4], lung cancer is second most frequent cancer in men (with 14.6% of total new cancer cases) and women (with 9.4% of total new cancer cases), and also the most frequent cancer in both of these groups combined. Lung cancer is the most common cause of death in both men (with 25.8% of total cancer deaths) and women (with 18.1% of total cancer deaths).

Tobacco smoking is the main etiological factor in lung carcinogenesis. Other factors include genetic susceptibility, poor diet and alcohol intake, occupational exposures as asbestos, heavy metals, silica, polycyclic aromatic hydrocarbons, diesel exhaust, air pollution, chronic inflammation from infections and other medical conditions, ionizing radiation [5].

Primary lung cancers are classified into two main types due to its distinct biological and clinical features: Non-Small Cell Lung Cancer [NSCLC] and Small Cell Lung Cancer [SCLC]. NSCLCs generally grow slower, metastasize later, and show limited chemosensitivity compared to SCLC. This type of cancer is histologically divided into lung adenocarcinoma [LUAD], lung squamous cell carcinoma [LUSC] and large-cell carcinoma, with LUAD being the most common subtype. In contrast, SCLC is characterized by rapid growth, early metastatic spread and higher chemosensitivity [6]. NSCLCs, depending on the clinical stage of the disease, are treated usually by surgical resection and radiotherapy. The standard treatment for SCLC patients comprises chemotherapy completed with chest radiotherapy.

2. Staging of lung cancer

The Veterans Administration Lung Group (VALG or VA) system is commonly utilized for staging Small Cell Lung Cancer (SCLC). This classification distinguishes SCLC into two categories**:** limited-stage SCLC and extensive-stage SCLC. Limited-stage SCLC (LS-SCLC) is defined as tumor confined to one hemithorax (one side of the chest) and which can be encompassed within a single tolerable radiotherapy field, with or without regional lymph node involvement (e.g. ipsilateral or contralateral mediastinal or supraclavicular nodes) and without

distant metastasis. Extensive-stage (ES) is defined as disease that has spread beyond the boundaries of the limited-stage, including malignant pleural effusion, distant metastases and contralateral lung involvement [7]. ES-SCLC is more common diagnosed stage of small-cell lung cancer, even two thirds of patients have ES-SCLC at initial diagnosis [8].

The TNM staging system, formulated by the American Joint Committee on Cancer (AJCC), is used for staging Non-Small Cell Lung Cancer (NSCLC). The TNM staging system allows to specify the stage of cancer by use of three variables: the size and extent of the primary tumor (T), presence/absence of tumor in lymph nodes in the region of the primary tumor (N), and the presence of metastasis (M). TNM combinations sharing similar survival outcome with treatment were grouped into stages ranging from stage IA1 to stage IVB, where the stage IVB has the worst sixty-month survival based on the stage [9]. Lung cancer presents a significant public health challenge due to its poor prognosis, primarily driven by late-stage detection, with the majority of patients (>75%) diagnosed at stage III or IV. Prognosis is strongly stage-dependent, with 5-year survival rates of approximately 60% for clinical stage IA, declining sharply to between 40% and less than 5% for stages II to IV [6].

3. Radiotherapy

Radiotherapy (RT, RTx, XRT) is a localized method of treatment for malignant tumors that employs ionizing radiation to induce ionization within living cells, activating a series of physical, chemical, and biochemical reactions that result in biological effects. These effects include elimination of malignant cells or cell growth control. The radiation therapy can be classified into different categories due to various variables. RT basically can be divided based on criteria, including the type of radiation, the position of the radiation source, therapeutic indication [10, 11]. Based on type of radiation RT can be divided into two categories: radiotherapy using electromagnetic radiation (e.g. X-rays, gamma rays), and radiotherapy using particle radiation (such as protons or carbon ions). Radiotherapy can also be categorized based on the position of the radiation source relative to the patient. The main types include: External Beam Radiotherapy (EBRT) and Brachyterapy (internal radiotherapy or sealed source radiotherapy). EBRT is a type of RT, in which the radiation source is located outside the patient's body. High-energetic beams are emitted at the tumor using a linear accelerator or other external devices. Brachyterapy, in contrast to EBRT, is using the source of radiation placed inside or very close to the tumor within the body of the patient. Radiotherapy can also be categorized based on its therapeutic indication, therefore we distinguish: curative radiotherapy (intended for achieving complete eradication of the tumor with curative intent), adjuvant radiotherapy (delivered after primary treatment to eliminate microscopic residual

disease and reduce the risk of recurrence), neoadiuvant radiotherapy (administered before primary treatment to reduce the tumor and aid with resection) and palliative radiotherapy (intended for relieving symptoms and improving quality of life of the patient with advanced stage of cancer) [12]. As radiotherapy technology develops, more and more specialized forms of treatment are emerging. Stereotactic radiotherapy, also known as stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), is a highly precise form of EBRT that accurately delivers a high dose of irradiation in one or few treatment fractions to an extracranial target [13]. This technique is commonly used for treating small, localized tumors, particularly in the lungs, brain, or liver, with curative intent, often with an effectiveness similar to that of surgery. Another worth mentioning technique is respiratory-gated conformal radiotherapy (RGRT). RGRT synchronizes the delivery of radiation with the patient's breathing cycle. This approach minimizes radiation exposure to surrounding healthy tissues by targeting the tumor only when it is within a specific position during respiration. This method can reduce toxicities of radiation treatment, especially the pulmonary, cardiac, and esophageal late toxicities[14]. Radiotherapy is the only treatment approach with applications across all disease stages of neoplastic disease and for patients of varying state of health. Taking into account all the above information, radiotherapy is currently a key treatment approach, used in more than 50% of cancer patients, either as a standalone therapy or, more frequently, in combination with surgery and chemotherapy to manage various types of cancer [15]. Research model indicates that 77% of lung cancer patients have clinical indications for radiotherapy at some stage of their treatment [16].

4. Role of radiotherapy in treatment of Non-Small Cell Lung Cancer

Treatment for NSCLC depends on the clinical stage at which it is diagnosed. For patients with stage I or II NSCLC, and for stage IIIA in patients without the N2 characteristic (with potentially resectable disease), the preferred treatment is radical pulmonary parenchyma resection with lobectomy as a method of choice [17]. In cases where surgical resection is contraindicated due to significant medical factors or patient refusal, radical radiotherapy (RT) or radiochemotherapy (RCHT) should be considered. Treatment planning should utilize modern PET-CT-based techniques, including dose intensity modulation and respiratory gating. A total dose of 60–66 Gy, delivered in 2.0 Gy fractions, is recommended. In patients with a peripherally located lung tumor, small tumor volume (T1 or T2 characteristic) and without lymph nodes involvement identified on PET-CT, who have contraindications for surgical resection due to respiratory and/or cardiovascular medical problems, treatment method of

choice is stereotactic radiotherapy (SABR or SBRT) [18]. There is no clear guidelines for using SABR in perihilar/central NSCLC [19].

The comparison of the effectiveness between SABR and surgical resection of the early stage non-small cell lung cancer has been the subject of many retrospective studies. For stage I/II NSCLC, surgery is associated with favorable overall survival (OS). However, as matching characteristics between surgical treatment and stereotactic body radiotherapy (SBRT) increased, differences in survival rates diminished to the extent of becoming statistically insignificant. Similarly, there were no significant differences in cancer-specific survival (CSS) or recurrence rates (local, regional, or disseminated) between surgical resection and SBRT [20].

In order to compare the efficacy and safety of SABR with conventional radical radiotherapy (3DCRT) two studies were conducted: SPACE and CHISEL. In SPACE progression-free survival (PFS) and overall survival (OS) were comparable between patients treated with SBRT and those receiving conventional therapy, although the SBRT group showed a trend toward improved disease control, better health-related quality of life (HRQL) and lower toxicity levels [21]. In CHISEL, the SBRT group resulted in better local control of the NSCLC without worsened toxicity levels [22]. In both of the researches stereotactic radiotherapy should be the method of choice in treatment of early stages of non-small cell lung cancer.

The role of postoperative radiotherapy after surgical resection of early stage NSCLC is complex. In PORT meta-analysis the postoperative radiotherapy is detrimental and should not be used routinely [23]. Adjuvant radiotherapy is indicated following postoperative histological confirmation of malignant cells at the surgical margins – incomplete resection R1 or R2. However, it is not recommended after complete tumor resection with tumor-free margins (R0) and pN0 or pN1 status. Adjuvant RT is delivered at a total dose of 60–66 Gy, using conventional fractionation (2.0 Gy per fraction per day). Treatment should be administered within six weeks of surgery [24].

Preoperative radiochemotherapy (RCHT) does not enhance treatment outcomes in general. However, its use is indicated for patients with superior sulcus tumors (called Pancoast tumors), where the combination of chemotherapy and radiotherapy may enable complete tumor resection by surgery [25]. It is indicated to administer a total dose of 50–60 Gy. Surgery is recommended 4–6 weeks after completing RCHT[18].

For NSCLC stage IIIA (patients with unresectable disease) and stage IIIB the method of treatment of choice is radiochemotherapy or (less often) radiotherapy alone, if there are

contraindications to chemotherapy [26]. Concurrent chemoradiotherapy typically achieves significantly better overall survival (OS) outcomes compared to sequential chemotherapy and radiotherapy protocols [27]. Conventional radical radiotherapy involves delivering a dose of 60–66 with fractionation 2.0 Gy per day and should be administered to the primary cancer site with the ipsilateral hilar and mediastinal lymph nodes. The primary surgical resection of tumor it these stages can be performed only in selected group of patient with locally advanced tumor – surgery may be considered in patients with T4N0 or T4N1 stages [18].

Radical RT or RCHT is not recommended for patients with poor PS (WHO grade 2 or above), pleural effusion, active infections, weight loss exceeding 10% of their baseline in the three months prior to treatment, or significant comorbidities such as severe cardiovascular or respiratory failure, recent myocardial infarction, stroke, or renal failure. In such cases, palliative treatment is advised [24, 26]. Patients not suitable for radical treatment are up to 61% of the entire group of patients in stage III NSCLC [28]. The palliative chemoradiotherapy treatment shows better results for RR, OS, and PFS in stage IIIA–IIIB NSCLC patients with contraindications for radical radiochemotherapy, though its relatively high toxicity is specific cases must be considered [29].

NSCLC in stage IV is the most advanced stage of disease, characterized by presence of distant metastases. The treatment of patients with disseminated NSCLC is usually palliative. There are many possibilities for palliative treatment and it depends on clinical situation of patient. There are CHT or EGFR, ALK, and ROS1 TKIs, immunotherapy or immunochemotherapy, palliative RT, or symptomatic treatment in use. The indications for palliative radiotherapy include chest symptoms (cough, dyspnoea, haemoptysis or pain from the primary tumor), symptomatic bone metastases or CNS metastases. Radiotherapy can administered using various protocols, such as 20 Gy in 5 fractions over 5 days, 30 Gy in 10 fractions over 12 days, or 16 Gy delivered in 2 fractions of 8 Gy with a one-week interval [18].

For the primary cancer with a single metastasis, radical treatment may be considered after thorough disease assessment via PET-CT. In a single metastasis to the adrenal gland, central nervous system or in synchronous opposite lung lesion it is possible to perform surgical resection of metastasis. If this is unsuited or contraindicated, stereotactic radiotherapy methods should be considered [30]. A multicenter, randomized, controlled phase 2 study compared local consolidative therapy (LCT), which included [chemo]radiotherapy or resection of all lesions, to maintenance therapy or observation in patients with oligometastatic NSCLC who had not progressed after first-line systemic therapy. These results suggest that

LCT may offer significant benefits in prolonging PFS and delaying the emergence of new lesions in this patient population [31].

Brachytherapy has its place in lung cancer treatment, particularly in palliative care for obstructive lung disease caused by endobronchial tumors. Endobronchial brachytherapy, often combined with other methods like laser therapy or stent placement, helps alleviate symptoms like airway obstruction, improving quality of life in advanced-stage patients [32]. In the review assessing the effectiveness of palliative EBB and EBRT in patients with advanced NSCLC, the results showed no conclusive evidence favoring EBB over EBRT for survival or symptom relief, inferring EBB alone is less effective than EBRT alone in palliative treatment [33].

5. The role of radiotherapy in treatment of Small-Cell Lung Cancer

Concurrent chemoradiotherapy is the method of choice for limited-stage (LS) SCLC, combining cisplatin-etoposide with chest radiotherapy. If simultaneous initiation of CHT and RT is not feasible, RT should be administered no later than alongside the second cycle of CHT [34]. Concurrent RCHT is more effective than sequential RCHT due to increased chance of cure or long-term remission with prolonged survival [35]. Recommended protocols for radiotherapy include conventionally fractionated radiotherapy (60–66 Gy in 30–33 fractions) or hyperfractionated radiotherapy (45 Gy, administered as 1.5 Gy twice daily for 3 weeks, with a minimum 6-hour interval between doses) [18].

In patients with LS-SCLC who has responded to initial treatment, radiochemoterapy or chemotherapy, prophylactic cranial irridation (PCI) is proposed. PCI reduces the risk of metastases in central nervous system and increases overall survival and disease-free survival in patients with SCLC in complete remission[36]. Guidelines recommend administration of 25 Gy in 10 fractions with treatment started within 2–5 weeks of completion of radiochemotherapy or chemotherapy [18]. Higher doses of radiation may correlate with higher incidence of chronic neurotoxicity caused by PCI [37].

In extensive stage (ES) SCLC the treatment of choice is chemotherapy or chemoimmunotherapy. In cases where SCLC responds to the treatment, PCI also should be considered [18]. Prophylactic cranial irradiation in ES-SCLC patients who respond to chemotherapy reduces the risk of symptomatic brain metastases, disease-free and overall survival. Side effects do not influence patients' quality of life [38]. There are evidences that adding thoracic irradiation after an objective response to CHT improve overall survival and progression-free survival. The authors concluded that thoracic radiotherapy should be considered for all patients with ES-SCLC who respond to chemotherapy [39].

Palliative radiotherapy may be considered for the treatment of symptoms caused by CNS metastases or symptoms related to disease recurrence in the chest [40].

6. Conclusion

Lung cancer remains a significant public health challenge due to its high incidence, mortality, and poor prognosis, which is primarily driven by late-stage detection. Advances in radiotherapy techniques offer promise to improve outcomes for patients with both Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC).

For NSCLC, modern radiotherapy techniques such as stereotactic radiotherapy (also called stereotactic body radiotherapy [SBRT] or stereotactic ablative radiotherapy [SABR]) have demonstrated comparable effectiveness to surgery in early-stage cases while minimizing toxicity. In more advanced stages, concurrent chemoradiotherapy has proven to be the optimal approach for inoperable stage III disease. Palliative radiotherapy remains a key component of treatment for advanced NSCLC, addressing symptoms and improving quality of life.

For SCLC, concurrent chemoradiotherapy is the standard for limited-stage disease, offering the best chance for long-term survival. Prophylactic cranial irradiation (PCI) has been shown to reduce the risk of brain metastases and improve overall survival in both limited- and extensive-stage SCLC. Using PCI and thoracic radiotherapy enhances survival for patients with extensive-stage SCLC who respond to chemotherapy.

Authors contributions

Conceptualization - Dawid Komada and Katarzyna Doman; methodology - Julia Nowak and Dawid Komada; software - Katarzyna Doman and Urszula Kaczmarska; check - Daria Oleksy and Kamil Hermanowicz; formal analysis - Marcin Mycyk and Aleksandra Woźniak; investigation - Urszula Kaczmarska and Marcin Mycyk; resources - Agnieszka Najdek and Julia Nowak; data curation - Kamil Hermanowicz and Michał Jakub Cioch; writing - rough preparation - Dawid Komada; writing - review and editing - Daria Oleksy; visualization - Katarzyna Doman, Michał Jakub Cioch, Aleksandra Woźniak; supervision - Agnieszka Najdek; project administration - Dawid Komada.

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