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A practical general review of lung cancer

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Abstract

Lung cancer, also known as lung carcinoma, is a malignant tumor that begins in the lung. Lung cancer is caused by genetic damage to the DNA of cells in the airways and is often caused by cigarette smoking or inhalation of harmful chemicals. Damaged airway cells gain the ability to multiply unchecked, causing tumor growth. Without treatment, tumors spread throughout the lungs, damaging lung function. Eventually, the lung tumors metastasize and spread to other body parts. On the other hand, lung cancer or bronchogenic carcinoma refers to tumors originating in the lung parenchyma or within the bronchi. It ranks among the primary causes of cancer-related mortality globally. It is estimated that there is an increasing rate of new cases of lung cancer worldwide annually, with an approximately high mortality rate because of lung cancer. It is worth mentioning that lung cancer was a relatively uncommon condition at the beginning of the 20th century. Its dramatic rise in later decades is primarily attributable to the increase in smoking among both males and females. Treatments include surgery, chemotherapy, immunotherapy, radiation, and targeted drugs. This review article describes lung cancer's causes, pathophysiology, and presentation.

Keywords: Lung cancer, Etiology, Diagnosis, Treatment

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Introduction

Lung cancer, also known as bronchogenic carcinoma, denotes the development of tumors within the lung parenchyma or bronchi. It stands as a prominent contributor to cancer-related mortality in the United States. Since 1987, lung cancer has surpassed breast cancer as the leading cause of death among women. Annually, an estimated 225,000 new cases of lung cancer are diagnosed in the United States, resulting in approximately 160,000 fatalities. Notably, lung cancer was a relatively uncommon ailment at the onset of the 20th century, with its substantial escalation in subsequent decades largely attributed to the heightened prevalence of smoking among both genders **(Figure 1)** (1, 2).

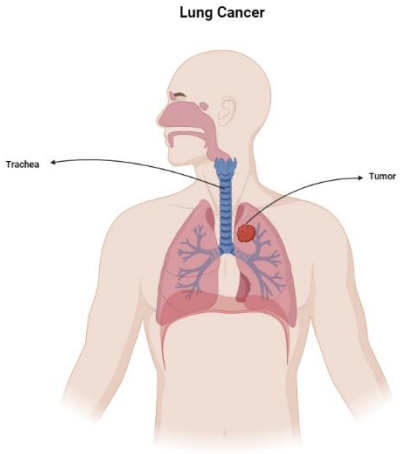

Figure 1. A schematic picture of the location of lung cancer.

Etiology

The predominant factor contributing to the development of lung cancer is smoking. It is approximated that smoking accounts for 90% of lung cancer cases (3). The highest risk of developing lung cancer is observed in male individuals who engage in smoking. This risk is further exacerbated by exposure to additional carcinogens, such as asbestos. The relationship between the incidence of lung cancer and the quantity of cigarette packs smoked annually is not directly correlated, owing to the intricate interaction between smoking habits and various environmental and genetic influences. Additionally, the risk of developing lung cancer as a result of passive smoking is augmented by 20 to 30% (3). Additional factors to consider are the use of radiation therapy for the treatment of cancers other than lung cancer, particularly non-Hodgkin's lymphoma and breast cancer (4). Exposure to certain metals, including chromium, nickel, arsenic, and polycyclic aromatic hydrocarbons, has been linked to an increased risk of lung cancer. Additionally, lung diseases such as idiopathic pulmonary fibrosis can independently raise the risk of lung cancer, regardless of smoking habits. Asbestos and radon are well-established risk factors for lung cancer (5). The risk of lung cancer associated with asbestos exposure, particularly in occupational settings, increases proportionally with the dose and varies based on the type of asbestos fiber. The risk from nonoccupational asbestos exposure is less clearly defined. However, the United States Environmental Protection Agency (EPA) has established standards for acceptable low-level nonoccupational asbestos exposure. The EPA states that if asbestos is undisturbed and does not release respirable particles, the health risk to occupants of a building is not significant (6). Radon exposure in uranium miners was associated with a small but significant risk of lung cancer (7). Radon has been demonstrated to build up in residential environments as a byproduct of the decay of uranium and radium. A comprehensive analysis of studies conducted in Europe revealed significant risks associated with residential radon exposure, particularly for individuals who smoke. This exposure was found to be accountable for approximately 2% of all lung cancer-related deaths in Europe (8).

Epidemiology

Lung cancer is the most frequently identified form of cancer on a global scale, constituting around 12.4% of all cancer diagnoses worldwide, and stands as the primary contributor to cancer-related mortality (9). The American Cancer Society projects that there will be more than 234,000 new cases of lung cancer and over 154,000 deaths associated with lung cancer in the United States annually (9). Based on the 2020 Global Cancer Statistics report, it was found that lung cancer continued to be the primary contributor to global cancer-related mortality, resulting in approximately 1.8 million deaths (10). In the past, the prevalence of lung cancer appeared to primarily affect developed nations. However, recent evidence indicates a significant increase in lung cancer incidence, with nearly half of

new cases, 49.9%, being diagnosed in underdeveloped regions(11). In the United States, there is a higher mortality rate among men compared to women. While there is no racial disparity in the occurrence of lung cancer overall, the age-adjusted mortality rate is elevated in African-American males in comparison to Caucasian males. This distinction is not observed among women (3).

Pathophysiology

The pathophysiology of lung cancer is a multifaceted and not fully elucidated process. It is postulated that recurrent exposure to carcinogens, particularly from cigarette smoke, results in the development of dysplasia in the lung epithelium. Prolonged exposure further leads to genetic mutations and disrupts protein synthesis (12). This consequently interrupts the process of cell division and encourages the formation of cancer. The prevalent genetic alterations associated with the onset of lung cancer include MYC, BCL2, and p53 for small cell lung cancer (SCLC), and EGFR, KRAS, and p16 for non-small cell lung cancer (NSCLC) (13, 14). The histopathological categorization of lung cancers is crucial for their diagnosis and management, and is based on cellular and molecular subtypes. The 2021 World Health Organization (WHO) classification system divides lung cancers into various categories, including precursor glandular lesions, adenocarcinomas, adenosquamous carcinomas, squamous precursor lesions, squamous cell carcinomas, large cell carcinomas, sarcomatoid

carcinomas, lung neuroendocrine neoplasms, salivary gland-type tumors, neuroendocrine tumors, neuroendocrine carcinomas, and other epithelial tumors. The WHO emphasizes the identification of histologic features, measurement of invasion depth, and mode of spread for prognostic purposes. For instance, the presence of tumor spread through air spaces is associated with a higher recurrence rate after limited resections and should be documented in pathological evaluations. Additionally, the WHO has discontinued the clear cell, rhabdoid, and signet ring subtypes in the most recent classification, as they are considered to be cytologic features that can occur in any adenocarcinoma. The WHO classification system places significant emphasis on the use of immunohistochemical staining to classify cancers that may not exhibit typical cytologic features under light microscopy **(Figure 2).** In the 2015 classification system established by the World Health Organization (WHO), poorly differentiated carcinomas underwent reclassification based on specific biomarker expressions. Those exhibiting p40 expression were reclassified as squamous cell carcinomas, while those demonstrating thyroid transcription factor 1 expression were categorized as adenocarcinomas with solid subtype. Additionally, carcinomas showing positivity for chromogranin and synaptophysin were reclassified as neuroendocrine carcinomas.

Precursor Glandular Lesions

These lesions encompass atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ. AAH serves as a precursor to lung adenocarcinoma and typically presents as a lesion measuring $\leq$ 5 mm. Adenocarcinoma in situ can manifest as either mucinous or nonmucinous and is generally a localized lesion of 3 cm or less. It exhibits a "lepidic" growth pattern, characterized by growth confined along the alveolar structures. This type of lesion is non-invasive and demonstrates intact alveolar septa.

Adenocarcinoma

The pathology of adenocarcinoma involves the development of neoplastic gland formation and the expression of pneumocyte markers such as thyroid transcription factor 1 (TTF-1) with or without napsin expression, or intracytoplasmic mucin. It is further categorized based on the extent and structure of neoplastic gland formation as either mucinous or non-mucinous. The non-mucinous subtypes include acinar, papillary, micropapillary, lepidic, and solid subtypes. Accurate pathological identification of these subtypes is crucial for determining prognosis. Specifically, the solid, micropapillary, and cribriform (a subtype of acinar non-mucinous adenocarcinoma) patterns are associated with unfavorable prognostic implications (15). Mucinous adenocarcinomas may exhibit various architectural patterns such as papillary, micropapillary, solid, and cribriform. However, the World Health Organization (WHO) does not provide grading recommendations for mucinous carcinomas based on these growth patterns. Other less common forms of adenocarcinoma include colloid, enteric-like,

lymphoepithelial, and fetal forms. Minimally invasive adenocarcinoma (MIA) is characterized by a small, solitary adenocarcinoma measuring ≤ 3 cm with minimal invasion (less than 5 mm) and a predominant lepidic growth pattern, resembling similar precursor glandular lesions. If the invasion exceeds 5 mm, it is classified as lepidic-predominant adenocarcinoma. Invasive mucinous adenocarcinoma, previously known as mucinous bronchioloalveolar carcinoma, encompasses mucinous lesions that do not meet the criteria for MIA. Lesions with more than 10% of mucinous and non-mucinous growth patterns should be classified as mixed adenocarcinoma.

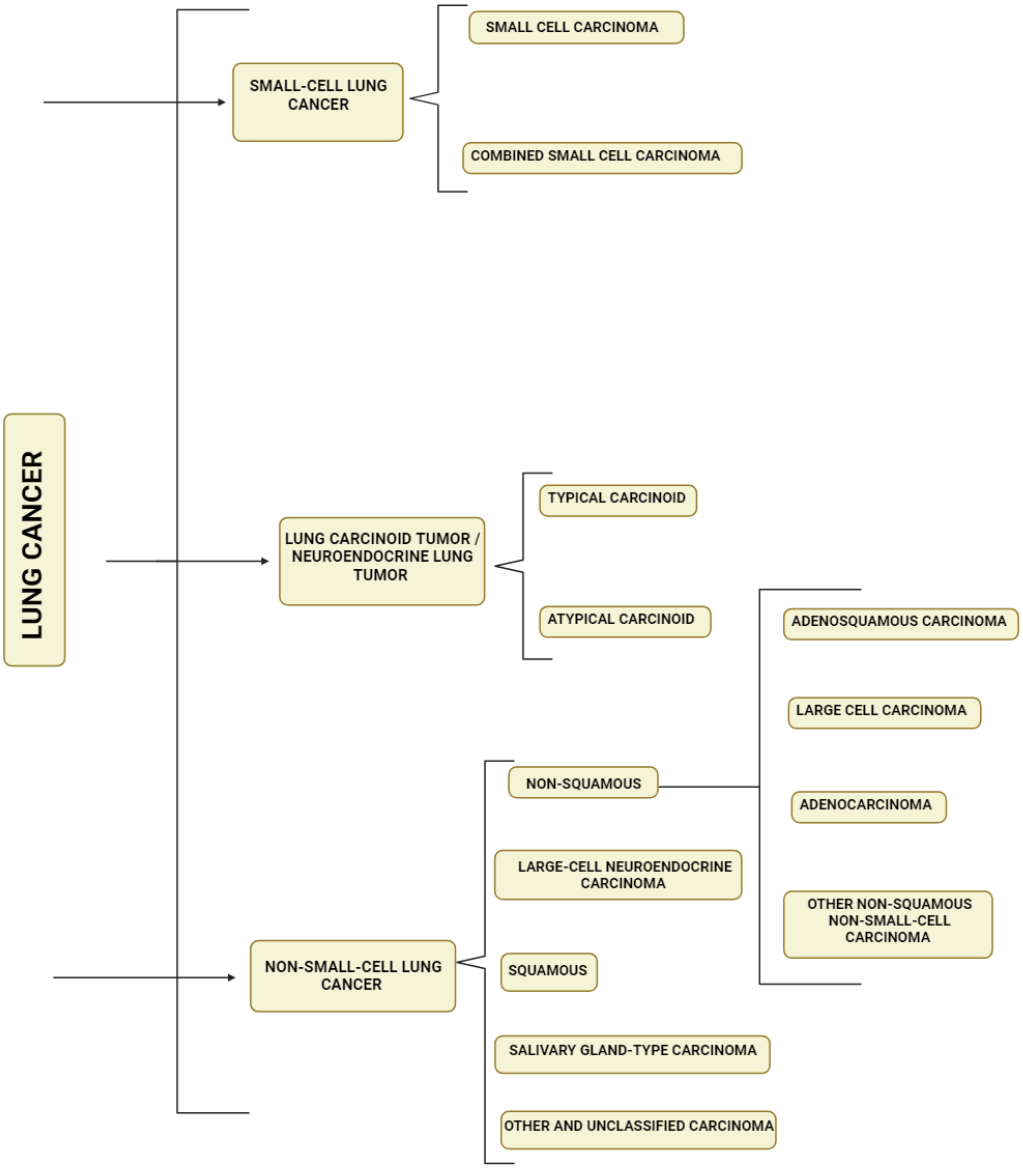

Figure 2. Small cell lung cancer, Lung carcinoid tumor/neuroendocrine lung tumor and non-small cell lung cancer.

Adenosquamous Carcinoma

Adenosquamous carcinomas are a type of lung tumor characterized by the presence of more than 10% glandular and squamous components. This subtype of lung cancer is rare and known for its aggressive nature. Current guidelines suggest the use of adjuvant chemotherapy, even in cases of Stage I tumors that have been completely removed through surgery, along with postoperative prophylactic radiotherapy to the entire brain. This approach is recommended due to the elevated likelihood of recurrence and the development of brain metastases associated with adenosquamous carcinomas (16).

Squamous Cell Carcinoma

Squamous cell pathology is characterized by the presence of keratin and/or intercellular desmosomes on cytology or by immunohistochemical (IHC) evidence of p40, p63, CK5, CK5/6, or desmoglein expression. The subtypes of squamous cell carcinoma encompass non-keratinizing, keratinizing, and basaloid cancers. Squamous cell carcinomas exhibit extensive central necrosis leading to cavitation. These cancers may manifest as coastal tumors and hypercalcemia. Pancoast tumors, located in the superior sulcus of the lung, are a specific type of squamous cell carcinoma. Postoperative recurrence in patients with Pancoast tumors most commonly occurs in the brain.

Large Cell Carcinoma

Large cell carcinoma (LCC) is an aggressive epithelial tumor characterized by the absence of cytological characteristics associated with glandular, squamous, or neuroendocrine malignancies. Immunohistochemical analysis typically reveals negative expression of p40 and TTF-1, and lacks cytological features indicative of small cell carcinoma. LCCs are typically comprised of round to polygonal cells with prominent nucleoli, exhibiting large size, abundant cytoplasm, and a lack of defining features. The diagnosis of LCC is primarily based on the exclusion of other specific tumor types (17).

Sarcomatoid Carcinoma

These are uncommon types of carcinomas characterized by the presence of malignant epithelial elements and characteristics resembling sarcomas. These subtypes encompass pleomorphic carcinomas, carcinosarcomas, and pulmonary blastomas.

Small Cell Carcinoma

Small cell carcinoma (SCLC) is characterized by the presence of round, oval, or angulated cells with minimal cytoplasm, similar in size to a resting lymphocyte, and lacking distinct nucleoli. SCLCs exhibit extensive necrosis and typically demonstrate positive staining for chromogranin and synaptophysin. The World Health Organization (WHO) has previously categorized SCLC into three cell subtypes: oat cells, intermediate cells, and combined cells (SCLC with non-small cell lung cancer component, squamous, or adenocarcinoma). However, research indicates that these classifications lack significant clinical relevance or prognostic value (18).

History and Physical

Lung cancer typically does not exhibit specific signs or symptoms, and many patients are diagnosed with advanced disease upon presentation. Symptoms of lung cancer manifest as a result of the localized impact of the tumor, including coughing due to bronchial compression, stroke-like symptoms from brain metastasis, paraneoplastic syndrome, and kidney stones caused by persistent hypercalcemia (19). Cough is observed in 50 to 75 percent of individuals diagnosed with lung cancer (2). Mucinous adenocarcinoma is characterized by the production of copious amounts of thin mucoid secretions, often leading to coughing. In cases where there are exophytic bronchial masses, coughing may indicate the development of secondary post-obstructive pneumonia. Additionally, hemoptysis, or coughing up blood, is reported in 15–30% of patients with lung cancer (2). Chest pain is reported in around 20-40% of individuals diagnosed with lung cancer, while dyspnea may be present in as high as 25-40% of cases at the time of diagnosis (2). Nevertheless, these indications may be predominantly attributed to lung cancer or underlying bronchopulmonary ailment, and pleural engagement in lung cancer can present as pleural thickening/nodules or malignant pleural effusion. Throughout the progression of their condition, around 10-15% of individuals with lung cancer will experience malignant pleural effusion, with certain cases exhibiting unilateral pleural effusion as the sole initial manifestation (20). Bronchogenic carcinoma accompanied by malignant pleural effusion on the same side is typically deemed inoperable. It is important to acknowledge that not all pleural effusions in individuals with lung cancer are of a malignant nature (21). Non-cancerous accumulation of fluid in the pleural cavity can result from lymphatic blockage, postobstructive pneumonitis, or atelectasis. In cases where two successive cytology samples yield negative results for malignancy in individuals with bronchogenic carcinoma, it is advisable to conduct surgical thoracoscopy or medical pleuroscopy to assess the pleural space prior to surgical removal of the primary lesion (22). Pleuroscopy in the medical field demonstrates a sensitivity exceeding 90% in the identification of malignancy among individuals with

bronchogenic carcinomas (23). The manifestation of small cell lung cancer often includes superior vena cava syndrome, characterized by the presence of dilated neck veins, facial and upper extremity edema, and a plethoric appearance. These symptoms may serve as the initial indication of the disease. Chest radiography typically reveals mediastinal widening or a mass in the right hilar region (24). As mentioned previously, lung cancers located in the superior sulcus are associated with PanCoast syndrome, characterized by shoulder pain, Horner syndrome, and signs of bony destruction, along with muscle atrophy in the hand. The metastasis of lung cancer to the bone often manifests with symptoms, such as bone pain at the metastatic site, accompanied by elevated serum alkaline phosphatase and hypercalcemia. Approximately 20% of patients with non-small cell lung cancer may initially (25), experience bone pain due to metastasis, while the percentage rises to 30-40% in patients with small-cell lung cancer (26). Imaging typically identifies osteolytic lesions, with the vertebral bodies being the most prevalent location for metastasis. Adrenal metastases are also present in lung cancer, although they are seldom symptomatic and are generally detected during staging. Nevertheless, not all adrenal lesions are cancerous, and positron emission tomography (PET) scanning is advised for distinguishing between benign and malignant adrenal lesions (27). Brain metastasis is a prevalent characteristic of both small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). In SCLC, the occurrence of brain metastases may be observed in approximately 20 to 30% of patients at the time of diagnosis (28). Other common sites of metastasis in lung cancer include the liver, often manifesting symptoms only in the advanced stages of the illness.

Paraneoplastic Syndromes Associated with Lung Cancer

Symptomatic hypercalcemia resulting from lung cancer may arise from the production of parathyroid hormone-related proteins or widespread bone metastases **(Figure 3).** Patients typically exhibit anorexia, nausea, constipation, and lethargy as common manifestations of hypercalcemia, and they generally have a bleak prognosis due to their correlation with advanced disease (29). The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is linked to small cell lung cancer (SCLC) and manifests with symptoms of low sodium levels. Neurologic paraneoplastic syndromes are immune-mediated conditions connected with SCLC, encompassing Lambert-Eaton myasthenic syndrome (LEMS), encephalomyelitis, limbic encephalitis, cerebellar ataxia, sensory neuropathy, and autonomic neuropathy (30). The production of adrenal corticotropin in an abnormal location, known as ectopic production, can lead to the development of Cushing syndrome. This condition is linked to small cell lung cancer (SCLC), large cell neuroendocrine carcinoma, and carcinoid tumors of the lung, and is indicative of a poorer prognosis (31). Additional non-pulmonary clinical presentations of lung cancers encompass hypertrophic pulmonary osteoarthropathy, dermatomyositis, and polymyositis.

Standard phase for surgery of Lung Cancer

The standard treatment for patients with stage I and II, as well as some patients with stage IIIA, non-small-cell lung cancer (NSCLC) involves surgical removal of the tumor. After the surgery, patients may be recommended to undergo adjuvant systemic therapy. In the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, patients with completely removed NSCLC received adjuvant systemic therapy with a cisplatin-based doublet regimen. The benefit of adjuvant therapy varied depending on the stage of cancer, with stage IB (tumor ≥ 4 cm) patients having a 3% decrease in the risk of death at 5 years. It is important to note that the benefit of adjuvant chemotherapy was only significant for stage IB patients who had a high risk of recurrence. The benefit of adjuvant chemotherapy increased to 13% for stage III lung cancers when compared to no chemotherapy (32). Adjuvant chemotherapy usually comprises four cycles of a cisplatin-based combination and is recommended for patients with completely resected stage IB (high-risk) to IIIA non-small-cell lung cancers (33). Despite administering post-operative chemotherapy, approximately half of stage IB lung cancer patients (tumor size ≥ 4 cm) and three-quarters of stage IIIA lung cancer patients experience recurrence of metastatic disease (32). Until 2020, no additional systemic therapy was recommended after adjuvant chemotherapy. However, recent data has shown that further adjuvant treatment with

immunotherapy or oral tyrosine kinase inhibitor (TKI) therapy may be necessary and challenge the current standard of care. Osimertinib, a third-generation oral EGFR–TKI, can selectively bind to both EGFR driver mutations and EGFR resistance mutations T790M (34). It has been approved for adjuvant therapy of stage II and III NSCLC after complete resection. The ADAURA trial studied adjuvant osimertinib therapy vs placebo for up to 3 years (35). The study enrolled patients who had undergone complete surgical removal of stage IB (tumor > 3 cm) to IIIA non-small cell lung cancer (NSCLC) and had EGFR exon 19 deletion or exon 21 L858R driver mutations. The study reported a 37% increase in two-year disease-free survival (DFS) and an 80% relative improvement in two-year DFS(35). There is increasing interest in using immunotherapy in the adjuvant setting due to its effectiveness in treating stage III and IV disease. The IMpower010 study showed that adjuvant atezolizumab is effective in treating patients with stage IB (tumors ≥ 4 cm) to IIIA NSCLC who have undergone surgery and up to four cycles of adjuvant chemotherapy(36). In the primary analysis of patients with stage II-IIIA NSCLC and PD-L1 expression on at least 1% of tumor cells, 16 cycles of atezolizumab resulted in a 44% relative improvement in 3-year DFS compared to best supportive care (36). Several additional trials are currently underway to evaluate adjuvant oral TKI or immunotherapy. The most highly-anticipated Canadian study is BR31, which is a phase III placebo-controlled trial investigating adjuvant durvalumab in completely resected NSCLC(37). The overall survival data for both ADAURA and IMpower010 are not yet available. However, chemotherapy as the only adjuvant therapy for completely resected stage IB (tumors ≥ 4 cm) to IIIA NSCLC may soon be outdated. To treat curative lung cancer, clinicians should aim to enroll patients in clinical trials that assess the role of additional adjuvant therapy with immunotherapy or oral TKI.

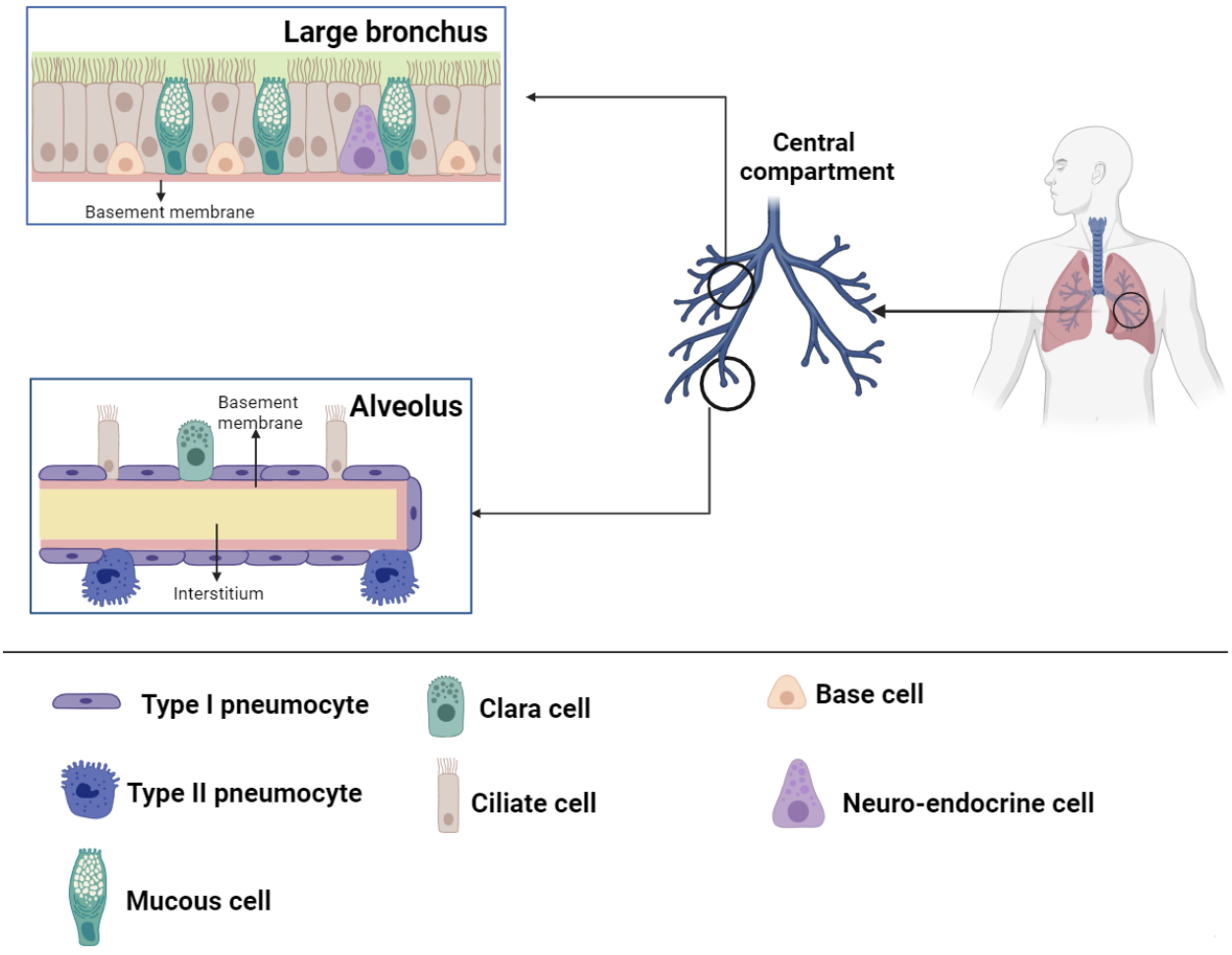

Figure 3. Histological combinations of lung cancer.

Stage III Non-Small-Cell Lung Cancer (NSCLC)

At initial diagnosis, approximately 20% of cases are classified as Stage III NSCLC, which includes tumors that have metastasized to mediastinal lymph nodes (Any T stage, N2) or large tumors that may involve local lymph nodes (T3N1 and T4N0) (38). Stage III non-small cell lung cancer (NSCLC) is a complex disease, and the treatment approach varies depending on different factors such as the size of the tumor, the severity of symptoms, and patient-specific criteria. The role of surgery in treating stage III NSCLC is a matter of debate. In a specific group of patients with single station mediastinal lymph node involvement, a trimodality treatment approach consisting of neoadjuvant chemotherapy and radiation followed by surgery can be considered. In the Intergroup 0139 study, patients who were eligible for lobectomy showed a significant survival benefit with the addition of surgery after preoperative chemotherapy and radiation. However, patients needing pneumonectomy didn't demonstrate the same benefit due to the perioperative risks involved (39). The process of selecting suitable patients for surgery is of utmost importance and should ideally involve a multidisciplinary approach. A majority of patients diagnosed with stage III NSCLC are considered unsuitable for surgery due to reasons such as their own choice, high tumor burden or not being fit for surgery. The combination of chemotherapy and radiation therapy, given either concurrently or sequentially, has been proven to provide the best chances of long-term survival for such patients. It has been observed that survival rates are better when chemotherapy and radiation therapy are given concurrently rather than sequentially (40). Patients need to have a good performance status and be able to tolerate multimodality therapy. Some common side effects that patients may experience include esophagitis, hematological toxicity, and pneumonitis. For patients with a borderline performance status, an alternative treatment option is sequential treatment with chemotherapy, followed by radiation. With this approach, the approximate five-year survival rate is 10% (40). For many years, studies have attempted to improve combination chemotherapy and radiation for unresectable stage III NSCLC. Increasing the number of chemotherapy cycles and radiation doses has not improved overall survival in these patients (41, 42). It has been shown for the first time that the inclusion of immunotherapy after concurrent chemotherapy and radiation therapy has resulted in an improvement in overall survival for patients. The latest update of the PACIFIC trial revealed that consolidation therapy with durvalumab for one year reduced the risk of death by 29% when compared to the placebo. Patients who received immunotherapy had a four-year overall survival rate of 49.6%, while those who did not had a rate of 36.3%. (43). It is recommended to undergo a baseline CT scan after completing chemotherapy or radiation treatment in order to rule out radiation pneumonitis and disease progression. Treatment should commence within a period of 42 days following the completion of chemotherapy and radiation therapy. Immunotherapy poses a small but clinically significant risk of pneumonitis, as well as an increased risk of thyroid dysfunction(44). Durvalumab is usually administered every two weeks. However, some provinces have approved the agent's administration on a 28-day cycle to reduce the travel burden and potential exposure during the COVID-19 pandemic. There is renewed interest in neoadjuvant strategies due to the poor outcomes for stage III NSCLC and high rates of local relapse. For instance, patients with stage III NSCLC involving single or multiple mediastinal lymph nodes underwent neoadjuvant durvalumab immunotherapy and chemotherapy, followed by surgery. In this study, 62% of patients achieved a major pathological response, which was defined as having less than 10% of viable tumor cells at the time of surgery. An additional 10% of patients had a complete pathological response (45). These points have been linked to the patient's overall survival, and there are numerous ongoing studies investigating the use of immunotherapy in the pre-treatment setting. If patients are not eligible for multiple treatment approaches, definitive radiation or palliative radiotherapy can effectively manage symptoms.

Metastatic Non-Small-Cell Lung Cancer (NSCLC)

The majority of individuals with lung cancer are initially diagnosed with distant metastases, although some with early-stage or locally advanced disease may

subsequently develop metastasis. The primary goals in managing metastatic non-small cell lung cancer (NSCLC) are to improve or maintain quality of life and prolong overall survival. Early integration of palliative care has been demonstrated to improve quality of life, reduce depression, and extend overall survival(46). In systemic therapy, the available treatment modalities encompass chemotherapy, targeted therapy, and immunotherapy. It is recommended that all non-squamous tumors undergo testing for driver mutations, particularly in individuals with a limited or absent history of smoking. For squamous histology tumors in non-smokers, the consideration for driver mutation testing should be individualized. Targeted therapy is generally the preferred approach for patients with mutations in EGFR, ALK, or ROS1, as it offers greater efficacy and lower toxicity. The International Association for the Study of Lung Cancer advocates for testing for EGFR, ALK, and ROS1 as a minimum requirement, and more recent guidelines also suggest testing for BRAF, KRAS, MET, NTRK, and RET (14, 47). This review centers on prevalent driver mutations that have actionable targets. Patients lacking a driver mutation have treatment options such as single-agent immunotherapy, combination immunotherapy regimens, or chemotherapy alone. A comprehensive summary of the treatment for metastatic NSCLC can be found in Figure 1.

Immunotherapy

Various standard and specialized approaches are available for the treatment of lung cancer (Figure 4). Immunotherapy has brought about substantial changes in the management of patients with metastatic non-small cell lung cancer (NSCLC). In 2015, a pivotal study on immunotherapy showcasing its efficacy in NSCLC was published in the Phase II Checkmate 063 trial. Nivolumab exhibited significant efficacy and manageable toxicity in heavily treated patients (48). In the few years since then, several immunotherapy approaches have been created. Some patients with metastatic non-small cell lung cancer (NSCLC) have achieved prolonged survival, referred to as the "tail of the survival curve" (49). The effectiveness of immunotherapy is influenced by the level of tumor PDL-1 expression. PDL-1 expression is commonly classified into three groups: PDL-1 negative (less than 1% of tumor cells express PDL-1), PDL-1 low positive (1–49%), and PDL-1 positive (more than 50%). The duration of response and overall survival rates are positively correlated with higher PDL-1 expression levels. In patients with PDL-1 positive tumors, single-agent immunotherapy has consistently demonstrated superior outcomes compared to chemotherapy, with lower toxicity and improved survival rates. For instance, in the KEYNOTE-024 study, the median survival with pembrolizumab reached 26.3 months, and notably, 31.9% of patients achieved a five-year survival, which is the highest reported in a phase III study to date (50). Comparable research conducted on patients with PDL-1-positive status has demonstrated that immunotherapy agents such as atezolizumab and cemiplimab exhibit superior efficacy compared to chemotherapy (51, 52). These studies have shown, for the first time, that some patients with metastatic non-small cell lung cancer (NSCLC) may be able to avoid chemotherapy. For patients with PDL-1 negative (<1%) or PDL-1 (1–49%) tumors, newer combination strategies have become the standard of care in the initial treatment. In the KEYNOTE-189 study, patients with metastatic nonsquamous NSCLC were randomly assigned to receive either carboplatin and pemetrexed or the same regimen in combination with pembrolizumab. The combination of chemotherapy and immunotherapy resulted in an overall survival of 22 months and reduced the risk of death by 44% compared to chemotherapy alone (53). In the same vein, the concurrent administration of chemotherapy and pembrolizumab resulted in a 36% decrease in the mortality risk among individuals diagnosed with metastatic squamous non-small cell lung cancer, as demonstrated in the KEYNOTE-407 clinical trial. The chemotherapy regimen utilized in this study comprised carboplatin and a taxane(54). Clinical trials have also investigated the use of a combination of dual immunotherapy for metastatic non-small cell lung cancer (NSCLC). In the Checkmate-9LA study, patients with nonsquamous or squamous histology were randomly assigned to receive either a platinum doublet or a combination of ipilimumab and nivolumab, along with two cycles of a platinum doublet. The arm receiving the dual immunotherapy-chemotherapy combination demonstrated a median overall survival of 15.8 months and a 28% reduction in the risk of death compared to chemotherapy alone(50). The comparative efficacy of dual immunotherapy

combinations in relation to chemotherapy-immunotherapy combinations has not been established, and further investigation is required to determine potential benefits for specific subgroups with longer-term follow-up.

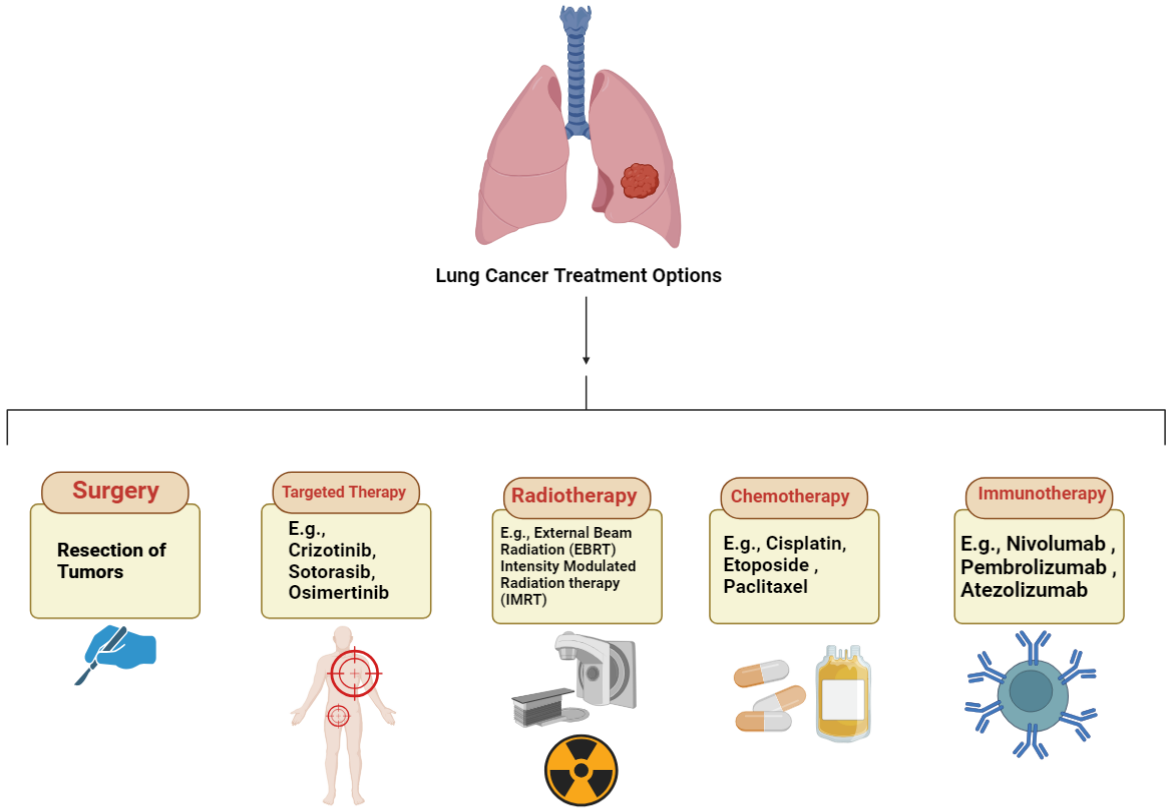

Figure 4. Details of standard ways of treatment for lung cancer including surgery, targeted therapy, radiotherapy, chemotherapy and immunotherapy.

Chemotherapy

Chemotherapy remains a primary treatment option for patients who are not suitable candidates for single-agent immunotherapy or combination immunotherapy regimens. These patients may have contraindications to immunotherapy, such as pre-existing autoimmune conditions, or there may be concerns about their performance status and the potential for toxicity with combination immunotherapy regimens. In such cases, platinum doublets are commonly utilized. For patients with nonsquamous metastatic NSCLC, a typical example would involve the use of carboplatin or cisplatin in combination with pemetrexed for 4–6 cycles, followed by maintenance pemetrexed until disease progression or unacceptable toxicity. In the case of squamous metastatic NSCLC, a platinum doublet may consist of carboplatin or cisplatin in combination with either paclitaxel or gemcitabine.

Biomarker testing

Tailoring medical treatment by focusing on specific molecular targets within tumors has led to enhanced survival rates for individuals with non-small cell lung cancer (NSCLC) (55). Various specific drugs have demonstrated efficacy in treating mutations in the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Genomic testing has identified additional molecular alterations such as ROS1 and RET gene rearrangements, MET amplification, and activating mutations in BRAF, HER2, and KRAS genes. These findings suggest potential targets for future therapeutic interventions.

Epidermal growth factor receptor (EGFR) gene

The EGFR receptor is a tyrosine kinase receptor located on the surface of cells, capable of initiating signaling pathways related to cellular growth and

proliferation upon activation. In the context of cancer, mutations in the EGFR gene result in unregulated cell division due to continuous activation. These mutations are observed in 10-15% of lung cancer adenocarcinoma patients of European and Asian ancestry, particularly in individuals who have never smoked and in females (56-58). Although these traits are prevalent, mutation testing plays a crucial role in identifying individuals who would gain from targeted tyrosine kinase inhibitor treatment. Mutations in EGFR commonly arise in exons 18–21, which confer sensitivity to EGFR tyrosine kinase inhibitors; these exons encode a segment of the EGFR kinase domain. Roughly 90% of these mutations consist of exon 19 deletions and the L858R point mutation on exon 21, and are associated with a 70% response rate in patients undergoing erlotinib or gefitinib therapy (59).

KRAS

The KRAS oncogene is frequently mutated in non-small cell lung cancer (NSCLC) through missense mutations that result in the substitution of an amino acid at positions 12, 13, or 61. Mutations at residues G12 and G13 are particularly prevalent. These mutations are more commonly found in adenocarcinomas, individuals of Caucasian descent, and those with a history of smoking (60). Roughly 10 to 25% of individuals diagnosed with adenocarcinoma exhibit tumors that are associated with KRAS mutations (61). In the context of concurrent occurrence with other cancer-causing genetic mutations, KRAS has been primarily identified in tumor types that lack mutations in EGFR and ALK, indicating that these mutations represent a distinct molecular subset of non-small cell lung cancer (NSCLC). Recent evidence indicates that KRAS mutations may have potential prognostic significance, but their ability to predict the response to EGFR tyrosine kinase inhibitors or cytotoxic chemotherapy is limited (55, 59). A study has proposed the feasibility of specifically targeting a subset of KRAS mutations using small-molecule inhibitors designed to address the prevalent G12C mutation in lung cancer, which is more common in smokers than non-smokers. These potential new agents depend on binding to the mutant cysteine and do not impact the wild-type KRAS protein, demonstrating specificity for a particular subtype (62).

Anaplastic lymphoma kinase (ALK)

Roughly 3-7% of lung tumors exhibit ALK mutations, (63-65) which are frequently observed in younger patients. Koh et al. found that individuals with ALK mutations had a median age of 49, while those without ALK mutations had a median age of 61 ($P<0.001$; n=221) (66). ALK mutations are also prevalent in adenocarcinoma patients with acinar histology or signet ring cells, as well as in those who have no history of smoking (67, 68). The predominant ALK rearrangement observed in non-small cell lung cancer (NSCLC) patients is the EML-4-ALK rearrangement. This genetic alteration occurs on chromosome 2p23 and involves the fusion of the 5' end of the EML-4 gene with the 3' end of the ALK gene, resulting in at least nine distinct fusion variants. EML-4 mutations are frequently identified in adenocarcinomas of individuals with no history of smoking or light smoking, whose tumors do not exhibit mutations in either EGFR or KRAS genes (63, 68). ALK mutations do not overlap with other oncogenic mutations linked to non-small cell lung cancer, such as EGFR or RAS mutations (68, 69). Additional ALK mutations unrelated to EML-4, such as KIF5B-ALK and TFG-ALK, have been identified. Patients with EML4-ALK fusions or ALK rearrangements do not derive therapeutic benefits from EGFR-specific tyrosine kinase inhibitor therapy (70).

Presently, there exists an FDA-approved medication, crizotinib (Xalkori®, Pfizer), which is designed to target constitutively activated receptor tyrosine kinases resulting from EML4-ALK and other ALK fusions. A single arm study of ALK-positive metastatic NSCLC(71), demonstrated objective response rates of 50–61% in patients. In a trial involving previously untreated advanced non-squamous ALK-positive NSCLC, patients were randomly assigned to receive either crizotinib 250 mg orally twice daily (n=172) or intravenous chemotherapy (pemetrexed 500 mg/m2 plus either cisplatin 75 mg/m2 or carboplatin target area under the curve 5–6 mg/mL/min (PPC group); all administered intravenously every three weeks for ≤6 cycles, n=171). The primary endpoint of the study was progression-free survival, while secondary endpoints included overall response rate, overall survival, safety, and patient-reported outcomes. The study revealed that crizotinib extended progression-free survival to 10.9 months compared to 7 months in patients receiving

PPC. Additionally, the overall response rate was higher in patients receiving crizotinib at 74% compared to 45% in patients receiving PPC. Overall, crizotinib demonstrated significant improvements in progression-free survival and overall response rate compared to standard chemotherapy, and its safety profile was deemed acceptable (71). This landmark study solidified crizotinib as the recommended treatment for individuals with advanced ALK-positive non-squamous non-small cell lung cancer who have not received prior therapy.

BRAF

The BRAF gene is classified as a proto-oncogene, functioning as a controlled signal transduction serine/threonine protein kinase that has the capability to stimulate cell proliferation and viability (72). Somatic mutations in the BRAF gene have been identified in 1–4% of non-small cell lung cancer (NSCLC) cases, with the highest prevalence observed in patients diagnosed with adenocarcinomas (61, 73-77). These mutations are frequently associated with individuals who have a history of smoking, either currently or in the past (76, 77). The localization of BRAF mutations within the kinase domain varies between lung cancer and breast cancer patients. A study involving 697 individuals diagnosed with lung adenocarcinoma revealed that 3% of the patients harbored BRAF mutations, with the identified mutations being V600E (50%), G469A (39%), and D594G (11%) (76). The majority of BRAF mutations in non-small cell lung cancer (NSCLC) have been identified as distinct from other oncogenic mutations, such as EGFR mutations and ALK rearrangements.

Conclusion

Lung cancer is the primary contributor to cancer-related fatalities on a global scale, resulting in the highest mortality rates for both genders. Approximately 85% of lung cancer cases are attributed to smoking. Diagnosis of lung cancer frequently occurs at advanced stages, limiting treatment options. Screening individuals at high risk has the potential to facilitate early detection and significantly enhance survival rates. Implementing primary prevention strategies, such as tobacco control measures and minimizing exposure to environmental risk factors, has the potential to decrease the occurrence of lung cancer and ultimately save lives. Considerable progress has been achieved in mitigating occupational health risks related to lung cancer, particularly in the context of smoking, and in the prevention of diverse disorders. In recent years, targeted therapy and immunotherapy have significantly contributed to the enhanced management of lung cancer. Furthermore, genetic and biomarker testing are aiding in the personalized management of different types of lung cancer. Through personalized management of non-small cell lung cancer (NSCLC), treatments are tailored to individual patients and can specifically target mutations with greater precision, aiming to prolong progression-free survival. Immunotherapy involves the concept of enhancing and directing the body's own immune defenses to combat cancer cells. Ongoing clinical trials are exploring the use of vaccines for treating NSCLC. Given that lung cancer is the leading cause of cancer-related deaths in the United States, ongoing research efforts are focused on developing innovative treatments.

In the past ten years, the landscape of lung cancer treatment in Canada has experienced rapid changes. New targets have been identified, leading to significant benefits for patients with metastatic non-small cell lung cancer (NSCLC), particularly those without a history of smoking. The integration of immunotherapy has altered the standard of care for patients with metastatic NSCLC and is now being incorporated into earlier stages of treatment. Physicians treating lung cancer must now be able to identify and manage the specific toxicities associated with immunotherapy. This review has only addressed some of the complexities involved in treating NSCLC and has not delved into the details of therapy sequencing. Despite these advancements, lung cancer continues to impose a substantial burden of morbidity and mortality on the Canadian population. Smoking cessation and screening high-risk individuals are crucial strategies for alleviating this burden.

Author contribution

MP conceptualized and wrote the manuscript. **TYK** edited the final version of the manuscript. **RAE** accompanied in writing of some sections of the paper. All authors have read and confirmed the final revised version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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