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Review Article

UNDERSTANDING THE ETIOLOGY, DIAGNOSIS AND TREATMENT OF LUNG CANCER

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ABSTRACT
As technology has advanced, it has become clear how strenuous cancer diseases may be worldwide, with lung cancer topping the list of cancer with the highest death rates. The only cause behind this growing loss of life is the overdue diagnosis of the disease, as in the early stage, it is unresectable. According to studies, lung cancer affects smokers and tobacco users, and nonsmokers in large numbers. This review will emphasize lung cancer and its categorization, diverse diagnosis methods, namely biopsy CT scan, acknowledge specific treatment plans given, including chemotherapies, radiation therapies and various genetic and environmental factors that affect lung cancer. The ultimate purpose of this assessment is to summarize our know-how of this disease and the advances done in lung cancer treatment in the past few decades, and how it has affected the survival rates.

Keywords: Biopsy, Chemotherapies, Lung cancer, Radiation therapies, Smokers.

1. INTRODUCTION
India ranks third in the list regarding the number of cancer patients. Cancer is a grave public health concern not only in developing countries like India but also for developed countries like the USA and many others [1]. Despite advancements in treatment, the prevalence of lung cancer continues to rise in most nations throughout the world. Though fatality rates have reduced in recent years due to changes in smoking habits, it is still a prevalent occurrence in India [2]. As studies infer that lung cancer is a heterogeneous disease and earlier classification of lung cancer into Small Cell Lung Cancer (SCLC, 13% of the cases) and Non Small Cell Lung Cancer (NSCLC, 83% of the cases) proposed by WHO is now considered less appropriate over genomic and histological parameters as basis of lung carcinoma categorization [3-6]. In almost every case of lung cancer, it has been found that the patient has a sort of tobacco smoking exposure [4, 7]. Indian statistics say of all oncology cases, lung cancer cases are 5.9% and responsible for 8.1% of all cancer-related fatalities; also, the data says that 80% of patients with lung cancer have a smoking history, be it direct or indirect [8-9]. In a population, various risk factors like clinical history, geographic location, nationality, air pollution, smoking habits, exposure to radiation, or carcinogens like asbestos strongly influence lung cancer pathology and epidemiology [10-11]. As India is the world's 2nd leading consumer and 3rd largest producer of tobacco, 28.6% of the overall Indian population uses tobacco products which are approximately around 267 million therefore concluding, tobacco usage has a drastic effect on health, and according to the report stated by National Cancer Registry Programme 2020, of all cancers, tobacco-related cancers are around 27% in our country.

2. LUNG CANCER CATEGORIZATION
Being a heterogeneous disease, lung cancer has various subtypes with pathological relevance [5, 12, 13]. Depending on the histotype and microscopic appearance of the tumors, prognosis and different types of treatment, lung cancer is categorized into two principal groups: Small cell lung cancer, non-small cell lung cancer, and a few other types that are very uncommon, such as bronchial carcinoid. SCLC is very aggressive, grows more vigorously than the different types, and is diagnosed after it has metastasized extensively. NSCLC is a more common lung cancer than SCLC, and with the advancement in molecular profiling and targeted therapies, NSCLC is classified into three types: adenocarcinoma (ADC), squamous cell carcinoma (SqCC), and large cell lung carcinoma (LCLC) [7, 13].

A significant part of NSCLC is represented by adenocarcinoma and squamous cell carcinoma, which hold around 39% and 20% of all lung cancer cases, respectively. The remaining numbers are expressed by LCLC, salivary gland type tumors and sarcomatoid carcinomas [14].

Adenocarcinoma: A malignant epithelial tumor that produces mucin that can be easily detected by mucicarmin, napsin A marker, or thyroid transcription factor 1 [15].

Squamous cell carcinoma: As per WHO definition, it is a malignant epithelial tumour that can show either keratinization or express IHC markers like p40, p63, and cytokeratins 5/6 [15].

Large cell lung carcinoma: It is an undifferentiated carcinoma that neither shows mucin production nor histological confirmation of IHC marker expression. The first step in its diagnosis is to eliminate SCLC, ADC, and SqCC [15].

3. MOLECULAR ALTERATIONS OF LUNG CANCER

Recent studies in lung cancer have confirmed an elevation in the number of molecular alterations identified in SCLC and NSCLC, and most of them now represent biomarkers for cancer therapies [5]. The following are a few critical molecular alterations that have emerged as potential biomarkers for targeted therapies.

3.1. Epidermal growth factor receptor (EGFR)

At position 12 of chromosome 7, the short arm EGFR gene is present, encoding a transmembrane glycoprotein of the protein kinase superfamily [16]. Female never smokers are likely to have tumors with EGFR mutations, and this mutation is treated with EGFR TKIs such as afatinib and gefitinib [5].

3.2. Anaplastic lymphoma kinase (ALK)

At position 23 of chromosome 2 short arm, the ALK gene is present, and in 3-7 % of lung tumors, ALK translocation is found with its ubiquitous fusion partner, Nucleophosmin [17-20]. FISH, IHC, and RT-PCR are a few techniques for determining ALK status.

3.3. Human epidermal growth factor receptor (HER2)

At position 12 of chromosome 17, this proto-oncogene is present, which is also an EGFR family member and plays a vital role in cell growth, differentiation and survival [21].

3.4. ROS Proto-oncogene 1 (ROS)

At position 2 of chromosome 6 long arm A ROS1 proto-oncogene is present and is a type 1 integral membrane protein belonging to the tyrosine kinase insulin receptor gene family. ROS1 functions as a growth or differentiation factor receptor.

3.5. RET proto-oncogene (RET)

At position 11.2 of chromosome 10 long arm, the RET gene is present. Its main function is to encode tyrosine kinase, which participates in cell proliferation, differentiation, and migration [22].

4. ETIOLOGY

There are various etiologic factors for lung cancer apart from smoking, as it has been found that lung cancer is not only a concern for active smokers but also for nonsmokers with no history of smoking and yet battling with lung cancer [23-27]. Other risk factors that serve as causes for the development of lung cancer include:

- Second-hand smoking: Current studies suggest passive smoking plays a modest role [28].
- According to an epidemiological study, expression of estrogen receptors is identified in lung tumors, and the estrogen receptor is more likely to be associated with lung carcinogenesis [29-30].
- Any minor alterations or rearrangements in genetic factors like EGFR, ROS1, RET, MET, or ALK result in the development of lung cancer. As per a review submitted by Matakidou et al. [31], people with a family history of being already diagnosed with lung cancer have a higher risk of getting affected in future generations.
- Exposure to various carcinogens: The International Agency for Research on Cancer (IARC) has a list of carcinogens that includes asbestos, silica, heavy metals, and polycyclic aromatic hydrocarbons [32].
- Air pollution, diabetes, and an unhealthy diet are all considered risk factors for lung cancer [33-35].

Lung cancer symptoms are indistinct from many other benign diseases and infective conditions.

Some of the most common symptoms of lung cancer include chronic coughing, shortness of breath, chest pain, sudden weight loss, blood-stained sputum, and recurrent bouts of pneumonia.

5. SCREENING AND DIAGNOSIS

For early-stage cancer detection, screening methods are done, and in the case of lung cancer, screening methods are different from the regular screening for breast and

cervical cancers [36]. Regular screenings recommended for lung cancer usually include chest X-ray, CT scan, PET scan, bronchoscopy, fine needle aspiration, biopsy, MRI of the brain, EBUS-TBNA, mediastinoscopy, thoracotomy, blood tests, and pulmonary function tests. These screening tests aid in determining whether the patient has cancer, what stage it is, and whether it has spread to other parts of the body. The most productive screening for lung cancer is low-dose computed tomography, preferred over other methods like chest radiography and sputum cytology [37]. Furthermore, NSCLC is present in the lungs' peripheral tissues; it can be detected early on without causing a delay in treatment and has a higher survival rate than SCLC [38]. The initial step in diagnosing lung cancer is to screen patients with a chest X-ray, and if the results are unusual, a CT scan is suggested. Furthermore, different diagnostic procedures are performed based on the location of tumors. Bronchoscopy is preferred for centrally located tumors because it offers clear visualization of tumors and the airways, while USG-guided biopsy or CT-guided biopsy is used for peripheral tumors. Some invasive methods like thoracoscopy, mediastinoscopy, and thoracotomy are reserved for those cases where the above mentioned techniques fail to yield a diagnosis. Even though sputum cytology is a non-invasive means of diagnosis, a negative result does not rule out lung cancer [39].

6. STAGING AND PROGNOSIS

Appropriate staging is crucial for lung cancer prognosis and management. A complete history and physical examination should be accomplished, as should a chest X-ray and a CT scan of the upper abdomen and chest, including the liver and adrenals. A bone scan and a CT scan of the brain should be conducted if the history and physical examination show bone or CNS spread [40]. Pulmonary function testing and invasive mediastinal staging are only performed on patients who are candidates for curative surgical resection or radical radiation therapy. The TNM system is used to stage NSCLC [41]. Prognosis and management of both NSCLC and SCLC vary depending on the extent of disease and performance status.

6.1. NSCLC management

The only possible curative treatment for NSCLC is surgical resection. Unfortunately, it can only be administered to a small percentage of patients, as two-thirds to three-fourths of NSCLC patients will have an advanced, potentially unresectable illness. Individuals at stages IA to IIIA are offered surgery as long as they can tolerate it. Patients with more advanced stages of cancer have chemotherapy, radiation therapy, or chemoradio-therapy as an option for their treatment. Surgery is technically difficult or impossible in patients with coronary artery disease and chronic obstructive pulmonary disease.

Patients with early-stage NSCLC who are medically unfit for surgical resection are treated with radiation therapy with a curative goal [42-43]. Radiation therapy alone can be given as a treatment to patients at stage I-II with a dose of 6000 Gy that results in five-year survival of 10%-27% of cases [43-44], whereas in the case of unresectable IIIA and IIIB stage patients, radiation therapy along with chemotherapy is taken as standard care [45-46].

Chemotherapy is a type of management that is given as a neoadjuvant or adjuvant approach for patients, mostly with advanced stage IIIB and IV lung cancer. Patients with good performance status are likely to get pre-operative chemotherapy and, as per studies done by Rosell and Roth, neo-adjuvant chemotherapy showed an improvement in survival rate from 3 years to 5 years [47-48]. For patients with stage IB to IIIA, 3-4 cycles of adjuvant chemotherapy are considered the standard type of management after surgery.

6.2. SCLC management

Small cell lung cancer is different from NSCLC in its penchant for early spread. The staging system is more straightforward, separating the disease into limited and extensive stages. The type of management involved in a limited stage is mediastinal node dissection followed by chemotherapy and postoperative radiotherapy [49]. In the extensive stage, combination therapies using cisplatin and etoposide, or cyclophosphamide, adriamycin, and vincristine have higher survival rates [50-51].

7. FACTORS THAT AFFECT LUNG CANCER SURVIVAL

Lung cancer survival has improved dramatically over the last decade, from a median overall survival of 11 months to a 17.8% 5-year survival rate [52]. This is mainly owing to the availability of targeted therapy medications and appropriate patient selection, and it has been achievable only because of molecular oncology. Molecular testing for lung cancer is now required, is included in all management guidelines worldwide, and

is readily available in India [53]. Others have adopted the notion to enhance patient outcomes [54].

Overall 5-year survival rates for SCLC and NSCLC are approximately 6.7% and 26.3%, respectively [55]. Bronchioloalveolar carcinoma (BAC) is an earlier term for a kind of NSCLC that is currently considered a subtype of lung adenocarcinoma. When BAC is detected early and only one tumor is present, the survival rate is much higher than the other types of NSCLC. According to the studies, patients with minimally invasive adenocarcinoma have a 5-year overall survival rate of 98% after surgery [56]. The survival rate for those with severe stages of the disease is significantly reduced. While this information is valuable to some extent, the above-mentioned survival rate statistics may not always provide an exact indication of how long a person will live with the disease.

There are numerous factors that influence lung cancer survival rates that should be considered. The following are a few parameters:

Age: Younger the patent is, the greater the odds are of living a long life [57].

Gender: At any stage, females have a higher probability of recovering from the disease than males.

Race: Compared to whites or Asians, African Americans appear to have lower survival rates [58].

Medical conditions: Patients with other major medical illnesses, such as heart disease or diabetes have a lower chance of survival than those with no prior health concerns.

Response to treatments: Chemotherapies typically have brief side effects, but medication and radiation can cause serious health problems like hypertension, CAD, heart damage, or lung damage, leading to a decline in survival rates [59].

Smoking: Continuing to smoke after a lung cancer diagnosis will lower the chances of survival [60].

8. CONCLUSION

Lung cancer is a diverse and complicated group of diseases that necessitates a multidisciplinary approach to screening, diagnosis, and treatment. Large-scale molecular profiling and targeted therapy are the most promising future for individualized and effective cancer treatment. Lung cancer incidence has risen dramatically over the past three decades, with a particularly alarming surge in India and many other developing countries. Despite the high prevalence in these nations, establishing an efficient lung cancer screening and diagnosis program remains challenging. However, the high cost of screenings and treatments, inadequate infrastructure, a lack of human resources, a shortage of qualified labor, and a lack of financial resources complicate such a program's implementation. For developing countries, an ideal screening method should be easily accessible, simple to use, and cost-effective so that a large number of patients can get treatment at an early stage without causing a delay in diagnosis and treatment, which in turn will decrease the death rates.

Conflict of interest

None declared

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