Screening on Lung Cancer:Treatment…,

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Abstract:

Lung cancer was the most common type of cancer diagnosed worldwide and also the main cause of cancer-related deaths among men globally in 2008.For women, it was the fourth most common cancer diagnosed and the second leading cause of cancer death. Lung cancer is one of the most common malignant cancers in most countries and is the biggest cause of death from cancer diseases around the world. Even though there have been continuous improvements in diagnosing and treating lung cancer, the survival rates for patients diagnosed with it are still not very good. Small-cell lung cancer (SCLC) makes up about 15% of all lung cancers and is known for growing quickly, spreading early, and having a poor prognosis. Exposure to the harmful chemicals in cigarettes is strongly connected to the development of SCLC. Only about one-third of patients are diagnosed with an early stage of the disease that can be treated with curative approaches. Genomic studies of SCLC have found that it has a high number of genetic mutations and widespread chromosomal changes, often involving the inactivation of the TP53 and RB1 tumor suppressor genes. The expression levels of key transcription factors have been used to classify different types of SCLC and to understand the variations within tumors. These variations are linked to how tumors grow, spread, and become resistant to treatment. Even though progress in treating SCLC has been limited, a better understanding of the disease's biology has uncovered new possible targets for treatment. The use of immune checkpoint inhibitors, a new treatment approach, has provided benefits for some patients, though only a small number experience long-term success. There is an urgent need to develop strategies that can better tailor treatments to those most likely to respond and to expand the benefits of effective immunity against cancer to more patients. These strategies are currently being explored.

Keywords: treatment; diagnosis.

Introduction:

A decade ago, the concept of tumor-promoting inflammation and avoiding immune destruction were added to the list of hallmark features that define cancer [2].

Since 1985, lung cancer has been the most common cancer globally, both in terms of new cases and cancer-related deaths. Worldwide, it is the largest contributor to new cancer cases (around 1.35 million cases) and to deaths caused by cancer. Malignant lung cancer continues to be a serious clinical issue and poses a significant threat to people around the world [8,14,15].Cancer is characterized by uncontrolled cell growth and the ability to spread to other parts of the body. In most cases, the activation of oncogenes and/or the deactivation of tumor suppressor genes lead to uncontrolled cell division and the loss of programmed cell death [4]. Lung cancer originates from the cells that line the airways and can be broadly categorized into two main types. Small-cell lung

cancer (SCLC) is a highly aggressive neuroendocrine cancer that affects most current or former smokers and typically has a poor prognosis [7,11]. SCLC accounts for about 15% of all lung cancer cases. Patients with SCLC often experience symptoms such as coughing, difficulty breathing, or coughing up blood, and imaging often shows a centrally located mass in the lung and involvement of nearby lymph nodes. Two-thirds of these patients already have distant cancer spread at the time of diagnosis [11]. The most common sites where SCLC spreads include the opposite lung, brain, liver, adrenal glands, and bones. The number of circulating tumor cells in SCLC is among the highest found in any solid tumor, which shows its strong tendency to spread [12].Although more than half of lung cancer cases are diagnosed at a late stage when a cure is unlikely, even patients with early-stage disease have surprisingly low survival rates [6,10]. Normally, the immune system detects and destroys malignant cells as soon as they appear, a process known as immune surveillance [2].Lung cancer was the most commonly diagnosed cancer and the leading cause of cancer-related deaths in men worldwide in 2008 [2]. For women, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths [1]. Surgery and adjuvant platinum-based chemotherapy may be used in a small number of patients diagnosed with extremely early-stage disease. However, most patients with early-stage or locally advanced disease are treated with combined radiation and platinum-based chemotherapy [13].Up to 80% of cancer patients suffer from a severe wasting syndrome known as cancer cachexia, which results in the death of up to one-third of affected patients [3].

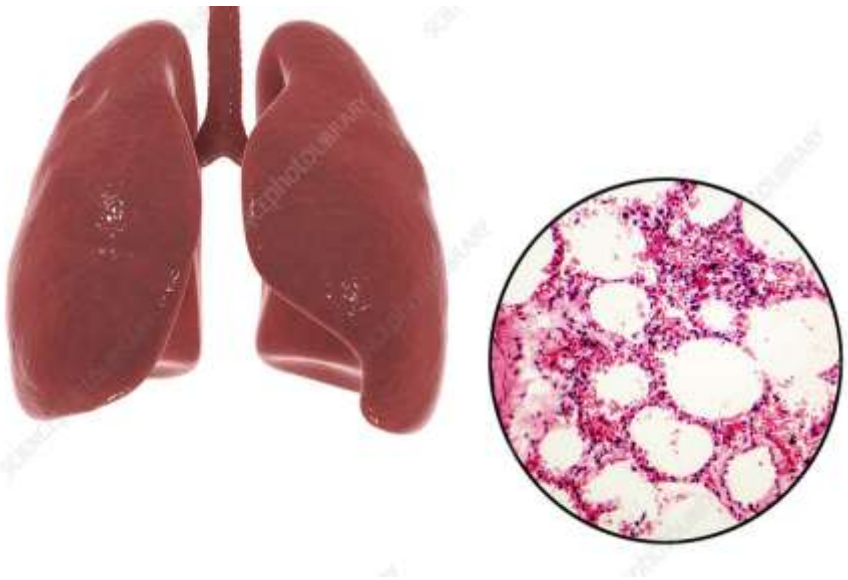

Fig1: Lung Histology

Treatment/Diagnosis:

Determining the stage of lung cancer includes evaluating the status of the primary tumor (T), regional lymph nodes (N), and any metastases (M) [8].

Local treatments include surgery and radiation therapy:

For systemic treatment, conventional chemotherapy and newer targeted therapies are used. Targeted therapies are interventions that specifically target molecular features of tumors. Chemotherapy is usually given in combination, as long as the patient's condition allows [10]. Treatment for lung cancer is often a combination of different approaches. Radiation therapy and chemotherapy are sometimes given together as radiochemotherapy. Chemotherapy, radiation, and radiochemotherapy can be used before surgery (neoadjuvant therapy) or after surgery (adjuvant therapy) [27].

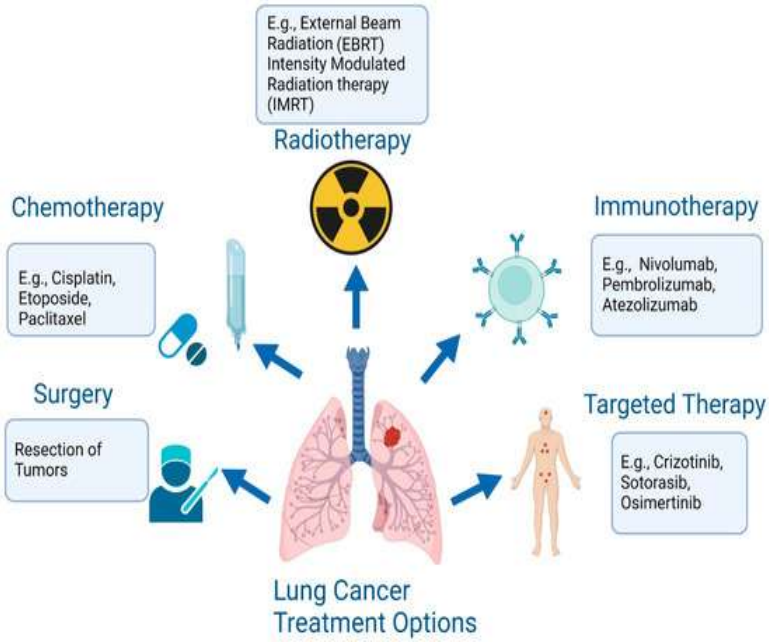

Fig5: Lung Cancer Treatment

1.Molecular Alterations and Targeted Therapies in Lung Cancer:

In recent years, with the development of new targeted therapies, there has been a lot of effort to identify potential drug targets, especially for known mutations.

Although many mutations have been identified in lung adenocarcinoma, the mutation status is unknown in more than 50% of cases. To date, therapeutic targets can only be identified in about 20% of lung cancers [29,10].

2.Genotype-Phenotype Correlations in Lung Cancer:

Adenocarcinoma is the most common type of lung cancer, making up over 50% of cases in recent studies. So far, most of the validated and experimental biomarkers that predict treatment responses have been found in adenocarcinoma compared to other types. A new classification system for adenocarcinoma has been introduced by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society. This system is based on the molecular characteristics of these tumours. The current classification of lung adenocarcinoma by the World Health Organization recognizes several distinct morphological subtypes, such as papillary, acinar, solid, and lepidic. Most lung adenocarcinomas show a mix of

these different patterns. While the biological reasons behind these subtypes are still being studied, there is evidence that certain subtypes may be linked to specific molecular changes or may lead to better outcomes.

3.Targeted Therapies in Lung Cancers With Epidermal Growth Factor Receptor Abnormalities:

Epidermal Growth Factor Receptor (EGFR) is known to have different mechanisms of action in non-small cell lung cancer (NSCLC). These include mutations in the tyrosine kinase domain of the EGFR gene and amplification of the EGFR gene itself. The EGFR mutation status is best found through gene sequencing, but it can also be detected by gene copy testing methods like fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization, and by checking protein levels with immunohistochemistry using mutation-specific antibodies. Several mutations in the tyrosine kinase domain of EGFR have been identified in recent years. EGFR is present in about half of all NSCLCs, and its presence is linked to a worse prognosis. These two factors make EGFR and its related proteins key targets for developing targeted therapies. Mutations in the EGFR kinase domain affect four exons and are located around the adenosine triphosphate-binding site of the enzyme. In some cases, lung cancers with EGFR mutations also show gene amplification, and this is associated with cancer progression. Some lung adenocarcinomas show EGFR activation through mutations and/or amplification, but the relationship between these two is not entirely clear. Using new techniques such as EGFR mutation-specific immunohistochemistry, Sholl and others studied a group of patients who had a high rate of EGFR mutations. They found that lung adenocarcinomas with EGFR amplification had different genetic changes, unique clinical features, and worse outcomes. Additionally, EGFR mutations and amplifications are spread out within the same tumor. These findings are significant, as they can influence the effectiveness of tyrosine kinase inhibitors for patients with EGFR-mutated lung adenocarcinoma. Recent discoveries have introduced EGFR mutation-specific antibodies that can help quickly identify lung cancers with these mutations. Mutations in the tyrosine kinase domain of EGFR have a prognostic significance, as patients with EGFR-mutated NSCLC tend to have longer periods without disease progression, regardless of the treatment they receive. Although EGFR mutations predict a better response to EGFR tyrosine kinase inhibitors, they do not seem to predict a significant difference in overall survival.

4.Targeted Agents Against Lung Cancer With EGFR Mutations:

The two currently approved tyrosine kinase inhibitors (TKIs) for treating lung cancers with EGFR mutations are gefitinib (introduced in 2002) and erlotinib (introduced in 2003). EGFR mutations are a specific target for these drugs, and they are a reliable biomarker for treatment response. The usefulness of this biomarker is supported by clinical trials showing that using TKIs as first-line treatment improves progression-free survival in patients with EGFR mutations. Based on the current information, predictive biomarker tests for EGFR should focus on identifying mutations. Mutation-specific antibodies for EGFR can be used for initial screening, but negative results from immunohistochemistry tests should be followed up with mutation analysis to check for less common mutations not detected by these antibodies. EGFR FISH testing is not as effective in predicting the response rate to TKIs compared to mutation testing, and it should not be used to select patients for EGFR TKI treatment. Resistance to TKI therapy is linked to KRAS mutations and specific acquired EGFR mutations like T790M.

Other genetic changes involving c-Met amplification, ERBB3 overexpression, and epiregulin activation also contribute to around 50% of cases of TKI resistance.

5. Genotype-Phenotype Correlations:

For patients with lung adenocarcinoma who received treatment with erlotinib and bevacizumab, those who had a favorable response were linked to adenocarcinomas with lepidic patterns. This led to further studies involving gefitinib and erlotinib, which found that between 17% and 22% of patients showed a response to gefitinib [50.51]. The connection between the EGFR mutation status and the specific subtype of adenocarcinoma remains a topic of heated discussion [52,53]. Genetic irregularities can be observed across different histological subtypes, though the frequency varies. One notable correlation is that mucinous adenocarcinoma (as shown in Figure 2) tends to be negative for TTF1 and EGFR mutations but might have Ras mutations and express CDX2. This could be due to its presumed origin from bronchiolar mucinous goblet cells [54].6.

6.Targeted Therapies With Angiogenesis Inhibitors in Nonsquamous NSCLC:

Recent findings suggest that non-squamous NSCLCs, compared to squamous cell carcinomas, show a stronger tendency to respond to treatment with bevacizumab. Bevacizumab (Avastin, manufactured by Genentech/Roche, located in South San Francisco, California) is a monoclonal antibody with a high affinity for vascular endothelial growth factor (VEGF). Although bevacizumab may offer benefits for certain patients with advanced, previously untreated NSCLC [55,56], its appropriate use is limited due to safety concerns—especially in patients with lung squamous cell carcinoma (SCC). This requires accurate diagnosis of the tissue obtained from before treatment starts. The first evidence of bevacizumab's clinical effects came from chemotherapy-naive patients with inoperable, locally advanced, metastatic, or recurring NSCLC. Currently, only those with non-squamous NSCLC histology benefit from bevacizumab when combined with chemotherapy [55]. It is against the guidelines to use bevacizumab in patients with SCC, based on a recent phase II trial [48], where 31% of SCC patients experienced severe or fatal hemoptysis. The risk of life-threatening bleeding complications with bevacizumab is significantly reduced when patients with SCC are excluded.

7. Targeted Therapies in Lung Cancers With Anaplastic Lymphoma Kinase Abnormalities:

On August 26, 2011, the U.S. Food and Drug Administration approved crizotinib for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) that tests positive for anaplastic lymphoma kinase (ALK) via fluorescence in situ hybridization (FISH) (as depicted in Figure 3). The ALK gene was first identified through the cloning of a translocation (t(2;5)(p23;35)) in a subset of anaplastic large cell lymphomas (ALCLs), a type of T-cell lymphoma [57,58]. ALK encodes a receptor with tyrosine kinase activity that is normally expressed only in certain nerve cells. In ALK-rearranged ALCLs, the intracellular part of ALK is fused with the N-terminal part of nucleophosmin (NPM), creating a chimeric protein with constant kinase activity. Other balanced translocations involving ALK have been found in ALCLs, yet all resulting proteins maintain the ALK kinase domain [59]. The significance of this kinase activity is evident in ALK-rearranged ALCL cell lines, as they rely on ALK's enzymatic function for their growth and survival. Recently, ALK rearrangements were identified in rare NSCLC cell lines and in isolated primary adenocarcinomas from Japanese and Chinese

individuals [60,61]. Most ALK rearrangements in NSCLCs result from an interstitial deletion and inversion on the 2p chromosome arm, creating the EML4-ALK fusion gene [60,61]. Animal tumors, human cell lines, and recent clinical trials show that lung cancers expressing EML4-ALK are sensitive to inhibitors of ALK kinase activity [62-64]. Hence, it is essential to efficiently detect ALK rearrangements in lung adenocarcinomas during routine practice to guide suitable treatment. None of the ALK-rearranged adenocarcinomas showed co-occurring EGFR mutations. Studies also indicate that ALK-rearranged adenocarcinomas are more likely to occur in younger, never-smoking patients at a more advanced stage compared to those without ALK rearrangements. Most ALK-rearranged adenocarcinomas have a distinct histological appearance, marked by solid tumor growth and frequent signet ring cells with large amounts of intracellular mucin (as illustrated in Figure 4) [65]. The emerging guidelines from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology on molecular testing for lung cancers suggest that (1) ALK rearrangements should typically be evaluated using molecular cytogenetic methods like FISH, and (2) commercially available ALK monoclonal antibodies may potentially assist in screening lung cancers for ALK rearrangements. However, some antibodies perform poorly, while others are not commercially available or have limited published data and test cases. Therefore, it is not yet advisable to recommend that immunohistochemistry be used to identify ALK-rearranged cases. In the meantime, FISH remains the preferred test for detecting ALK.

Other Molecular Abnormalities That Show Promise for Targeted Therapies in Lung Cancer:

1. **Human Epidermal Growth Factor Receptor 2 (HER2/neu) :–**

   Unlike the other members of the human epidermal growth factor receptor (HER) family, HER2/neu is not strictly a receptor tyrosine kinase because no high-affinity endogenous ligand has been identified. HER2/neu functions as a signaling network coordinator and amplifier when it forms heterodimers with other HER family members. HER2/neu mutations occur in 2% of non-small cell lung cancers (NSCLC) [66,67]. These mutations are in-frame insertions in exon 20 that target the corresponding tyrosine kinase domain, similar to EGFR insertions. These mutations occur in the same subpopulation as those with EGFR mutations, including adenocarcinoma, never-smokers, East Asians, and women. Although HER2/neu mutations occur in only 2% of patients, HER2/neu is frequently overexpressed (to some degree) in NSCLC and is associated with drug resistance, increased metastatic potential, increased vascular endothelial growth factor (VEGF) production, and poor prognosis. HER2/neu-mediated resistance to DNA-damaging agents requires the activation of Akt, which phosphorylates murine double minute 2 (MDM2), leading to enhanced MDM2-mediated ubiquitination and degradation of p53. Blocking the Akt pathway mediated by HER2/neu increases the cytotoxic effect of DNA-damaging drugs in tumor cells with wild-type TP53. Furthermore, recent studies have shown that the G/G genotype of the MDM2 polymorphism is linked with worse overall survival among patients with early-stage NSCLC, especially those with squamous cell histology [68]. Trastuzumab is a chimeric monoclonal antibody targeting HER2/neu. Combinations of trastuzumab with chemotherapy are well tolerated, showing response rates of 21% to 40% [69]. One trial found that patients whose tumors highly overexpressed HER2/neu (3+ by immunohistochemistry) or exhibited amplification by FISH had good responses. It appears that highly

overexpressing HER2/neu cases of NSCLC, although relatively rare (3%–9%), may benefit from trastuzumab treatment. MET Proto-oncogene – MET can be activated through mutations, autocrine or paracrine growth, gene amplification, or decreased degradation. Germline and somatic MET gene mutations have been reported in hereditary and sporadic papillary renal cell cancers [70].

In other cancers, MET gene mutations and amplifications have been identified as predictors of therapeutic response [65]. Expression of MET and phospho-MET has been studied in lung cancer; recent studies have shown that 40% of lung cancer tissues overexpress MET [71,72,73]. Recent studies have demonstrated that patients with NSCLC who have 5 or more copies per cell have worse survival compared to those with less than 5 copies; also, MET gene amplification leads to resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant patients. Anti-hepatocyte growth factor antibodies, anti-MET antibodies, and small-molecule MET tyrosine kinase inhibitors (TKIs) are all in various stages of development, and identifying predictive biomarkers for MET inhibitors will be important for future trials and treatment decisions [70].

2. **Other Targeted Molecular Therapies –**

There has been significant research and investment in the development of small molecules that target key proteins in cell signaling pathways that are altered in disease, particularly in cancers like lung cancer. For instance, receptor tyrosine kinases (RTKs) are potential therapeutic targets in several solid tumors, including lung cancer. The RTK c-KIT is highly expressed in small cell lung carcinomas, even though it is not mutated, which has led to clinical trials using the specific c-KIT inhibitor STI571 (Gleevec [imatinib], Novartis, East Hanover, New Jersey), both alone and in combination. However, these trials have not shown meaningful benefits from imatinib treatment. Antibodies against the angiogenic factor VEGF and small molecules that target VEGF receptors, such as SU5416 (an inhibitor of Flk-1 receptor), are being tested in NSCLC and other tumor types. More recently, modifications in gene expression using small interfering RNAs (siRNAs) have shown promise as the most powerful tool yet [69].

Conclusion:

Risk factors for lung cancer have been largely understood and well characterized. Primary prevention of this disease, therefore, seems relatively easy to implement by eliminating environmental hazards and smoking. Despite this, lung cancer remains the leading cause of death among malignant cancers in all highly developed countries. The causes of this phenomenon should be sought in the growing problem of environmental pollution, but above all in the difficulty of eliminating the addiction to smoking. The basic factor in the prevention of lung cancer is not smoking. Tobacco smoke is the most common cause of lung cancer. It is worth noting that electronic cigarettes are also not recommended as a preventive measure. The lack of proper education means that young people continue to use nicotine-containing products, starting with e-cigarettes and then traditional cigarettes. However, nicotine addiction is extremely strong in many people, and eliminating the addiction using traditional methods (psychotherapy, nicotine replacement therapy, pharmacotherapy) proves difficult. In such cases, reducing the health risks associated with smoking can be achieved by replacing cigarettes with smokeless products containing

nicotine. Many scientific studies have shown that aerosols from e-cigarettes and tobacco heating devices contain over 90% fewer carcinogenic substances than cigarette smoke [28]. The clinical application of molecular diagnostic techniques has enabled a more precise and rapid assessment of lung cancer and will help to triage patients to "personalized" therapies that have the highest success rates for eradicating the tumor. Our knowledge about lung cancer has changed dramatically in the past decade, and progress mainly depends on identifying new predictive biomarkers. We need to better understand both the tumor and host biology that underlie tumor sensitivity and resistance in order to provide a rationale for specific targeted therapy. Since many targets can be evaluated by multiple laboratory methods, such as sequence analysis, in situ hybridization, and immunohistochemistry, it is critical that efforts focus on standardizing methodologies for biomarker testing.

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