

EPIDEMIOLOGICAL CHARACTERISTICS AND RECENT ADVANCES IN CLINICAL MANAGEMENT OF NON-SMALL CELL LUNG CANCER

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Abstract: Non-small cell lung cancer (NSCLC) constitutes 80%-85% of all lung cancer cases. Epidemiological data reveal global variations in incidence, with rates increasing with age, higher prevalence in males, and a shift from squamous cell carcinoma to adenocarcinoma as the dominant subtype. Although the 5-year survival rate remains low, prognosis has shown gradual improvement. Advances in diagnostic technologies, including PET-CT and video-assisted biopsy techniques, have enhanced diagnostic precision. Current treatment strategies prioritize surgery-based multimodal regimens, complemented by personalized approaches. Targeted therapies and immunotherapies now offer novel therapeutic avenues for NSCLC patients.

Keywords: Non-small cell lung cancer; Epidemiology; Clinical diagnosis and treatment; Therapeutic innovations

INTRODUCTION

As the predominant pathological subtype of lung cancer, NSCLC imposes a significant global health burden. Recent environmental changes, population aging, and diagnostic advancements have driven marked shifts in its epidemiology and clinical paradigms[1]. Epidemiologically, NSCLC exhibits geographical and demographic heterogeneity. While smoking remains a primary risk factor, multifactorial interactions (e.g., genetic susceptibility, occupational hazards) complicate prevention efforts. In clinical practice, advancements in imaging, liquid biopsy, and multidisciplinary therapeutic integration are redefining NSCLC management[2]. This review synthesizes epidemiological trends and clinical innovations to guide future research and practice.

1 OVERVIEW OF NON-SMALL CELL LUNG CANCER

Non-small cell lung cancer (NSCLC) is the main pathological type of lung cancer, accounting for about 80-85% of all lung cancer cases, and mainly includes subtypes of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [3]. Its development is closely related to factors such as smoking, environmental exposure (e.g. radon, asbestos), and genetic susceptibility. Epidemiological data show that lung cancer is the malignant tumor with the highest morbidity and mortality rate worldwide, and China, as a country with high incidence of lung cancer, has more than 1 million new cases each year, accounting for more than 40% of the global total [4]. Clinical features of NSCLC show a high degree of heterogeneity, with insidious early symptoms, and about 70%-80% of the patients have already progressed to an advanced stage at the time of initial diagnosis (stage III-IV), resulting in a 5-year survival rate of only 10%-13% [5].

2 EPIDEMIOLOGICAL CHARACTERISTICS OF NON-SMALL CELL LUNG CANCER

2.1 Global and Regional Distribution

The global distribution of non-small cell lung cancer (NSCLC) shows significant geographic variations. According to the Global Cancer Statistics 2022, there are more than 2 million new cases of lung cancer, of which about 85% are NSCLC, and the high prevalence areas are concentrated in countries and regions with a high degree of industrialization [6]. Regions with the highest prevalence in men include Europe (e.g., Eastern Europe), East Asia (e.g., China, Japan), and North America, while sub-Saharan Africa has the lowest prevalence; high prevalence areas in women are dominated by North America, Northern Europe, Australia/New Zealand, and East Asia [7]. This difference in distribution is closely related to smoking prevalence, air pollution levels and occupational exposure. China, as the country with the heaviest burden of lung cancer in the world, accounts for about one-third of the global total number of new cases each year, and domestic data show that the mortality rate of lung cancer exhibits a gradient of "high in the north, low in the south, high in the east, and low in the west", with the mortality rate in the northeastern region and the eastern coastal provinces (e.g., Shanghai and Tianjin) being significantly higher than that in the northwestern and southwestern regions [8]). This phenomenon may be related to PM2.5 pollution due to coal combustion for winter heating in the north, occupational carcinogen exposure (e.g., asbestos, arsenic) in industrialized areas in the east, and regional differences in smoking prevalence [9].

2.2 Population Characteristics

The population distribution characteristics of non-small cell lung cancer (NSCLC) are influenced by multiple factors such as gender, age, smoking history, occupational exposure and genetic factors. The incidence of NSCLC is significantly higher in men than in women (male-to-female ratio of about 2.3:1), but the proportion of female patients has been rapidly increasing in recent years, which may be associated with passive smoking, indoor air pollution (e.g., cooking fumes), and changes in hormone levels [10]. Smoking prevalence in Chinese men has long been maintained at around 50%, and the risk of disease in smokers is 16 times higher than that in nonsmokers, while the proportion of nonsmokers is higher in female patients, suggesting the potential role of environmental exposure and genetic susceptibility.^{1 6} In terms of age distribution, NSCLC occurs predominantly in people older than 40 years of age, but the incidence of the disease has shown a tendency to be younger in recent years, especially the proportion of young and middle-aged patients with adenocarcinomas has increased [11]. Smoking-related lung cancers (e.g., squamous carcinoma) are more common in men over 50 years of age, while adenocarcinomas are more common in women and non-smokers, and the proportion of adenocarcinomas in East Asia is more than 50%, which may be related to the popularity of low-tar cigarettes, resulting in the penetration of carcinogens deeper into the periphery of the lungs [12]. Occupational exposure is an important risk factor, and about 10%-15% of NSCLC is associated with exposure to carcinogens such as asbestos, arsenic, and chromium, which are commonly found in people working in the mining, metallurgy, and construction industries.^{3 5} With regard to genetic factors, the risk of disease is increased by 1.8-fold in people with a history of lung cancer in first-degree relatives, and the mutation rate of the EGFR gene is as high as 40%-50% in Asian populations, which is significantly higher than that in Western populations (10%-16%) and predominantly in females, nonsmokers and adenocarcinoma patients, while KRAS mutations are mostly found in smokers and European and American populations [13].

Table 1 Characteristics of the non-small cell lung cancer population

Factor	Key Features
Gender	The incidence rate is significantly higher in males than in females, with a male-to-female ratio of about 2.3:1; the proportion of female patients has been rising rapidly in recent years
Age	Mainly occurs in people over 40 years of age; in recent years, the incidence of the disease tends to be younger, and the proportion of young and middle-aged patients with adenocarcinoma has increased.
Smoking History	Smokers have 16 times the risk of disease as nonsmokers; adenocarcinoma is weakly associated with smoking, squamous carcinoma is highly associated with smoking
Occupational Exposure	About 10%-15% of NSCLC is associated with occupational carcinogen exposure such as asbestos, arsenic, and chromium
Genetic Factors	First-degree relatives with a history of lung cancer have a 1.8-fold increased risk of the disease; EGFR mutation rates are significantly higher in Asian populations than in European and American populations

2.3 Transformation of Disease Types

Non-small cell lung cancer (NSCLC) may undergo histologic type transformation during disease progression or treatment, with transformation to small cell lung cancer (SCLC) being the most typical. This transformation phenomenon occurs mostly in patients with EGFR mutations receiving targeted therapy, with an incidence of 3%-10% [14]. The mechanism has not been fully clarified, and two main hypotheses exist: the theory of genealogical plasticity and the theory of tumor heterogeneity. The former suggests that NSCLC cells acquire the ability of neuroendocrine differentiation under specific genetic alterations (e.g., TP53 and RB1 deletion), which then transforms into SCLC; the latter hypothesizes that there was originally an undetected SCLC component within the tumor, and that after selective inhibition of the NSCLC clone by targeted therapies, the SCLC component gradually predominates [15]. The risk of transformation is strongly associated with specific gene mutations, and Kicken P M et al [16] showed that patients carrying EGFR-sensitive mutations (e.g., exon 19 deletion) with concomitant inactivation of the TP53 and RB1 genes have a significantly elevated risk of transformation. Histologic transformation may occur in approximately 42.8% of such triple mutation (EGFR/TP53/RB1) patients [17]. Transformed tumors usually retain the original EGFR mutation but lose EGFR signaling dependence, resulting in failure of targeted therapy [18].

3 NEW PROGRESS IN CLINICAL DIAGNOSIS AND TREATMENT RESEARCH ON NON-SMALL CELL LUNG CANCER

3.1 Advances in Diagnostic Technology

3.1.1 Diagnostic imaging

High-resolution CT (HRCT) and PET-CT have become important tools for the early diagnosis of non-small cell lung cancer (NSCLC). HRCT, through thin-layer scanning and three-dimensional reconstruction techniques, can clearly display tiny lung lesions (e.g., nodules <1 cm in diameter), and the detection rate of early lesions such as sub-solid nodules and hairy-glass shadows is significantly improved [19]. Its advantage lies in the high spatial resolution, which can accurately assess the tumor morphology, margin features and relationship with surrounding tissues, and reduce the risk of missed diagnosis. PET-CT, on the other hand, by detecting the glucose metabolic activity of tumor cells (e.g., the standardized uptake value SUV_{max}) combined with anatomical and structural information, can differentiate between

benign and malignant lesions and assess systemic metastasis, and has an accuracy of 85% to 90% for the staging of NSCLC [20].

3.1.2 Liquid biopsies

Liquid biopsy technology provides a minimally invasive and dynamic monitoring tool for NSCLC diagnosis by analyzing biomarkers such as circulating tumor cells (CTC) and circulating tumor DNA (ctDNA) [21]. CTC detection, which utilizes tumor cell surface markers (e.g., EpCAM) or physical properties for enrichment, can reflect tumor invasiveness and metastatic potential, but it is limited by the fact that blood CTC content is extremely low (about 1-10 CTC/mL), and the sensitivity still needs to be improved [22]. ctDNA detection, on the other hand, identifies tumor-related gene mutations (e.g., EGFR, KRAS) by NGS technology, with 70%-90% concordance with tissue biopsy, and is particularly suitable for patients who cannot obtain tissue samples or need real-time monitoring of drug-resistant mutations (e.g., EGFR T790M) in patients [23]. Miao WQ, Lin XH [24] et al. showed that persistent postoperative ctDNA positivity could indicate micro residual disease (MRD) and predict the risk of recurrence with a specificity of more than 95%.

3.2 Advances in Treatment

3.2.1 Surgical treatment

The popularization of minimally invasive surgical techniques has significantly improved the surgical safety and patient recovery efficiency of non-small cell lung cancer (NSCLC). Thoracoscopic surgery (VATS) accomplishes the resection of lung lobes or segments through tiny incisions, with less trauma, less intraoperative bleeding, a reduction of postoperative complication rates by about 30%-50% compared with traditional open-heart surgery, and a shorter hospital stay of 3-5 days [25]. Robot-assisted thoracoscopic surgery further improves the precision of the operation and is particularly suitable for tumor resection in complex anatomical sites, such as the hilar or mediastinal regions. In addition, the paradigm of surgery combined with neoadjuvant therapy (e.g., chemotherapy, targeted or immunotherapy) is becoming the standard. Neoadjuvant therapy reduces tumor size and stage, allowing otherwise inoperable patients with locally advanced disease to have the opportunity for radical resection, and increasing the 5-year postoperative survival rate to 40%-50% [26].

3.2.2 Radiotherapy

Stereotactic radiation therapy (SBRT) has demonstrated local control rates comparable to surgery (90%-95%) in the treatment of early-stage NSCLC, and is particularly suitable for elderly patients with poor cardiopulmonary function or those who refuse surgery. Its advantage lies in the high dose and short course of treatment (usually 3-5 sessions), which precisely destroys the tumor while protecting the surrounding normal tissues [27]. The combined application of radiotherapy and immunotherapy has become a research hotspot. Radiotherapy can enhance the immune response by releasing tumor antigens, while immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors) can prolong the distant effects of radiotherapy, and the two synergistically significantly enhance the objective remission rate (ORR) and progression-free survival (PFS) of patients with advanced disease [28].

3.2.3 Chemotherapy

Improvements in novel chemotherapeutic agents and delivery modalities aim to balance efficacy and safety [29]. Yihui Li, Luyang Dong et al. [30] showed that albumin-bound paclitaxel improves drug solubility and reduces the risk of allergic reactions through nanoparticle carriers, and has enhanced penetration into tumor tissues, which is particularly suitable for patients with squamous carcinoma. Optimization of chemotherapy regimens focuses on individualized dose adjustment and beat-to-beat chemotherapy (low-dose, high-frequency administration) to reduce side effects such as myelosuppression. In addition, targeted chemotherapeutic drug delivery systems (e.g., liposome-encapsulated cisplatin), which can increase local drug concentrations and reduce systemic toxicity, have been advanced in preclinical studies [31].

3.2.4 Targeted therapy

In addition to classical targets such as EGFR and ALK, drugs targeting MET exon 14 jump mutations, RET fusions and KRAS G12C mutations (e.g., topotinib, pratinib, sotolacib) have been approved for use, covering about 5%-10% of NSCLC patients [32]. Resistance mechanism studies reveal that EGFR-TKI resistance is often associated with MET amplification and EGFR C797S mutation, and resistance can be partially overcome by combinations (e.g., ositinib + MET inhibitor) or quadruple-generation TKIs (e.g., BLU-945) [33-34]. Rong Gao, Hong Zhao [35] Studies showing targeted therapy combined with chemotherapy or immunotherapy have explored that EGFR-TKI combined with anti-angiogenic drugs (e.g., bevacizumab) can delay resistance and enhance PFS, but with caution about bleeding risk.

3.2.5 Immunotherapy

The development of novel immune checkpoint inhibitors is gradually expanding the beneficiary population of non-small cell lung cancer treatment [36]. In addition to the widely used PD-1/PD-L1 inhibitors, drugs targeting new targets such as LAG-3 and TIM-3 have entered the clinical trial stage. preliminary [37] studies by Xu Q, Hua X et al. have shown that such drugs have some therapeutic potential for patients with negative traditional PD-L1 expression, providing a new direction for immunotherapy-resistant populations. In the field of combination therapy, the combination of PD-1 inhibitors with platinum-containing chemotherapy has become a first-line option for driver gene-negative patients, with objective remission rates elevated to 50%-60% and median overall survival extended to 18-22 months [38]. Combination strategies of PD-L1 inhibitors with anti-angiogenic agents (e.g., bevacizumab) have been demonstrated to be effective for the treatment of PD-L1-negative patients, by improving vascular structure in

tumor microenvironment and function and enhancing immune cell infiltration, further expanding the therapeutic options for patients without driver mutations [39]. Dual-immunity combination therapies (e.g., PD-1 inhibitors combined with CTLA-4 inhibitors) for advanced patients can increase 5-year survival to 20%-25% by synergistically activating different immune pathways, a breakthrough that marks an important step toward chronic disease management in advanced lung cancer. These advances reflect the evolutionary trend of immunotherapy from single pathway inhibition to multidimensional modulation [40].

4 CONCLUSION

The epidemiologic characteristics and clinical diagnosis and treatment strategies of NSCLC have undergone profound changes in recent years. In terms of disease distribution, geographical differences and population heterogeneity have become increasingly prominent, the interaction between traditional risk factors and emerging environmental exposures has reshaped the pattern of disease burden, and the dynamic evolution of subtype composition further suggests the complexity of carcinogenesis. In the clinical field, the deepening of the concept of precision medicine has pushed the diagnosis and treatment mode from "single intervention" to "full integration", and the imaging and liquid biopsy technologies have enhanced the possibility of early diagnosis and treatment, and individualized treatment under the guidance of molecular typing has gradually become a reality. The innovation of treatment strategies is particularly significant, with the popularization of minimally invasive surgery, the precision of radiotherapy, the iteration of targeted drugs and immunotherapy, and the optimization of multidisciplinary joint protocols, all of which have built a more efficient and safer intervention system. The analysis of drug resistance mechanisms and the development of new drugs have brought hope to patients with advanced disease, while the combined application of immunotherapy marks a paradigm shift in tumor therapy from "confrontation" to "regulation". In the future, how to target high-risk groups in complex etiology, break through treatment bottlenecks in drug-resistance dilemma, and balance costs and benefits in the wave of technology will remain the core challenges in the field. By exploring the etiological mechanisms in multiple dimensions and optimizing the whole management pathway, the prevention and control of NSCLC is expected to move towards a new stage of greater precision and inclusiveness.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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