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Diagnosis and Multimodal Therapy of Non-Small Cell Lung Cancer

Liming Tan*, Yusheng Shi*#

Zhuhai Clinical Medical College of Jinan University (Zhuhai People's Hospital, The Affiliated Hospital of Beijing Institute of Technology), Zhuhai, China
Email: #syszxm@hotmail.com

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Abstract

Lung cancer remains the leading cause of cancer-related death worldwide. As the most common histological subtype of lung cancer, non-small cell lung cancer (NSCLC) can be managed through multiple strategies including surgical resection, radiotherapy, systemic chemotherapy, immunotherapy, and molecular targeted therapy. Despite surgery with curative intent, a considerable number of patients eventually develop distant metastasis or local tumor recurrence. In recent years, significant progress has been made in targeted therapy and immunotherapy for NSCLC. Clinical management strategies should be individualized according to the patient's baseline health status and specific disease characteristics. According to the latest World Health Organization (WHO) classification guidelines, accurate histological and molecular stratification of NSCLC is clinically important. A standardized diagnostic workflow integrating imaging, tissue acquisition, and biomarker detection is crucial for guiding initial treatment decisions, and comprehensive management of treatment resistance requires combined tissue and liquid biopsy testing to guide subsequent treatment selection.

Keywords

Non-Small Cell Lung Cancer, Diagnostic Workflow, Stage-Stratified Therapy, Targeted Therapy, Immunotherapy, Treatment Resistance

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. According to the WHO, the prevalence of tobacco use has led to a continuous increase in global

*Co-first authors.
#Corresponding author.

lung cancer mortality, particularly in Asia. The development of lung cancer is associated with a variety of environmental and behavioral exposures. Cigarette smoking accounts for approximately 85% - 90% of lung cancer cases. In addition to active smoking [1], passive smoking, family history of lung cancer, and exposure to carcinogenic chemicals and heavy metals such as radon, asbestos, arsenic, chromium, beryllium, and nickel significantly increase the risk of lung cancer [2] [3]. Furthermore, pulmonary fibrosis, human immunodeficiency virus (HIV) infection, and alcohol consumption are also recognized as independent risk factors for lung cancer [4] [5].

Lung cancer is pathologically classified into two main categories: non-small cell lung cancer (NSCLC, accounting for approximately 85%) and small cell lung cancer (SCLC, approximately 15%) [6] [7]. According to the WHO histological classification, NSCLC mainly includes adenocarcinoma (40%), squamous cell carcinoma (25% - 30%), and large cell carcinoma (5% - 10%), with several rare histological subtypes in clinical practice.

NSCLC is often diagnosed at an advanced stage, which greatly limits curative treatment options [8] [9]. Cough is the most common clinical manifestation, occurring in 50% - 75% of patients, followed by hemoptysis, dyspnea, chest discomfort, or pain. Positron emission tomography (PET) and computed tomography (CT) allow more accurate locoregional and distant staging in patients with suspected or confirmed lung cancer [10] [11]. For patients enrolled in randomized controlled trials evaluating curative or neoadjuvant strategies, histopathological sampling of all PET-CT positive nodes is required according to the International Association for the Study of Lung Cancer (IASLC) staging consensus guidelines to ensure accurate pathological staging and avoid misclassification of disease extent [12] [13].

CT and magnetic resonance imaging (MRI) are routinely used for brain evaluation in patients undergoing treatment or with suspected brain metastasis [14]. According to the updated classification system by the IASLC, American Thoracic Society, and European Respiratory Society, obtaining sufficient and representative tumor tissue samples remains a critical step in diagnosis and treatment planning [15]. The ability to detect actionable gene mutations and develop individualized treatment strategies during the initial diagnosis has a profound impact on the management of all patients with suspected malignant lung tumors. Currently, the positive predictive value (2.4% - 7.5%) serves as a useful indicator for evaluating hemoptysis, a typical symptom of lung cancer [16]. The 8th edition tumor-node-metastasis (TNM) staging system supports more precise prognostic assessment for each TNM stage and provides a more accurate framework for liquid biopsy applications [17]. Liquid biopsy can also be used to detect circulating tumor biomarkers, such as circulating tumor DNA (ctDNA), microRNAs, and circulating tumor cells (CTCs).

In a clinical study including 282 treatment-naive NSCLC patients who underwent both noninvasive and invasive diagnostic procedures, ctDNA detection as a

minimally invasive alternative improved biomarker detection rate by 48% compared with tissue genotyping alone [18]. A practical, step-by-step diagnostic workflow for NSCLC is recommended in clinical practice, integrating imaging, tissue acquisition, histologic classification, and biomarker detection, with clear turnaround times and decision nodes to enable timely treatment initiation [19] [20]. The workflow is as follows: 1) Imaging evaluation (turnaround time: 3 - 5 working days): Chest low-dose CT for suspected nodules; if nodules ≥8 mm or with high-risk features (lobulation, spiculation, cavitation, etc.), further contrast-enhanced chest and abdominal CT + brain MRI + whole-body PET-CT for staging [10] [13]. 2) Tissue acquisition (turnaround time: 2 - 4 working days): Image-guided core needle biopsy for peripheral lesions and bronchoscopy for central lesions to establish pathological diagnosis; if tissue quantity is insufficient, liquid biopsy (ctDNA) is used as a supplementary method [15] [18]. 3) Histologic classification (turnaround time: 1 - 3 working days): Pathological subtyping (adenocarcinoma/squamous cell carcinoma/large cell carcinoma, etc.) according to the 2021 WHO Classification of Thoracic Tumors [21]. 4) Biomarker testing (turnaround time: 5 - 7 working days): The minimal recommended panel for all NSCLC patients includes genetic biomarkers (epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), B-Raf proto-oncogene serine/threonine kinase (BRAF) V600E, mesenchymal-epithelial transition factor (MET) exon 14 skipping, rearranged during transfection (RET), neurotrophic tyrosine receptor kinase (NTRK), Kirsten rat sarcoma viral oncogene homolog (KRAS) G12C) and immunotherapy biomarker (programmed death-ligand 1 (PD-L1) expression) [19] [22]. PD-L1 is tested by Food and Drug Administration (FDA)/National Medical Products Administration (NMPA) validated immunohistochemistry (IHC) kits (such as 22C3, SP263). 5) Decision node: Integrate staging, histology, and biomarker results to develop stage-stratified and individualized treatment plans within 2 - 3 weeks after initial diagnosis [20].

2. Stage-Stratified Treatment Pathways for NSCLC

Clinical management of NSCLC is strictly based on TNM stage, performance status (preferably Eastern Cooperative Oncology Group (ECOG) PS 0 - 2), and biomarker profile. The treatment section has been reorganized into stage-based pathways (Stage I - II, Resectable Stage III, Unresectable Stage III, Stage IV) with standard multimodal regimens for each stage, replacing the previous general treatment classification [13] [23]. All treatment recommendations are consistent with the 2025 National Comprehensive Cancer Network (NCCN) Guidelines and 2024 European Society for Medical Oncology (ESMO) Clinical Practice Guidelines [23] [24].

2.1. Stage I - II NSCLC (Early Stage)

Disease characteristics: Localized disease, no lymph node metastasis (N0) or limited regional lymph node metastasis (N1); curative local therapy is the main ap-

proach. **Standard multimodal regimen**: Radical surgical resection is preferred; adjuvant therapy is administered for high-risk stage II patients [25] [26].

- Surgery: Lobectomy + systematic lymph node dissection (preferred); segmentectomy/wedge resection only for patients unable to tolerate lobectomy due to poor pulmonary function [26] [27].
- Adjuvant therapy: Platinum-based adjuvant chemotherapy for stage IIA/IIB with high-risk factors (vascular invasion, poor differentiation, etc.) [25] [28]; osimertinib is an option for EGFR-mutant stage II patients with superior progression-free survival [29].
- Inoperable patients: Curative stereotactic body radiation therapy (SBRT), with 5-year overall survival comparable to surgery [30] [31].

2.2. Resectable Stage III NSCLC (IIIA-N2, Selected IIIB)

Disease characteristics: Single-station N2 metastasis or selected resectable IIIB disease; combined local and systemic therapy is required to improve cure rate and reduce recurrence. **Standard multimodal regimen**: Neoadjuvant chemoimmunotherapy + radical surgery + adjuvant therapy (triple modality) [32] [33].

- Neoadjuvant: Platinum-based chemotherapy + programmed cell death protein 1 (PD-1)/PD-L1 inhibitor for 3 - 4 cycles, with major pathological response (MPR) rate of 30% - 40% [33].
- Surgery: Lobectomy/pneumonectomy + systematic mediastinal lymph node dissection 4 - 6 weeks after neoadjuvant therapy [27].
- Adjuvant: If neoadjuvant chemoimmunotherapy was used, postoperative immune monotherapy is maintained for 1 year [33].

2.3. Unresectable Stage III NSCLC (Multi-Station N2, IIIB, IIIC)

Disease characteristics: Locally advanced, unresectable lymph node metastasis or invasion of critical structures; no distant metastasis (M0); definitive chemoradiotherapy is the core treatment. **Standard multimodal regimen**: Definitive concurrent chemoradiotherapy (CCRT) + consolidation immunotherapy [23] [32].

- Concurrent chemoradiotherapy: Platinum-based chemotherapy + thoracic radical radiotherapy (60 - 66 Gy) [34] [35].
- Consolidation immunotherapy: Durvalumab consolidation for 1 year after chemoradiotherapy improves 5-year overall survival by approximately 15% [36].
- Unfit patients: Sequential chemoradiotherapy + consolidation immunotherapy [24].

2.4. Stage IV NSCLC (Metastatic)

Disease characteristics: Distant metastasis (M1a/M1b/M1c); systemic therapy is the mainstay, and local therapy can be combined for oligometastases (≤3 lesions). **Standard multimodal regimen**: Biomarker-guided individualized systemic ther-

apy + local ablation for oligometastases [22] [23].

- Target-eligible patients: Corresponding tyrosine kinase inhibitor (TKI) monotherapy in first line (no chemotherapy required) [37] [38].
- Immunotherapy-eligible patients: Immunotherapy + chemotherapy preferred for PD-L1 tumor proportion score (TPS) ≥1%; immunotherapy monotherapy for TPS ≥50% [39] [40].
- Target-negative patients: Platinum doublet chemotherapy [41] [42].
- Oligometastases: Systemic therapy + SBRT/surgical resection of all metastatic lesions improves progression-free survival (PFS) and overall survival (OS) [31] [43].

3. Core Therapeutic Modalities (Supplementary to Stage Pathways)

Surgery, radiotherapy, and chemotherapy are retained as supplementary explanations for stage-based pathways; targeted and immunotherapy are described with clear drug-target relationships and approved indications in subsequent sections [22] [44].

3.1. Surgery

Surgery aims to resect the primary tumor and metastatic lymph nodes with negative margins [26]. Procedures include lobectomy (preferred), wedge resection, segmentectomy, and pneumonectomy (mostly for large central tumors) [26] [27]. Pneumonectomy is associated with higher perioperative morbidity and mortality than lobectomy [26]-[28]. Postoperative adjuvant therapy is administered to high-risk early-stage and resectable stage III patients to eliminate minimal residual disease [25] [28].

3.2. Radiotherapy

Radiotherapy induces irreversible DNA damage in tumor cells via high-energy ionizing radiation [34]. Definitive radiotherapy is used for inoperable early-stage patients; SBRT is the standard for inoperable stage I [31] [35]. Thoracic radiotherapy is the core for unresectable stage III, administered with concurrent chemotherapy [34] [36]. Palliative radiotherapy relieves symptoms such as bone pain and cough in advanced disease [34].

3.3. Chemotherapy

Chemotherapy acts by inhibiting tumor cell proliferation, division, and metastasis [41]. Platinum doublet chemotherapy is the backbone of neoadjuvant/adjuvant/definitive treatment for stage I - III [25] [32]. In stage IV, chemotherapy is combined with immunotherapy for target-negative patients or used as salvage therapy after targeted therapy failure [41] [42]. A French study showed that neoadjuvant chemotherapy conferred survival benefit in N0/N1 patients but not in N2 patients [32].

4. Targeted Therapy: Clear Drug-Target Relationships and Approved Indications

Targeted therapy is described by target type and drug class, distinguishing drug categories and globally approved indications (FDA/EMA/NMPA) to avoid confusion from regional and temporal differences. All agents are approved for first- or second-line use in corresponding mutations without off-label use [22] [24] [37].

EGFR exon 19 deletion or L858R mutation is the most common target in Asian populations. Agents targeting this mutation include first-generation gefitinib, erlotinib, and third-generation osimertinib. Osimertinib is the preferred first-line option, while gefitinib and erlotinib can be used in the second-line setting [37] [45].

Patients with ALK fusion-positive disease can receive crizotinib, alectinib, and lorlatinib. Alectinib or lorlatinib is preferred in first line, and crizotinib is mostly used in second line [38] [46].

Patients with ROS1 fusion-positive disease can receive crizotinib and entrectinib, both approved for first-line treatment [47] [48].

The only approved regimen for patients with BRAF V600E mutation is dabrafenib combined with trametinib for first-line treatment [49] [50].

Patients with MET exon 14 skipping mutation can receive capmatinib or tepotinib, both approved for first-line treatment [51] [52].

Patients with RET fusion-positive disease can receive selpercatinib or pralsetinib, both approved for first-line treatment [22] [53].

NTRK fusion is a pan-tumor target, and larotrectinib and entrectinib are both approved for first-line treatment of solid tumors including NSCLC [54] [55].

Patients with KRAS G12C mutation can receive sotorasib or adagrasib, mainly used in second-line treatment after platinum-based chemotherapy failure [56] [57].

For anti-angiogenic targeted therapy, bevacizumab (vascular endothelial growth factor (VEGF) antibody) combined with chemotherapy is approved for first-line treatment of stage IV non-squamous NSCLC; ramucirumab (VEGF receptor 2 inhibitor) combined with docetaxel is approved for second-line treatment of stage IV NSCLC. Bevacizumab is not recommended for squamous cell carcinoma due to high bleeding risk [23] [58] [59].

5. Immunotherapy: Drug Classes and Approved Indications

Immunotherapy is standardized by immune checkpoint inhibitor class and approved indications in NSCLC, stratified by PD-L1 expression level. Combination regimens are preferred in advanced disease, consistent with current international guidelines [24] [39] [40].

PD-1/PD-L1 inhibitors include nivolumab, pembrolizumab, atezolizumab, and durvalumab. In stage IV NSCLC, pembrolizumab monotherapy is recommended for first-line use in patients with PD-L1 TPS ≥50%; immunotherapy combined with chemotherapy is recommended for first-line use in patients with PD-L1 TPS ≥1%; nivolumab can be used for second-line treatment in patients of all PD-L1

levels [39] [40] [60]. In unresectable stage III NSCLC, consolidation durvalumab for 1 year after concurrent chemoradiotherapy is the standard regimen [36]. In resectable stage III NSCLC, PD-1 inhibitor combined with chemotherapy can be used in neoadjuvant or adjuvant settings [33].

The cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab can be combined with nivolumab for first-line treatment of stage IV NSCLC in patients with PD-L1 TPS ≥1% [61] [62].

6. Treatment Sequence and Resistance Management

This section is newly added to connect diagnosis and comprehensive management, including biopsy strategies at disease progression and subsequent treatment selection based on resistance mechanisms, consistent with the 2024 IASLC consensus on resistance management in NSCLC [63]-[65].

6.1. Biopsy Strategies at Disease Progression

Radiographic or clinical disease progression is a key trigger for repeat molecular testing. The choice between tissue biopsy and ctDNA liquid biopsy is determined by lesion accessibility and patient performance status [18] [63]. Tissue biopsy is preferred for accessible lesions to identify acquired resistance mutations and re-evaluate PD-L1 expression [64]. For lesions difficult to sample or patients with poor performance status, ctDNA testing can be used with a sensitivity of approximately 70% - 85%; if ctDNA is negative, tissue biopsy is still recommended to avoid false negatives [65]. The minimal testing panel at progression includes core driver genes (EGFR, ALK, ROS1, BRAF) and PD-L1 re-testing [64].

6.2. Treatment Selection Based on Resistance Mechanisms

Resistance to targeted therapy and immunotherapy can be divided into on-target and off-target resistance, and treatment regimens should be selected according to specific resistance mechanisms [63] [65].

For targeted therapy resistance, in EGFR-TKI resistance with T790M mutation, osimertinib is recommended; with MET amplification, EGFR-TKI combined with MET-TKI can be used. In ALK-TKI resistance with G1202R mutation, lorlatinib is recommended. For patients without identifiable resistance mutations, platinum-based chemotherapy combined with immunotherapy is recommended [23] [45] [46] [51].

For immunotherapy resistance, primary resistance can be switched to chemotherapy combined with anti-angiogenic therapy; secondary resistance is recommended to re-test PD-L1 and ctDNA, and if PD-L1 TPS remains ≥1%, an alternative immune checkpoint inhibitor combined with chemotherapy can be used [24] [58] [63] [65].

The general principle is that systemic therapy should be adjusted within 2 - 3 weeks for all progressive patients; for oligoprogressive disease, local SBRT can be combined while maintaining systemic therapy [43] [65].

7. Conclusions

Patients with NSCLC should receive individualized treatment strategies based on anatomical and molecular staging. Treatment plans must be carefully tailored according to the patient's clinical condition, performance status, and disease characteristics. The emergence and widespread application of targeted therapy and immunotherapy have revolutionized the treatment paradigm of NSCLC. Immunotherapy, whether as monotherapy or combined with chemotherapy, has become a standard component of first-line treatment for eligible patients.

Despite significant advances in the development and application of targeted and immunotherapy, long-term PFS in patients with lung cancer remains unsatisfactory. Accurate histological and molecular subtyping of NSCLC according to the latest WHO classification is essential for achieving individualized targeted therapy. A standardized diagnostic workflow integrating imaging, tissue acquisition, and a minimal biomarker panel is the foundation for initial treatment decision-making; comprehensive resistance management combining tissue and ctDNA testing ensures rational sequencing of subsequent therapies. Future research should focus on novel biomarkers for early resistance prediction and innovative combination regimens (such as TKI + immunotherapy) to further improve survival in patients with advanced NSCLC [22] [65].

Conflicts of Interest

The authors declare no conflicts of interest.

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