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Clinical Characteristics and Management Challenges of Combined Small-Cell Lung Cancer: A Narrative Review

Fanshu Huang[1], Jiequn Ma[2], Zheng Zhao[2,*]

[1]The First Clinical Medical College, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Department of Internal Medicine, Shaanxi Provincial Cancer Hospital, Xi'an 710000, Shaanxi, China
Correspondence Author

Abstract: ***Combined small-cell lung cancer (CSCLC) is a distinct pathological subtype of small-cell lung cancer (SCLC), in which a small-cell carcinoma component coexists with one or more non-small-cell or non-classical small-cell components, including adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, or large-cell neuroendocrine carcinoma (LCNEC). This mixed histology carries direct clinical implications, as it complicates diagnosis, staging interpretation, and treatment selection. In routine clinical practice, small biopsy or cytology specimens often only capture a portion of the tumor, leading to missed or delayed identification of the combined histologic pattern. This narrative review summarizes current evidence on CSCLC, with particular focus on histopathological heterogeneity, diagnostic pitfalls, molecular reassessment, and treatment-related uncertainty. Rather than framing CSCLC as a purely molecular entity, we emphasize key issues that influence everyday clinical care: adequate tissue sampling, careful histopathological interpretation, systematic immunohistochemical work-up, selective molecular testing, and multidisciplinary treatment planning. A clearer understanding of CSCLC tumor heterogeneity may improve diagnostic accuracy and support the development of more individualized management strategies.***

Keywords: Combined small-cell lung cancer, Diagnosis, Pathology, Treatment strategy, Tumor heterogeneity, Clinical management.

1. Introduction

Combined small-cell lung cancer is defined as a tumor in which a small-cell lung cancer component coexists with a non-small-cell or other non-classical small-cell component [1]. This distinction is clinically relevant because mixed histology may influence prognosis, staging interpretation, and treatment planning [2]. Genomic profiling and microdissection-based transcriptomic studies further suggest that CSCLC is not simply conventional SCLC with an incidental second component. Instead, it appears to represent a heterogeneous disease entity with both shared ancestral alterations and component-specific molecular features [3, 4]. Recent case reports, real-world analyses, liquid genomic profiling data, prognostic modeling, and spatial studies have also strengthened the view that CSCLC requires integrated pathological and clinical interpretation [5-10].

Compared with pure SCLC, which usually follows a rapidly progressive course and is often treated according to relatively standardized protocols, CSCLC shows greater intertumoral and intratumoral variation. This variation can create discrepancies between small biopsy findings and surgical resection specimens. In clinical practice, CSCLC is often recognized only when sufficient tumor tissue is available. A small biopsy may capture the small-cell component while missing adenocarcinoma or squamous differentiation; conversely, it may show a non-small-cell component without adequately sampling the neuroendocrine component [2, 5-9]. Case-based evidence also indicates that liquid genomic profiling can complement tissue testing when histology evolves or when tissue-based testing is inconclusive [10]. These sampling and reassessment issues help explain why reported incidence, clinical behavior, and outcomes vary across published studies [2, 5-10].

For clinicians, the key task is to translate this biological and pathological complexity into a workable diagnostic and treatment pathway. Accordingly, this review focuses on how CSCLC is suspected, confirmed, stratified, reassessed, and managed in routine clinical settings.

2. Diagnostic Challenges in Clinical Practice

The diagnostic work-up of suspected CSCLC usually begins with chest computed tomography (CT), positron emission tomography-computed tomography (PET-CT), and bronchoscopy. These examinations are indispensable for tumor localization, staging, and biopsy guidance, but they cannot establish the histological subtype on their own [1, 2]. Imaging findings are often non-specific and may resemble either SCLC or NSCLC, depending on the dominant tumor component. A tumor dominated by small-cell morphology may present as a central mass with mediastinal lymphadenopathy, whereas an adenocarcinoma-predominant lesion may appear as a peripheral nodule or show ground-glass features [2,5, 8-10].

Histopathological evaluation therefore remains the cornerstone of diagnosis. Bronchoscopy, transthoracic biopsy, or surgical sampling may be selected according to tumor location, disease stage, and patient condition. The accuracy of pathological diagnosis, however, depends strongly on whether the specimen includes representative areas of the tumor. Surgical specimens are more likely to reveal the spatial relationship among components, whereas cytology or small biopsies are often insufficient to identify a combined pattern [2,5,6,8,9].

When morphology is equivocal, immunohistochemistry results should be interpreted in conjunction with routine

histological findings. Neuroendocrine markers, including synaptophysin, chromogranin A, CD56, INSM1, and TTF-1, can help identify the small-cell component. Markers such as Napsin A, p40, p63, and cytokeratin profiles may help detect adenocarcinoma or squamous differentiation [1,2,11]. Because SCLC itself is molecularly heterogeneous, subtype-associated transcription factors such as ASCL1, NEUROD1, POU2F3, and YAP1 should not be interpreted in isolation; their diagnostic value depends on the morphological and clinical context [12-22].

When the clinical course does not align with the original diagnosis, clinicians should consider repeat biopsy or expert review of the initial specimen, since underdiagnosis can directly alter treatment selection [6, 10]. Discordant treatment response, unexpected disease progression, or the emergence of new lesions all warrant pathological and molecular reassessment.

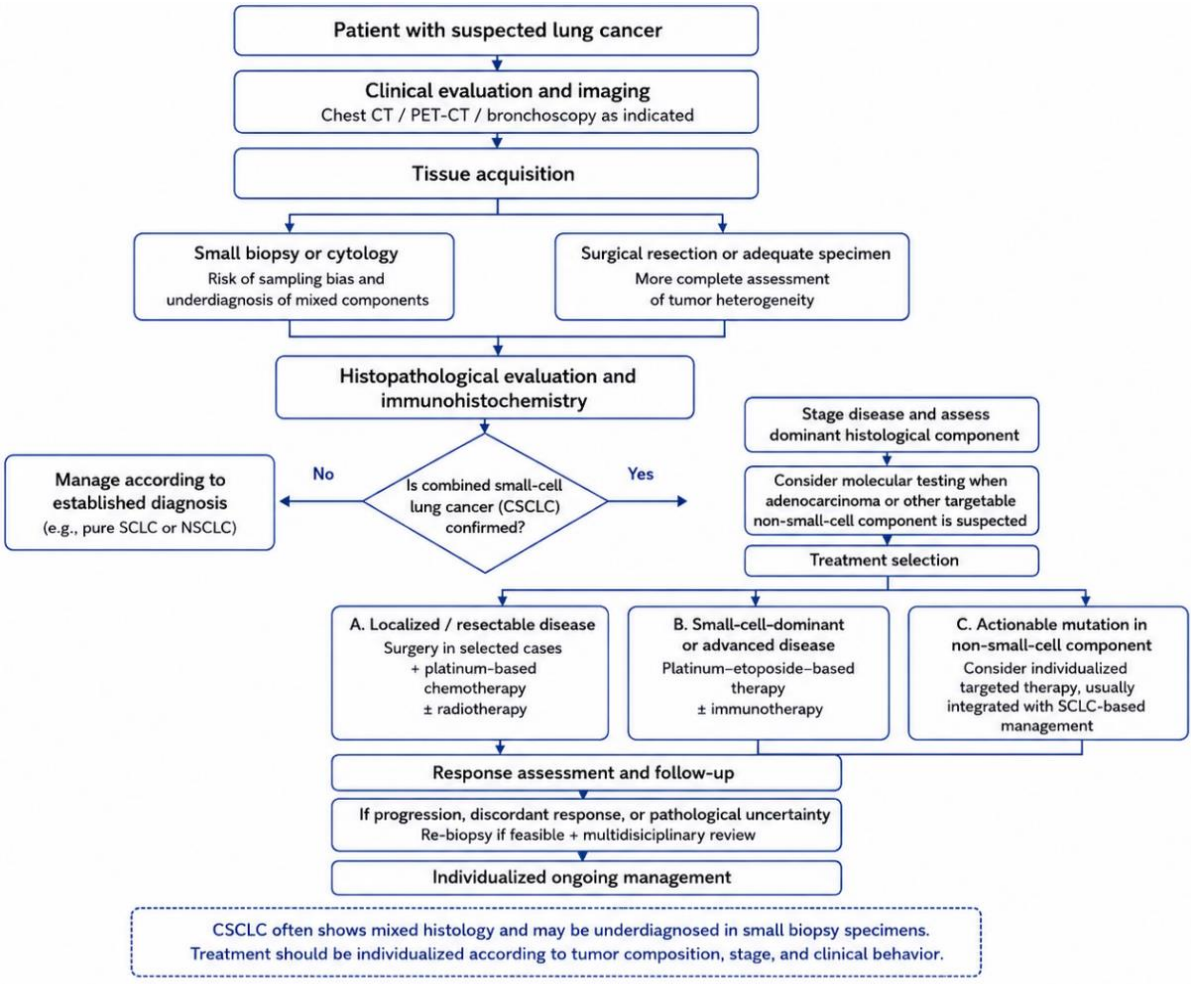

Figure 1: Diagnostic and Management Pathway for Combined Small-Cell Lung Cancer (CSCLC)

3. Histological Heterogeneity and Clinical Meaning

CSCLC is marked by intratumoral heterogeneity that is thought to arise from clonal divergence from a common progenitor cell. Available evidence suggests that early events such as TP53 and RB1 loss may establish a shared precursor clone, followed by divergent differentiation into different histological lineages [3, 4]. Spatial multi-omics data in CSCLC further support a monoclonal origin, neuroendocrine plasticity, and distinct microenvironmental niches across tumor components [23]. Studies of EGFR-mutant NSCLC evolving toward small-cell transformation also show that transformed tumors may develop distinct transcriptomic programs, lineage-reprogramming features, and potential precision-therapy opportunities [24-29].

Clinically, this heterogeneity increases the risk of sampling error, particularly in small biopsy specimens. It may also influence treatment selection, because the dominant tumor component and the component driving progression are not always the same. Different components may respond differently to chemotherapy, immunotherapy, radiotherapy, or targeted therapy [2-4,6]. For instance, a small-cell-dominant tumor is generally managed using an SCLC-based approach, whereas a tumor with a substantial adenocarcinoma component and an actionable driver alteration may require a more individualized strategy [10, 24-29].

Transcriptomic, methylation, and spatial studies provide biological support for these clinical observations. They indicate that tumor components and evolving clones can differ in cellular state, lineage plasticity, immune microenvironment, and therapeutic vulnerability [16-23]. Even so, advanced molecular or spatial profiling is not available in many routine clinical settings. For day-to-day patient management, the priorities remain adequate sampling, precise pathological reporting, and treatment planning based on the dominant or progressive component [2, 5-10].

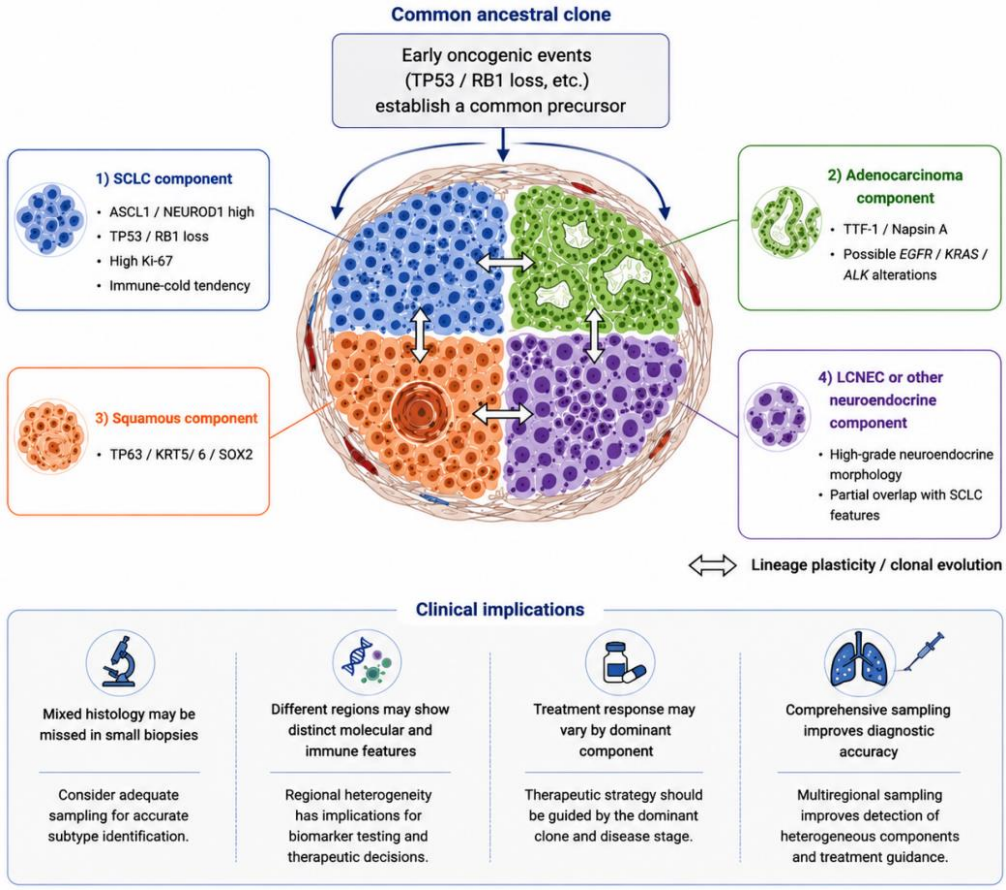

Figure 1: Histological Heterogeneity and Clonal Architecture of Combined Small-Cell Lung Cancer (CSCLC)

Table 1: Practical treatment stratification for CSCLC.

Clinical scenario	Stratification basis	Possible treatment strategy	Clinical concern
Small-cell dominant disease	Predominant SCLC component or rapidly progressive disease	Platinum-etoposide-based chemotherapy ± immunotherapy; radiotherapy when indicated	Early metastasis, aggressive course, and high relapse risk
Mixed histology without clear dominance	Substantial coexistence of SCLC and NSCLC components	Individualized multimodal therapy; multidisciplinary discussion recommended	Sampling bias, mixed response, and uncertain optimal sequencing
NSCLC-dominant or actionable mutation present	Adenocarcinoma/squamous component is clinically relevant, or targetable mutation is detected	Targeted therapy may be considered, usually integrated with SCLC-based management when needed	Histological transformation, resistance, and component-specific progression
Discordant response or uncertain progression	Clinical course is inconsistent with initial diagnosis or response differs across lesions	Repeat biopsy if feasible, reassess pathology and molecular profile, then adjust therapy	Dynamic tumor evolution and changing dominant component

4. Treatment Considerations

No universally accepted CSCLC-specific treatment algorithm is currently available. Management is therefore usually extrapolated from clinical evidence for SCLC or NSCLC, and adjusted according to disease stage, patient performance status, and the dominant histological component [2, 6].

Small-cell-dominant or advanced disease is commonly treated with platinum-etoposide-based chemotherapy, and immunotherapy is considered in line with contemporary SCLC clinical practice, supported by data from the IMpower133 and CASPIAN trials [30-34]. More recent advances—including lurbinectedin plus atezolizumab as maintenance therapy for extensive-stage SCLC, and DLL3-targeted bispecific T-cell engagement with tarlatamab for previously treated SCLC—may be appropriate for selected patients, although direct CSCLC-specific evidence remains limited [35-39].

When the non-small-cell component is substantial, particularly when adenocarcinoma is present, molecular profiling becomes clinically important. Alterations such as EGFR mutations, ALK rearrangements, or KRAS mutations may influence targeted therapy decisions [3,4,10, 24-29]. However, an actionable alteration does not guarantee that targeted therapy alone will be adequate, as the small-cell component may progress independently. Treatment sequencing or combination strategies should therefore be discussed in a multidisciplinary setting [2, 6, 7].

For early-stage or localized CSCLC, surgical resection may be considered when clinically appropriate. Surgery alone, however, is unlikely to be sufficient if the small-cell component is biologically or clinically significant. Adjuvant chemotherapy, radiotherapy, and close surveillance should be planned according to disease stage, resection findings, and histological component composition [2, 6, 7]. In relapsed or discordant disease, re-biopsy may help confirm whether progression is driven primarily by the small-cell or non-small-cell component [5-10].

5. Follow-up and Reassessment

Follow-up should go beyond simply measuring tumor size. Clinicians should also assess whether different lesions or tumor regions are responding differently to treatment. A mixed response may indicate that one component remains treatment-sensitive while another has developed resistance. Imaging review, pathological reassessment, and molecular retesting are particularly valuable when disease progression is unexpected or a new treatment option is being considered [5-10]. For patients with adenocarcinoma-associated transformation or actionable alterations, longitudinal molecular reassessment may help clarify whether resistance stems from the expansion of the transformed small-cell component or the persistence of the non-small-cell component [24-29].

Multidisciplinary discussion is central to the management of CSCLC, because CSCLC does not fit neatly into the conventional classifications of either SCLC or NSCLC. Treatment decisions require coordinated input from specialists across pulmonology, pathology, medical oncology, radiation oncology, thoracic surgery, radiology, and molecular diagnostics.

6. Current Limitations and Future Directions

Despite advances in molecular profiling and pathological classification, CSCLC remains incompletely characterized, due to its rarity and extensive biological heterogeneity. Most currently available evidence is derived from retrospective studies, case reports, or extrapolated from clinical trials for pure SCLC and NSCLC [2,5-10]. Prospective CSCLC-specific clinical trials are still lacking, and published patient cohorts often suffer from small sample sizes, inconsistent diagnostic criteria, and heterogeneous treatment regimens [6, 7].

Future research should prioritize standardized pathological reporting, clear documentation of the proportion of each histological component, component-specific molecular testing, and longitudinal tissue sampling collected before and after treatment. Single-cell sequencing, methylome sequencing, and spatial multi-omics approaches may help identify which patients can be effectively treated with SCLC-based regimens, and which require more tailored individualized treatment strategies [18, 23]. New therapeutic directions, including lurbinectedin-based maintenance therapy and DLL3-targeted bispecific antibodies, should also be evaluated in patients with mixed-histology tumors and therapy-related transformation [35-39]. DNA damage response targeting strategies, including PARP inhibitor- and ATR inhibitor-based regimens, may be effective for selected SCLC-like tumor components [40-43].

In addition, existing single-cell and spatial atlases of lung cancer provide valuable methodological frameworks for future CSCLC research on tumor plasticity, metastasis, and immune microenvironment remodeling [44-47]. Investigations into immunotherapy resistance and emerging antigen-targeted or epigenetic-directed therapies will further inform the development of individualized strategies for advanced or relapsed CSCLC [48, 49].

7. Conclusion

CSCLC represents a complex and clinically challenging lung cancer subtype characterized by pronounced histological and molecular heterogeneity. The primary clinical challenges include underdiagnosis in small biopsy samples, uncertainty in treatment selection, and dynamic changes in tumor composition during disease progression. Effective management requires comprehensive tissue sampling, accurate pathological evaluation, and individualized treatment strategies guided by tumor composition and dominant biological behavior. Multidisciplinary collaboration remains essential for optimizing outcomes in this heterogeneous disease entity.

Fund Project

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