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Review Article

Driver Gene Mutations and Risk of Lymph Node Metastasis in Non-Small Cell Lung Cancer

Feiyue Z[1,2], Li Z[1,2], Zhang Bing[1], Chen Benchao[1,2], Wang Shuting[1,2], Du Yu[1,2] and Gaofeng L[2]*

[1]Kunming Medical University, Kunming, China

[2]Department of Thoracic Tumor Surgery, Yunnan Cancer Center, Kunming, China

***Corresponding author:** Li Gaofeng, Department of Thoracic Tumor Surgery, Yunnan Cancer Center, Kunming, 650118, China

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Abstract

Non-Small Cell Lung Cancer (NSCLC) lymph node status is closely related to its diagnosis, treatment, and prognosis. The lymph node status is an important basis for formulating clinical treatment strategies of NSCLC, therefore comprehensive and profound understanding of risk factors for lymph node metastasis is essential. There are many known factors for lymph node metastasis in NSCLC, such as pathological subtypes, tumor size, tumor location. Meanwhile, whether the mutation of the driver gene affects the lymph node metastasis is still lacking enough research. This article aims to elaborate the relationship between NSCLC driver gene mutation and lymph node metastasis, from NSCLC lymph node metastasis-related risk factors, driver genes and lymph node metastasis, metastatic lymph node mutation status analysis and detection these several aspects to summarize the latest research progress in NSCLC driver gene mutation and lymph node metastasis risk. It also fully explained the correlation between driver gene mutations and NSCLC tumor biological behaviors such as lymph node metastasis.

Keywords: Non-small cell lung cancer; Lymph node metastasis; driver gene mutation; Heterogeneity; Analysis of tumor genetic characteristics

Background

The occurrence and development of cancer are driven by key mutations in driver genes. Furthermore, lymph node metastasis is related to driver gene mutations in Non-Small Cell Lung Cancer (NSCLC) [1], According to the protein encoded by mutant genes involved in the molecular pathways, these driver gene mutations were divided into different mutation subtypes (such as EGFR, MET, HER2, KRAS, BRAF, ROS1, ALK, RET, and wild type).Besides, many new potential oncogenes, such as PIK3CA mutations, FGFR1 amplification, and DDR2 mutations have been continuously identified [2-4]. Driver genes and targeted therapy have brought a revolution in the diagnosis and treatment of NSCLC [5]. The significance of studying the causes and mechanisms of NSCLC driver genes and lymph node metastasis cannot be underestimated.

Risk of Lymph Node Metastasis in NSCLC

Univariate and multivariate logistic regression analysis of factors showed that lymph node metastasis of NSCLC was closely related to age, tumor size, histology and differentiation, carcinoembryonic antigen level, vascular invasion (+), and pleural involvement (+) [6,7]. Tumor size has a great influence on lymph node metastasis. Besides tumor with micropapillary or solid components are associated with lymph node metastasis, while Ground-Glass Opacity (GGO) components are on the contrary [8,9]. Also, propensity score matching analysis shows that the risk of lymph node metastasis in lung adenocarcinoma is higher than that of lung Squamous Cell Carcinoma (SCC) [10]. Other studies suggest that patients with carcinoembryonic antigen levels greater than 5 ng/dL should be recommended for systemic lymph node dissection owing to the high risk of lymph node metastasis [11]. Far more than that, the central tumor location type and tumor long axis >2 cm but ≤3 cm are risk factors for lymph node metastasis [12]. Interestingly, studies have also shown that the tumor is located in the periphery, and the enlarged lymph nodes on CT are prone to lymph node metastasis [13]. Others, such as lymphatic invasion in tumors, are risk factors for lymph node metastasis in patients with NSCLC, and adjuvant therapy should be considered for such patients [14]. The role of driver gene mutations in NSCLC lymph node metastasis is still covered by a fascinating veil (Figure 1).

Driver Gene Mutations and NSCLC Lymph Node Metastasis

The role of driver gene mutations in NSCLC lymph node metastasis

Different genotypes of NSCLC have a different propensity for lymph node metastasis. Studies have suggested that compared with other genotypes, fusion gene mutation cases have a higher risk of lymph node metastasis, and these patients should adopt more in-depth treatment or monitoring strategies [2]. Comparing the accumulated genetic changes between the primary tumor and lymph node metastasis, it shows that p53 and EGFR mutations usually precede lymph node metastasis [15]. Another study conducted a comprehensive genomic and transcriptomic analysis of primary lung adenocarcinoma and corresponding lymph node metastasis and found that TP53 mutations are more abundant in the tumors of patients with metastases. This is very important for elucidating the molecular pathogenesis of metastatic lung adenocarcinoma [16]. It was EGFR mutations rather than KRAS mutations more related to N2 skipping metastasis (N2 lymph node metastasis without N1) in patients with lung adenocarcinoma [17].

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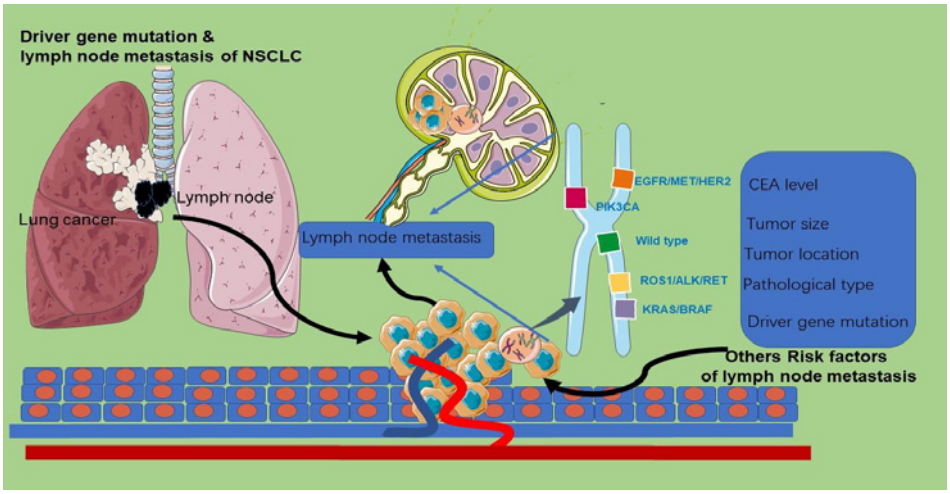

Figure 1: Driver gene mutation and risk of lymph node metastasis in non-small cell lung cancer. Which kind of driver gene mutation easily leading to the metastasis of lymph nodes in NSCLC?.

Apart from lung adenocarcinoma, an Array-based comparative genomic hybridization analysis shows that lymph node metastasis in patients with primary lung squamous cell carcinoma is related to specific genomic aberrations: loss of 4p and acquisition of 19q12 [18]. Different genome aberrations may be related to different biological characteristics. For example, FGFR gene mutation is an independent prognostic factor of lymph node metastasis in lung squamous cell carcinoma, and it is significantly related to the increased risk of lymph node metastasis in NSCLC patients with stage I to III [19].

Carcinogenic mutations that drive lymph node metastasis can also indicate metastatic disease in other organs or tissues [20]. In lung adenocarcinoma patients with EGFR mutations, compared with patients with wild-type EGFR, patients with EGFR mutations have a higher rate of including intrabronchial local infiltration rate including metastasis rate and pleural infiltration rate, although both have similar lymph node metastasis rates [21]. Another retrospective analysis showed that EGFR mutations, ALK gene fusion, and RET gene fusion in patients with advanced NSCLC play an active role as a driving gene in brain metastasis [22]. Besides, it was found that the frequency of EGFR mutations is reduced, while the incidence of ALK and ROS1 fusions are opposite by analyzing the relationship between the gene status of EGFR, ALK, ROS1, and RET in the resected specimens of patients with primary lung adenocarcinoma accompanied by N1-N2 lymph node metastasis [23]. Therefore, it is recommended to thoroughly evaluate the driver genes of lymph node metastasis after radical resection.

Mutational heterogeneity between primary tumor and metastatic lymph node of NSCLC

The existence of genetic heterogeneity affects the results of molecular detection in biopsy samples of primary or metastatic sites in patients with advanced NSCLC [24]. Evaluation of EGFR mutations in the surgically resected primary tumor and metastatic lymph nodes of NSCLC by DNA sequencing and heteroduplex analysis found that a significant difference in EGFR mutations between the primary tumor and metastatic lymph nodes of NSCLC [25]. The comparison of driver gene mutation maps can clarify and distinguish the origin of tumors between primary and metastatic tumors [26]. There are also many differences in the mutation profiles of key cancer-related genes in primary lung cancer and its associated lymph node metastasis [27]. Next-Generation Sequencing technology (NGS) can also be used to detect driver genes mutations in primary and metastatic tumors. Once it is confirmed that the gene mutations in lymph node metastasis are inconsistent, it may indicate the second primary cancer [28]. Unlike clinical and/or pathological diagnosis, cancer-specific mutations can be used as clonal markers to more accurately classify the pathology of lung cancer and its lymphatic metastasis. thereby which could improve the treatment options and effects based on the difference not only in the clinical/histopathological but also the genomic diagnosis [29]. Taking into account the difference in EGFR, KRAS, and BRAF mutation status between the primary tumor and the corresponding lymph node metastasis, different tyrosine kinase inhibitors ought to be selected for treatment correspondingly [30].

The clinical value of metastatic lymph node mutation status

Epidermal Growth Factor Receptor (EGFR) and its downstream factors KRAS and BRAF have different frequencies of mutations in NSCLC, which can predict the clinical response to EGFR inhibitors. Therefore when these mutations are used to select patients for EGFR-directed tyrosine kinase inhibitor therapy, the mutation status differences between the primary tumor and the corresponding lymph node metastasis should be considered [30]. The EGFR mutation status of Metastatic Lymph Node (MLN) is a predictor of the response to EGFR-TKI treatment in NSCLC patients [31]. Also, compound mutation profiles can provide more accurate prognostic information for patients with stage II NSCLC [32].

Biopsy of NSCLC Metastatic Lymph Node Gene Mutation Status

Lymph node status is considered to be one of the most reliable indicators of the prognosis of lung cancer patients, and the histological evidence of metastasis spread and mutation analysis is also crucial for the best clinical stage and treatment [33]. The lymph nodes of NSCLC patients are usually staged using 18F-Fluorodeoxyglucose Positron

Emission Tomography/Computed Tomography (FDG-PET/CT). However, micrometastasis such as occult lymph node metastasis should be selected by mediastinoscopy or Transbronchial Needle Aspiration (EBUS-TBNA) guided by endobronchial ultrasound [34]. More importantly, the mutation status of multiple genes such as EGFR, KRAS, and p53 in metastatic lymph nodes could be obtained through EBUS-TBNA [35]. Not limited to EBUS-TBNA, ultrasound-guided supraclavicular lymph node biopsy is a reliable and safe method for detecting advanced lung cancer metastasis, histological subtypes, and identifying EGFR mutations. It can replace invasive lung biopsy as the initial tissue confirmation of advanced disease [36].

Problems and Prospects

As a result of the heterogeneity in the gene spectrum between the primary tumor and the metastatic lymph node of NSCLC, the mutation spectrum of the lymph node deserves more attention. Moreover, the related mechanism of gene mutations involved in cell proliferation, invasion, and migration and lymph node metastasis is not clear yet. Characterize and analyze the metastatic lymph node at the genome level, mRNA, and protein level is essential for a better understanding of tumor biology [37]. For example, MiR-199b in miRNAs can regulate tumor cell migration, invasion, and metastasis [38]. Besides, targeted therapies represented by EGFR-TKI have increasingly become an indispensable part of the field of NSCLC treatment [39]. More importantly, as the Cancer Genome Atlas (TCGA) applies high-throughput sequencing technology and other sophisticated technologies in the field of lung cancer, new targeted carcinogenesis in non-small cell lung cancer have been discovered one after another [40]. All of us should broaden our horizons and excavate the essential role of driver gene mutations in the tumor biological behavior, not limited to lymph node metastasis.

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