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THE RELATIONSHIP BETWEEN GENE MUTATIONS AND PROGNOSIS IN PATIENTS WITH STAGE I NON-SMALL CELL LUNG CANCER AFTER SURGERY

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Abstract: This article discusses the relationship between gene mutations and prognosis in patients with stage I non-small cell lung cancer (NSCLC) after radical surgery. The study highlights that EGFR and ALK mutations are common in Stage I NSCLC patients and significantly affect both disease-free survival (DFS) and overall survival (OS). Patients with EGFR mutations respond well to EGFR-TKI treatment, significantly prolonging DFS; similarly, ALK mutation patients show improved prognosis with ALK inhibitor treatment. In contrast, patients with KRAS mutations have poorer outcomes, with common treatments including chemotherapy and immunotherapy. The importance of genetic testing in comprehensive postoperative treatment for early-stage NSCLC is highlighted, suggesting that individualized adjuvant therapy may play a role in improving long-term prognosis.
Keywords: Non-small cell lung cancer; Gene mutation; EGFR; ALK; KRAS; Prognosis; Targeted therapy

1 INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [1], with stage I NSCLC representing the earliest and most localized disease stage. The primary treatment for stage I NSCLC is surgical resection, followed by regular postoperative surveillance, which is the current standard approach. However, postoperative prognoses vary significantly, and some patients may experience recurrence or metastasis despite undergoing surgery. EGFR gene mutations and ALK gene fusions are common and clinically significant genetic alterations in NSCLC [2]. These mutations not only influence the biological behavior of tumors but also play a crucial role in determining patient prognosis. For patients with stage I NSCLC harboring specific genetic mutations, such as EGFR-positive mutations, the use of EGFR inhibitors (e.g., gefitinib or osimertinib) is recommended to reduce the risk of recurrence. Similarly, for ALK fusion-positive patients, ALK inhibitors (e.g., crizotinib or alectinib) are suggested as postoperative adjuvant therapy. The identification of these genetic mutations is critical for precision medicine. Genetic testing assists physicians in selecting the most appropriate treatment strategies, and targeted therapies can significantly improve survival outcomes, ultimately enhancing the treatment efficacy and survival rates of patients with stage I NSCLC.

2 COMMON GENE MUTATIONS IN STAGE I NSCLC

2.1 EGFR Mutations

Epidermal growth factor receptor (EGFR) gene mutations are the most common driver mutations in non-small cell lung cancer (NSCLC), particularly prevalent among Asian NSCLC patients, with an even higher incidence in non-smoking individuals, reaching 40% to 50%. The EGFR structure consists of an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic domain, which contains a tyrosine kinase domain and sites for tyrosine autophosphorylation [3]. Upon binding with extracellular ligands, EGFR forms functionally active homodimers or heterodimers. The most common EGFR mutations include exon 19 deletions (exon-19del) and the L858R substitution mutation in exon 21 [4]. The exon-19del mutation shortens the β3-αC helical structure, while the exon 21 L858R substitution locks the kinase domain into a constitutively active conformation [5], disrupting the inactive structure of EGFR and leading to dimerization and increased activity.
The presence of EGFR mutations is closely associated with tumor growth drivers, as these mutations result in abnormal activation of EGFR kinase activity, promoting tumor cell proliferation and survival. A study [6] analyzing genetic testing data from 254 NSCLC patients identified EGFR mutations in 132 cases, including 56 cases with exon 19 deletions and 76 cases with the exon 21 L858R substitution. Notably, the lymph node metastasis rate of patients with EGFR 19del and EGFR L858R mutations showed statistical significance. Targeted therapy with EGFR tyrosine kinase inhibitors (TKIs) has become the standard treatment for advanced EGFR-mutant NSCLC in recent years. The third-generation EGFR-TKI osimertinib has been validated in the ADAURA trial for use as postoperative adjuvant therapy in stage IB–IIIA NSCLC patients [7]. Other EGFR-TKIs, including first-generation inhibitors such as gefitinib and erlotinib, second-generation inhibitors such as afatinib and dacomitinib, and third-generation inhibitors such as almonertinib and furmonertinib, are currently undergoing various clinical trials.

2.2 KRAS Mutations

KRAS mutations are among the most common oncogenic alterations in non-small cell lung cancer (NSCLC), affecting approximately 20%–30% of patients [8]. These mutations are more frequently observed in smokers and lead to abnormal activation of cellular signaling pathways, promoting tumor growth and metastasis. KRAS-mutant patients typically do not respond well to targeted therapies and are associated with a poorer prognosis. A study [9] analyzing 69 NSCLC patients identified KRAS mutations in 13 cases, with the majority occurring in exon 2 and only one case in exon 3. The incidence of KRAS mutations was significantly correlated with gender, with male patients exhibiting a higher mutation rate than female patients. However, no significant associations were found between KRAS mutations and other factors such as patient age, histological subtype, smoking history, clinical TNM staging, tumor differentiation, or lymph node metastasis.

KRAS mutations exhibit high heterogeneity, and different KRAS mutation subtypes vary in their sensitivity to treatment, posing challenges for clinical management. Studies indicate that, compared to non-KRAS-mutant patients, those with KRAS mutations demonstrate better response rates and survival benefits when receiving monotherapy with immune checkpoint inhibitors. This may be due to alterations in the tumor immune microenvironment caused by KRAS mutations, making tumors more recognizable to the immune system. Combining immunotherapy with chemotherapy or other targeted therapies has been shown to significantly improve overall survival (OS) and progression-free survival (PFS) in NSCLC patients with KRAS mutations [10,11].

2.3 ALK Fusion

ALK gene rearrangement is a common genetic alteration in stage I non-small cell lung cancer (NSCLC), particularly prevalent among younger patients and non-smokers. The ALK gene is located on the short arm of human chromosome 2 (p23) and encodes the ALK receptor tyrosine kinase. Lung cancer with ALK fusion represents a distinct clinical subtype of NSCLC, with an incidence of approximately 2%–10% [12,13]. ALK fusion is associated with increased tumor aggressiveness and a higher risk of recurrence. A study [13] analyzed 735 early-stage NSCLC patients who underwent curative surgery and detected ALK fusion genes using fluorescence in situ hybridization (FISH). The results showed an overall ALK positivity rate of 3.8% (28/735), with rates of 6.8% in adenocarcinoma patients, 7.6% in female patients, and 8.9% in non-smokers. The median age of ALK-positive patients was 55 years, significantly lower than that of ALK-negative patients. Based on a median follow-up of 41.6 months, the overall survival (OS) of ALK-positive and ALK-negative patients was 97.7 months and 78.9 months, respectively, while the disease-free survival (DFS) was 76.4 months and 71.3 months, respectively, with no statistically significant difference. Additionally, ALK-positive patients tended to have a lower T-stage, predominantly classified as T1. Among adenocarcinoma patients, ALK-positive individuals had a higher level of lymph node metastasis, suggesting that despite their smaller tumor size, they exhibit a biological tendency for early lymph node spread.

Targeted therapies for ALK fusion, such as crizotinib, have been demonstrated to significantly reduce recurrence rates and improve survival outcomes [14]. ALK fusion can also coexist with other mutations, such as EGFR or KRAS, which may complicate the prognosis and therapeutic strategies for affected patients.

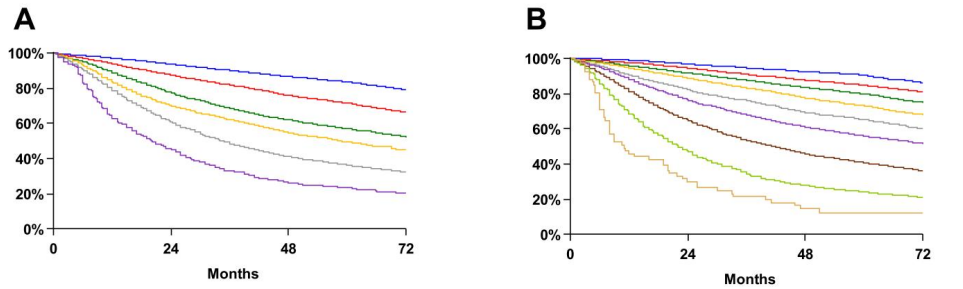
2.4 Other Mutations

In addition to common EGFR, KRAS, and ALK gene mutations, other genetic alterations such as ROS1, BRAF, and PIK3CA mutations are also present, though their incidence rates are relatively low. ROS1 fusion genes are predominantly found in younger non-smoking patients, whereas BRAF mutations are more commonly observed in smokers. Moreover, the specific type of BRAF mutation influences the choice of treatment strategy. PIK3CA mutations often coexist with other genetic alterations, and the presence of such co-mutations may affect patients' responses to targeted therapy as well as patterns of disease recurrence.

3 IMPACT OF GENE MUTATIONS ON THE PROGNOSIS OF POSTOPERATIVE STAGE I NSCLC

3.1 Survival Rate and Disease-Free Survival (DFS)

Research by Goldstraw et al. indicates that the 2-year and 5-year postoperative survival rates for stage I NSCLC (IA1, IA2, IA3, and IB) are 97%, 94%, 92%, and 89%, respectively, for 2 years, and 90%, 85%, 80%, and 73%, respectively, for 5 years [15] (Figure 1). Both EGFR and ALK mutations significantly impact the overall survival (OS) and disease-free survival (DFS) of stage I NSCLC patients. Studies have shown [17] that the application of EGFR-TKIs, such as osimertinib and erlotinib, in EGFR-mutant patients significantly reduces the risk of postoperative recurrence and prolongs DFS. Similarly, for patients with ALK fusion, ALK inhibitors such as crizotinib and alectinib have demonstrated remarkable efficacy as postoperative adjuvant therapies, leading to improved OS and DFS outcomes.



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1837 / 11423	NR	94%	83%
IB	2168 / 7711	NR	87%	71%
IIA	1514 / 3702	NR	77%	57%
IIB	1325 / 2776	58.9	70%	49%
IIIA	3467 / 5818	35.0	61%	36%
IIIB	364 / 506	20.0	45%	23%

Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

Figure 1 TNM Staging Classification Based on the 7th Edition (A) and Proposed 8th Edition (B). MST: Median Survival Time [15]

In contrast, patients with KRAS mutations tend to have a poorer prognosis [17], characterized by higher recurrence rates and shorter overall survival (OS). Unlike EGFR and ALK mutations, targeted therapies have shown limited effectiveness for KRAS-mutant patients, and the efficacy of chemotherapy is generally lower compared to patients with other genetic mutations[16]. The survival of KRAS-mutant NSCLC patients largely depends on the effectiveness of immunotherapy. While some patients experience significant survival benefits from immunotherapy, its overall efficacy remains limited.

3.2 Recurrence Risk and Patterns

Surgery is the most important treatment for stage I NSCLC; however, postoperative recurrence remains common. Existing literature reports that the recurrence rate after surgery for stage I NSCLC ranges from 14% to 36% [18,19]. Gene mutations also influence the recurrence patterns in stage I NSCLC patients. The primary recurrence and metastasis patterns for stage I NSCLC include local recurrence, regional recurrence, and distant metastasis. Studies show that the highest recurrence risk for 338 stage IA patients with postoperative recurrence of NSCLC occurs within 12 months after surgery [20]. This may be related to the immune homeostasis disruption caused by invasive surgery, with early metastasis patterns showing a distant metastasis rate of 14%–31%. Common metastatic sites include bone, the central nervous system, liver, and adrenal glands [21,22]. For EGFR-mutant NSCLC patients, adjuvant treatment with osimertinib for 3 years post-surgery has been shown to reduce the risk of recurrence or death by 83%–88%, significantly lowering the risk of both local and distant recurrence, including brain metastasis [7]. Additionally, patients with ALK fusion tend to experience distant metastasis, with common metastatic sites being the brain, liver, and bone. Early use of ALK inhibitors can significantly reduce the recurrence risk in these patients and effectively control tumor progression.

KRAS-mutant patients, however, often present with a pattern of both local recurrence and widespread systemic metastasis [23]. These patients typically experience local recurrence shortly after surgery, which gradually progresses into multi-system metastasis. Due to KRAS mutations' resistance to targeted therapies, treatment for these patients requires a multidisciplinary approach, combining chemotherapy, radiotherapy, and immunotherapy to prolong survival.

4 GENE MUTATIONS AND PERSONALIZED TREATMENT

4.1 Postoperative Treatment for EGFR and KRAS Mutant Patients

For stage I NSCLC patients with EGFR mutations, postoperative adjuvant EGFR-TKI treatment can significantly extend disease-free survival (DFS) [24]. The ADAURA study showed that osimertinib significantly reduced the risk of recurrence in patients with EGFR mutations in stages IB to IIIA of NSCLC. The use of postoperative adjuvant targeted therapy has made long-term disease-free survival after surgery a possibility for this group of patients. It is important to note that the use of EGFR-TKIs requires attention to the development of resistance, especially to secondary mutations like T790M that may emerge during long-term treatment.

For KRAS mutant patients, there is currently no effective targeted therapy, but immunotherapy is being gradually explored and may offer new options for these patients. KRAS G12C inhibitors, an emerging treatment approach, have

shown good results in some patients, though the overall efficacy still requires further clinical validation. For patients who are not suitable for immunotherapy, chemotherapy remains the primary postoperative treatment option.

4.2 Treatment Strategies for ALK and Other Mutations

For patients with ALK fusion, postoperative treatment with ALK inhibitors such as crizotinib or alectinib can significantly extend survival [13]. Especially in the early stages of postoperative adjuvant treatment, ALK inhibitors can effectively prevent tumor recurrence and reduce the risk of distant metastasis.

For other mutations, such as ROS1 fusion and BRAF mutations, targeted therapies are gradually becoming standard treatment options, improving patient prognosis. ROS1-positive patients typically respond well to crizotinib, while BRAF V600E mutation patients show favorable efficacy with BRAF inhibitors such as dabrafenib combined with trametinib. For these rare genetic mutations, the selection of targeted therapy should be based on specific genetic testing results and tailored to individualized treatment plans.

5 CONCLUSION

Gene mutations play a crucial role in the development and prognosis of stage I NSCLC. By detecting genes such as EGFR and ALK, it is possible to better predict patient prognosis and develop personalized treatment plans. Genetic testing is an important foundation for creating individualized treatment strategies, particularly in early detection and assessment of recurrence risk. In the future, personalized treatments based on genetic testing are expected to further improve survival rates and quality of life for stage I NSCLC patients. Moreover, with the continuous development of novel targeted therapies and immunotherapies, more patients will be able to benefit, thereby enhancing long-term disease-free survival.

CONFLICT OF INTEREST

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

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