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Clinicopathological Features of Skip N2 Lymph Node Metastasis in Non-Small Cell Lung Cancer (Postprint)

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Date: 2019-02-25T00:00:00+00:00

Abstract

Lung cancer is the leading cause of cancer-related mortality worldwide. Surgical treatment remains the mainstay of therapy, particularly for patients with early-stage non-small cell lung cancer, and lymph node metastasis status is crucial for disease staging and prognosis. Skip N2 metastasis is relatively common and is closely associated with patient prognosis. This article primarily summarizes the clinicopathological characteristics and survival prognosis of skip N2 metastasis in non-small cell lung cancer, aiming to provide guidance for clinical decision-making.

Full Text

Clinicopathological Features of Skip N2 Lymph Node Metastasis in NSCLC

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Abstract

Lung cancer is the leading cause of cancer-related death worldwide. Surgical intervention remains the dominant treatment modality, especially for early-stage non-small cell lung cancer (NSCLC) patients. Lymph node metastasis status is crucial for cancer staging and prognosis. Skip N2 metastasis is a relatively

common phenomenon that is closely associated with patient prognosis. This article aims to summarize the clinicopathological features and survival prognosis of skip N2 metastasis in NSCLC, providing guidance for clinical decision-making.

Keywords: NSCLC, skip N2 metastasis, clinicopathological features, prognosis

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, and its incidence continues to rise. In recent years, significant progress has been made in lung cancer treatment, including surgical techniques, targeted therapy, and immunotherapy, leading to improved survival outcomes. For patients with resectable tumors, especially NSCLC, surgical treatment remains the first-line choice, with anatomic lobectomy plus systematic mediastinal lymph node dissection being the standard approach. Surgical indications are evaluated based on the clinical stage of the primary lesion, with the Tumor-Node-Metastasis (TNM) staging system being the most widely used classification.

In 2016, the International Association for the Study of Lung Cancer (IASLC) updated the lung cancer staging system based on comprehensive analysis of 94,708 cases collected from 35 centers in 16 countries between 1999 and 2010, introducing the 8th edition TNM staging strategy [1-4]. This new edition, focused primarily on lung cancer prognosis, reclassified the T/N/M categories to provide more precise guidance for prognostic evaluation and clinical treatment decisions. The revised N staging system specifically lists skip N2 metastasis as N2a1 (Figure 1 [Figure 1: see original paper]). Although not further subdivided in the final TNM classification, this recognition was based on overlapping survival curves between some N1 and N2a1 patients, suggesting that N2a1 patients may have better pathological outcomes than other N2 patients, indicating a potential subgroup with more favorable prognosis.

It is widely accepted that N2 lymph node metastasis in lung cancer refers to metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes, including both N1(-)N2(+) and N1(+)N2(+) patterns. Skip N2 metastasis refers specifically to the former pattern, where N2 lymph node metastasis occurs without involvement of corresponding peribronchial or ipsilateral hilar lymph nodes. As early as 1971, Kirsh et al. first identified mediastinal lymph node skip metastasis in lung cancer [5]. Libshitz named this phenomenon "skip metastasis" in 1986 [6]. Over the past three decades, increasing cases have been reported, with data showing that 20-30% of NSCLC patients with N2 metastasis exhibit skip metastasis, and this subtype is associated with better prognosis [7-10]. This article aims to summarize relevant literature and review the clinicopathological characteristics of skip N2 metastasis in NSCLC.

1 Clinical Features of Skip N2 Metastasis in NSCLC

Skip N2 metastasis is not uncommon in NSCLC. According to various reports, the proportion of skip N2 metastasis among NSCLC patients with N2 positivity

ranges from 20% to 44%, with an average of approximately 31.6% [11, 12]. Multiple studies [13-15] have shown no differences in age or gender distribution, and no correlation with smoking history. However, Guerrera [12] reported in 2016 on 54 cases of skip N2 metastasis in lung adenocarcinoma, finding that skip N2 metastasis occurred primarily in non-smokers, though this does not establish smoking as an independent predictive factor.

Several studies [13, 16-18] have indicated that skip N2 metastasis is more common in primary tumors located in the right lung, particularly the right upper lobe. In contrast, Li [14] suggested that tumor size, especially lesions smaller than 3 cm, may be an independent factor influencing skip N2 metastasis, while tumor location showed no correlation. Nevertheless, most studies [19, 20] have found that lung cancers in different lobes have relatively specific skip N2 metastasis zones. Shigemoto [19] mapped these preferential drainage pathways based on literature reports, noting that right upper lobe and left upper lobe cancers tend to skip to stations 4 and 5, respectively, while lower lobe cancers predominantly skip to station 9. These findings align with those of Takahashi [17] and Kawano [21], with approximately 80% of patients following these patterns.

2 Pathological Features of Skip N2 Metastasis in NSCLC

NSCLC primarily includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounting for approximately 80% of all lung cancers, with adenocarcinoma being the most common. Some studies have found that skip N2 metastasis occurs more frequently in adenocarcinoma, particularly acinar-predominant adenocarcinoma, while non-skip N2 metastasis is more common in papillary-predominant adenocarcinoma [13]. However, Ilic [22] reported in 2007 on 21 NSCLC patients with skip N2 metastasis, finding that while N2 metastasis was more common in adenocarcinoma, skip N2 metastasis was more frequently observed in squamous cell carcinoma ($p < 0.001$). This finding is consistent with Tanaka [23] and Casali [24]. Ilic also suggested that the lower incidence of skip N2 metastasis in female patients might be related to the higher incidence of adenocarcinoma in women. Riquet [8] found no histological difference in N2 skip metastasis overall, but noted that among patients with single-station mediastinal lymph node metastasis, skip N2 metastasis was more common in adenocarcinoma and large cell carcinoma, while non-skip N2 metastasis was predominantly squamous cell carcinoma. In 2001, Wang Siyu [25] analyzed 176 cases of stage IIIA-N2 NSCLC and found that skip N2 metastasis was mostly single-station mediastinal lymph node metastasis (92.5%).

In 2015, Li [13] analyzed histopathological results from 45 lung adenocarcinoma patients with skip N2 metastasis, finding fewer lymphatic invasions and pleural infiltrations. Conversely, Japanese surgeon Atsuo Gorai [26] retrospectively analyzed 422 clinical stage IA NSCLC patients, including 21 with skip N2 metastasis of both adenocarcinoma and non-adenocarcinoma types, and found that skip N2 metastasis was associated with a higher probability of visceral pleural and lymphovascular invasion. Multivariate analysis indicated that visceral pleu-

ral invasion is an important predictor of skip N2 metastasis in early-stage lung cancer patients.

3 Molecular Biology and Marker Research in Skip N2 Metastasis

Genetic testing for lung cancer, particularly adenocarcinoma, has become quite mature and is widely used to guide targeted therapy. Guerrera [12] focused on skip N2 metastasis in lung adenocarcinoma, analyzing 54 of 279 patients and testing for common mutations (KRAS and EGFR). The results showed that 33% of skip N2 metastasis patients had EGFR mutations (especially exon 20 mutations), compared to only 10% in non-skip N2 metastasis patients ($p < 0.001$). No difference was observed in KRAS mutation rates between the two groups.

Pezzella [27] and Ohsaki [28] reported that Bcl-2 overexpression often indicates better prognosis in NSCLC patients. Prenzel [29] later found that Bcl-2 expression levels were higher in skip N2 metastasis patients than in non-skip patients, which may explain the better prognosis associated with skip metastasis. Similarly, p53 mutation, as an adverse factor, was found at higher levels in non-skip N2 metastasis adenocarcinoma compared to skip metastasis cases.

Research on biomarkers for skip N2 metastasis remains limited. Komatsu et al. [30] retrospectively analyzed 279 preoperative clinical stage IA NSCLC patients, including 12 with skip N2 metastasis, examining preoperative serum concentrations of CEA, Cyfra21-1, and SLX. The results showed that serum SLX concentration was significantly elevated in skip N2 metastasis patients compared to pN0 patients. Multivariate analysis indicated that SLX is an independent predictor of skip N2 metastasis in clinical stage IA NSCLC patients. However, the study lacked comparison between skip and non-skip N2 metastasis groups and did not provide specificity or sensitivity data.

4 Possible Mechanisms of Skip N2 Metastasis

Intra-thoracic lymph node metastasis in lung cancer is closely related to lymphatic drainage patterns, typically following a sequential pattern from intrapulmonary to hilar to mediastinal nodes, progressing from near to far and top to bottom. The mechanisms of skip metastasis are currently thought to include: (1) tumor invasion of visceral pleura with subsequent metastasis to mediastinal lymph nodes via subpleural lymphatic channels; (2) tumor cells bypassing N1 lymph nodes and metastasizing directly to mediastinal lymph nodes through intrapulmonary lymphatics; (3) failure of routine histopathology to detect micrometastases in N1 lymph nodes; and (4) genetic background alterations in lymph nodes.

In 2014, Japanese surgeon Takizawa and colleagues [31] used indocyanine green near-infrared fluorescence imaging to observe the actual pathway of direct skip

metastasis from a 23mm solid tumor in the right lower lobe to mediastinal lymph nodes, confirming the existence of skip metastasis. Histopathology confirmed N2 metastasis of lung adenocarcinoma involving stations 7 and 4R. Similarly, Imai [32] intraoperatively confirmed that lung cancer can bypass hilar lymph nodes and metastasize directly to mediastinal lymph nodes.

Increasing reports suggest that lymphangiogenesis can predict lymph node metastasis in various solid malignancies. Although no lung cancer-specific studies exist, Ohta [33] found differences in peritumoral lymphatic vessel density and vascular endothelial growth factor C expression between skip and non-skip N2 metastasis NSCLC, with higher peritumoral lymphatic density in skip metastasis cases. Moreover, among skip N2 metastasis patients, those with high lymphatic density had lower survival rates. Whether changes in the peritumoral microenvironment are directly related to skip N2 metastasis remains unproven.

5 Survival Analysis of NSCLC Patients with Skip N2 Metastasis

Reported 5-year survival rates for stage IIIA-N2 NSCLC patients range from 6% to 35% [34], with variations potentially related to treatment selection and tumor heterogeneity. However, numerous studies [7, 13, 16, 22, 29] have found that NSCLC patients with skip N2 metastasis have relatively better prognoses. Recently, Japanese surgeon Isaka [7] followed 1,012 surgically treated stage I-III NSCLC patients, including 48 with skip N2 metastasis, and found 5-year local recurrence rates of 96.1%, 84.1%, 85.0%, and 53.5% for N0, N1, skip N2, and non-skip N2 groups, respectively ($p < 0.0001$). No significant difference was observed between N1 metastasis and skip N2 metastasis patients regarding 5-year local tumor recurrence.

Guerrera [12] analyzed 54 of 279 lung cancer patients with skip N2 metastasis and found that these patients may have better overall survival (OS) (HR 0.656; P = 0.063; 95% CI 0.421–1.023). Skip N2 metastasis demonstrated an independent protective effect on OS (HR 0.503; P = 0.014; 95% CI 0.291–0.870). Additionally, skip metastasis patients had significantly lower 5-year tumor recurrence and metastasis risk compared to non-skip patients (0.71 vs. 0.45, p = 0.09). Similarly, patients with hotspot EGFR mutations also had lower 5-year recurrence rates.

We compiled 5-year survival rates from different literature reports on NSCLC patients with skip N2 metastasis . Citak [40] published data in 2015 specifically examining survival in left upper lobe NSCLC patients with aortopulmonary window lymph node metastasis who underwent surgical treatment. The results showed that skip N2 metastasis patients had better 5-year survival rates compared to non-skip N2 patients (29.9% vs. 19.2%). Riquet [8] also summarized data from several studies, concluding that skip N2 metastasis NSCLC patients have relatively better prognostic outcomes.

6 Discussion

For surgically treated NSCLC patients, the presence of N2 metastasis is a crucial factor influencing postoperative adjuvant therapy selection and prognosis. However, further research has revealed significant prognostic disparities even among N2-positive patients, prompting investigation into why identical tumor stages yield such divergent survival outcomes. Studies have examined single versus multiple N2 station involvement, N2 metastasis quantity and ratio, and the focus of this article—skip N2 metastasis. The interest in skip N2 metastasis stems from its association with relatively favorable prognosis and its potential impact on surgical decision-making.

The standard surgical approach for NSCLC is anatomic lobectomy plus systematic lymph node dissection. However, accumulating evidence from clinical trials suggests no statistically significant difference in survival outcomes between systematic and selective lymph node dissection for certain patients. Consequently, whether systematic mediastinal lymph node dissection is necessary for NSCLC, particularly early-stage disease, remains controversial. Furthermore, with the introduction of segmentectomy for early-stage lung cancer to maximize lung function preservation, questions arise regarding whether specific mediastinal lymph node sampling/dissection should be performed, whether surgical strategies should be modified accordingly, and whether indications require further standardization to avoid missing occult metastases and improve patient outcomes.

Recently, Cheng Xinghua [41] from Shanghai retrospectively analyzed clinicopathological features of 1,430 clinical stage I NSCLC patients, finding that patients with tumors <2 cm, negative pN1 status, no lymphovascular invasion, and lepidic adenocarcinoma had very low rates of mediastinal lymph node metastasis. Moreover, patients with adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic-predominant adenocarcinoma on final pathology showed no pN2 metastasis, with 5-year OS and recurrence-free survival rates of 99.3%. The team concluded that tumor histology can predict mediastinal lymph node metastasis in early-stage lung cancer, and selective mediastinal lymph node dissection may be appropriate for these low-risk patients. Zhang Chong [42] analyzed clinical stage Ia NSCLC patients and proposed that comprehensive hilar and mediastinal lymph node dissection should be standard for peripheral lung cancers >10 mm on CT mediastinal window that are closely adjacent to visceral pleura. Komatsu [30] found that clinical stage Ia NSCLC patients with ground-glass opacity components >75% rarely develop skip N2 metastasis. Therefore, extensive debate continues regarding surgical decision-making for early-stage lung cancer, particularly concerning systematic mediastinal lymph node dissection. Unfortunately, preoperative biopsy or intraoperative frozen section pathology cannot provide sufficiently detailed diagnoses to effectively guide surgical planning. However, combining clinicopathological features—such as a right upper lobe adenocarcinoma <2 cm without visceral pleural invasion and with EGFR mutation—may justify selective N2 biopsy, though higher-level

evidence is needed. As understanding of skip metastasis deepens, surgeons may more accurately predict its occurrence and guide surgical approach selection.

Additionally, research opportunities exist regarding targeted therapy and immunotherapy for skip metastasis lung cancer. Beyond NSCLC, skip metastasis also occurs in small cell lung cancer, pulmonary carcinoid tumors, esophageal cancer, gastric cancer, and other malignancies. Whether skip metastasis phenomena across different tumors share fundamental connections or causal relationships with tumorigenesis and progression requires further investigation.

In summary, skip N2 metastasis in lung cancer is generally associated with favorable prognosis, with right upper lobe adenocarcinoma showing higher incidence and relatively high EGFR mutation rates. Unfortunately, due to the lack of standardized, randomized, large-sample clinical data, high-level evidence to predict skip metastasis remains unavailable. Given the relatively specific mediastinal lymph node drainage patterns associated with skip metastasis, lobe-specific or selective mediastinal lymph node dissection may become mainstream for certain early-stage NSCLC patients in the future, pending substantial clinical evidence.

References

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Note: Figure translations are in progress. See original paper for figures.

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