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ORIGINAL RESEARCH

Brain Metastases in Lung Cancer: Associations with Primary Tumor Location and Histological Subtype

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Abstract

Introduction: Brain metastases (BM) are a common complication of lung cancer. Although histological subtype is associated with BM risk, the relationship between primary tumor location within the lung and BM remains unclear. This study evaluated the association of primary tumor location and histological subtype with the occurrence and distribution of BM. **Materials and Methods:** This retrospective cohort study included 496 patients with primary lung cancer diagnosed between January 2021 and December 2023. Patients with a previous primary malignancy were excluded. Demographic, clinical, pathological, and radiological data were retrospectively collected. BM was confirmed by contrast-enhanced magnetic resonance imaging. Patients were classified according to BM status at diagnosis or during treatment and follow-up. Associations between BM, primary tumor location, and histological subtype were assessed. **Results:** Among 496 patients, 468 (94.35%) had non-small cell lung cancer (NSCLC) and 28 (5.65%) had small cell lung cancer (SCLC). BM occurred in 97 patients (19.56%), including 87 (18.59%) with NSCLC and 10 (35.71%) with SCLC. Among patients with BM, 64 (65.98%) had left-sided, 25 (25.77%) right-sided, and 8 (8.25%) bilateral primary tumors. BM was more frequent in SCLC than NSCLC and, among NSCLC subtypes, in adenocarcinoma than squamous cell carcinoma (20.56% vs. 12.39%). Multiple intracranial lesions were present in 85.57% of patients with BM. The most frequently affected sites were the right parietal lobe, cerebellum, and frontal lobes. **Conclusion:** BM was more frequent in SCLC than NSCLC and occurred more commonly in adenocarcinoma than squamous cell carcinoma. A predominance of left-sided primary tumors was observed among patients with BM, particularly those with NSCLC. However, the independent effect of primary tumor location remains uncertain and requires confirmation in larger prospective studies using multivariable analyses.

Keywords: brain metastases; lung cancer; non-small cell lung cancer; small cell lung cancer; adenocarcinoma

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Introduction

Brain metastases (BM) are the most common intracranial metastatic tumors in adults and represent a major cause of morbidity and mortality among patients with advanced cancer [1, 2]. Lung cancer is the most common primary source of BM, accounting for approximately 40–50% of cases in population-based studies [3, 4]. The risk of BM varies according to disease stage, histological subtype, molecular characteristics, and other clinical factors.

Lung cancer is broadly classified into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). SCLC and lung adenocarcinoma have a particularly high propensity for intracranial dissemination. Previous studies have reported that approximately 10% of patients with newly diagnosed advanced NSCLC have BM at initial presentation, with substantially higher risks in selected clinical and molecular subgroups. The occurrence of BM is influenced by a complex series of processes, including hematogenous tumor dissemination, passage through the blood–brain barrier, and adaptation to the central nervous system microenvironment.

Several clinical, pathological, and molecular factors associated with BM risk have been investigated. However, the potential relationship between the anatomical location of the primary lung tumor and the occurrence of BM remains poorly characterized. It is also unclear whether the distribution of intracranial metastases differs according to the location or histological subtype of the primary tumor.

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Clarifying these relationships may contribute to improved risk stratification and more individualized surveillance strategies for patients with lung cancer.

Therefore, this retrospective study evaluated the frequency, distribution, and anatomical patterns of BM in patients with lung cancer according to primary tumor location and histological subtype. We specifically examined whether the site of primary lung involvement was associated with the occurrence of BM and characterized the intracranial distribution of metastatic lesions.

Materials and Methods

Study Design and Patient Selection

This retrospective observational study was conducted in the Department of Radiation Oncology at [Institution name]. Medical records of patients diagnosed with primary lung cancer between January 2021 and December 2023 were reviewed. Eligible patients had histologically confirmed primary lung cancer. Patients with a history of another primary malignancy were excluded.

Lung cancer was classified according to the World Health Organization (WHO) histopathological classification. The diagnosis of brain metastasis (BM) was established based on contrast-enhanced magnetic resonance imaging (MRI) findings interpreted by experienced radiologists.

Clinical and Tumor Characteristics

Demographic, clinical, pathological, and radiological data were extracted from institutional medical records. Variables included age, sex, smoking history, alcohol use, presenting symptoms, primary tumor location, histological subtype, and the presence and timing of BM.

Primary tumor location was categorized as left lung, right lung, or bilateral involvement. Lung cancer was classified as small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC). NSCLC was further categorized as adenocarcinoma or squamous cell carcinoma.

All patients underwent contrast-enhanced computed tomography (CT) of the thorax as part of the diagnostic evaluation, followed by tissue sampling when clinically feasible.

Patients with BM were categorized according to the timing of metastatic development into two groups:

1. BM present at the initial diagnosis of lung cancer.
2. BM developing during treatment or follow-up.

MRI Assessment of Brain Metastases

Patients with suspected intracranial involvement underwent conventional contrast-enhanced brain MRI. The MRI protocol included axial, sagittal, and coronal T1- and T2-weighted sequences, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) mapping, and post-contrast T1-weighted imaging.

MRI examinations were reviewed by experienced radiologists. BM was diagnosed based on radiological features considered consistent with metastatic disease.

Assessment of Brain Metastatic Distribution

The anatomical distribution of BM was assessed according to predefined brain regions, including the right and left frontal, parietal, temporal, and occipital lobes, cerebellum, and brainstem.

For patients with multiple metastatic lesions involving the same anatomical region, that region was counted once. Accordingly, the analysis assessed the frequency of involvement of each anatomical region rather than the total number of individual metastatic lesions.

Statistical Analysis

Descriptive statistics were used to summarize demographic, clinical, pathological, and radiological characteristics. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using appropriate measures of central tendency and dispersion. Associations between clinical or pathological characteristics and the occurrence of brain metastases (BM) were assessed using appropriate inferential statistical tests. Where applicable, variables associated with BM in univariable analyses were considered for further analysis to identify potential independent predictors. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

Patient Characteristics and Primary Tumor Distribution

A total of 496 patients with primary lung cancer were included in the study. Of these, 468 (94.35%) had non-small cell lung cancer (NSCLC) and 28 (5.65%) had small cell lung cancer (SCLC).

Among patients with NSCLC, the primary tumor was located in the left lung in 316 patients (67.52%), the right lung in 117 (25.00%), and bilaterally in 35 (7.48%). Among patients with SCLC, 15 patients (53.57%) had left-sided tumors, 8 (28.57%) had right-sided tumors, and 5 (17.86%) had bilateral involvement. Within the NSCLC group, adenocarcinoma was the predominant histological subtype, accounting for 355 cases (75.85%), while squamous cell carcinoma accounted for 113 cases (24.15%).

Incidence and Timing of Brain Metastases

BM were identified in 97 of the 496 patients (19.56%). Among patients with BM, 87 (89.69%) had NSCLC and 10 (10.31%) had SCLC.

At the initial diagnosis of lung cancer, BM were present in 9 patients with NSCLC and 2 with SCLC. Among patients who developed BM, the remaining 80 patients with NSCLC and 8 with SCLC developed intracranial metastases during treatment or follow-up. Thus, 9 of 87 patients with NSCLC-associated BM (10.34%) and 2 of 10 patients with SCLC-associated BM (20.00%) had BM at initial diagnosis. Although NSCLC accounted for the majority of the study population, the proportion of patients who developed BM was higher in the SCLC group. BM occurred in 10 of 28 patients with

SCLC (35.71%), compared with 87 of 468 patients with NSCLC (18.59%).

Among patients with NSCLC, BM were more frequent in those with adenocarcinoma than in those with squamous cell carcinoma. BM occurred in 73 of 355 patients with adenocarcinoma (20.56%) and 14 of 113 patients with squamous cell carcinoma (12.39%).

Association Between Primary Tumor Location and Brain Metastases

Among the 97 patients with BM, 64 (65.98%) had a left-sided primary tumor, 25 (25.77%) had a right-sided primary tumor, and 8 (8.25%) had bilateral lung involvement (Table 1). Among patients with left-sided primary tumors who developed BM, 58 (90.63%) had NSCLC and 6 (9.37%) had SCLC. Of the patients with right-sided primary tumors and BM, 22 (88.00%) had NSCLC and 3 (12.00%) had SCLC. Among those with bilateral primary involvement and BM, 7 (87.50%) had NSCLC and 1 (12.50%) had SCLC.

Because left-sided tumors also constituted the largest proportion of the overall study population, the distribution of BM cases by tumor location alone does not establish an increased risk of BM associated with left-sided primary tumors. Comparisons of BM rates according to primary tumor location are therefore required to determine whether tumor laterality is statistically associated with BM.

Distribution of Brain Metastatic Lesions

Among the 97 patients with BM, 14 (14.43%) had a solitary intracranial lesion, whereas 83 (85.57%) had multiple lesions. The most frequently involved anatomical regions were the right parietal lobe (51 patients, 52.58%), cerebellum (46, 47.42%), right frontal lobe (41, 42.27%), and left frontal lobe (40, 41.24%).

Among patients with adenocarcinoma-associated BM (n=73), the cerebellum was the most frequently involved region (42 patients, 57.53%), followed by the left frontal lobe (38, 52.05%) and right frontal lobe (32, 43.84%). Among patients with SCLC-associated BM (n=10), the cerebellum (6, 60.00%) and right frontal lobe (5, 50.00%) were the most frequently involved regions. In patients with squamous cell carcinoma-associated BM (n=14), the cerebellum was the most frequently affected region (9, 64.28%).

Factors Associated with Brain Metastasis

The frequency of BM was higher among patients with SCLC than among those with NSCLC (35.71% vs. 18.59%). Among patients with NSCLC, BM occurred more frequently in those with adenocarcinoma than in those with squamous cell carcinoma (20.56% vs. 12.39%).

Although left-sided primary tumors accounted for the largest proportion of BM cases, this finding reflects the distribution of primary tumor location in the overall cohort and should not be interpreted as evidence of an independent association between tumor laterality and BM without an appropriate comparative analysis.

Discussion

Brain metastases (BM) are a major complication of advanced malignancies and are substantially more common than primary malignant brain tumors [5]. Lung cancer represents one of the most frequent sources of BM, and the risk varies according to histological subtype, disease stage, molecular characteristics, and treatment-related factors [4,6]. In the present study, BM were identified in 97 of 496 patients with primary lung cancer (19.56%). This finding is consistent with the substantial burden of intracranial metastatic disease reported in patients with lung cancer.

In our cohort, the frequency of BM differed according to histological subtype. BM occurred in 35.71% of patients with SCLC compared with 18.59% of those with NSCLC. This higher frequency in SCLC is consistent with the recognized propensity of SCLC for early and widespread hematogenous dissemination, including intracranial spread [4, 6]. Among patients with NSCLC, BM were more frequent in those with adenocarcinoma than in those with squamous cell carcinoma (20.56% vs. 12.39%). The higher risk of BM associated with adenocarcinoma

Table 1. Distribution of Brain Metastases According to Primary Lung Cancer Characteristics

Characteristic	Total, n (%)	NSCLC, n (%)	SCLC, n (%)
Total lung cancer patients	496 (100.0)	468 (94.35)	28 (5.65)
Primary tumor location			
Left lung	331 (66.73)	316 (67.52)	15 (53.57)
Right lung	125 (25.20)	117 (25.00)	8 (28.57)
Bilateral	40 (8.06)	35 (7.48)	5 (17.86)
Brain metastases	97 (19.56)	87 (18.59)	10 (35.71)
At initial diagnosis	9 (9.28)	7 (8.05)	2 (20.00)
During treatment/follow-up	88 (90.72)	80 (91.95)	8 (80.00)
Primary tumor location among patients with BM (n=97)			
Left lung	64 (65.98)	58 (90.63)	6 (9.37)
Right lung	25 (25.77)	22 (88.00)	3 (12.00)
Bilateral	8 (8.25)	7 (87.50)	1 (12.50)

Abbreviations: BM, brain metastases; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

has also been reported in previous studies and may partly reflect differences in tumor biology and molecular characteristics between NSCLC subtypes.

The distribution of intracranial metastases in our study was characterized by a high frequency of multiple lesions. Multiple BM were present in 85.57% of affected patients, indicating that intracranial metastatic disease was frequently multifocal at the time of detection. The most commonly involved regions were the right parietal lobe, cerebellum, and frontal lobes. Similar preferential involvement of the cerebral hemispheres and cerebellum has been described in previous studies and is generally considered to reflect patterns of cerebral blood flow and the distribution of circulating tumor cells within the brain [7, 10-12].

Previous investigations have also suggested that metastatic distribution may vary according to the histological characteristics of the primary tumor. Graf et al. reported differences in the intracranial distribution of metastases according to lung cancer histology, including a greater frequency of cerebellar involvement in squamous cell carcinoma [7]. In our study, the cerebellum was the most frequently involved region among patients with adenocarcinoma, SCLC, and squamous cell carcinoma. However, the relatively small number of patients in the SCLC and squamous cell carcinoma groups limits the ability to draw definitive conclusions regarding histology-specific metastatic patterns.

The biological basis of organ- and site-specific metastatic distribution is complex. The classical "seed and soil" hypothesis proposed by Paget suggests that successful metastatic colonization depends on interactions between disseminated tumor cells and a permissive tissue microenvironment [9]. Differences in tumor-cell characteristics, vascular anatomy, endothelial interactions, and the brain microenvironment may therefore contribute to the preferential establishment of metastatic lesions at particular intracranial sites [8-12]. Nevertheless, these mechanisms remain incompletely understood and cannot be established from the present retrospective data.

An important finding of this study concerns the anatomical location of the primary lung tumor. Among the 97 patients with BM, 64 (65.98%) had left-sided primary tumors, 25 (25.77%) had right-sided tumors, and 8 (8.25%) had bilateral involvement. Although left-sided tumors represented the largest proportion of BM cases, left-sided tumors also constituted the majority of the overall cohort. Therefore, the higher absolute number of BM cases arising from left-sided tumors does not, by itself, indicate that left-sided tumor location increases the risk of BM. Based on the available cohort distribution, the crude BM rates were approximately 19.34% for left-sided tumors, 20.00% for right-sided tumors, and 20.00% for bilateral involvement. These findings do not suggest a substantial difference in BM frequency according to tumor laterality.

The apparent predominance of left-sided tumors among patients with BM should therefore be interpreted cautiously. It may primarily reflect the underlying distribution of primary tumor locations in the study population rather than a biological preference for intracranial dissemination from left-sided lung tumors. A larger prospective cohort with adjustment for potential confounders, including age, disease stage, histological subtype, molecular characteristics, and treatment, would be necessary to determine whether primary tumor location has an independent association with BM.

This study has several limitations. First, its retrospective single-center design limits the generalizability of the findings and introduces the possibility of selection and information bias. Second, the relatively small number of patients with SCLC and the limited number of patients with bilateral primary tumors reduce the statistical power for subgroup comparisons. Third, the study did not incorporate potentially important molecular and clinical variables that may influence the development of BM. Fourth, because intracranial imaging was performed based on clinical suspicion, asymptomatic BM may have been underdetected if routine brain MRI was not performed for all patients. Finally, the study primarily assessed the anatomical distribution of BM and does not establish causal relationships between primary tumor location and intracranial dissemination.

Despite these limitations, the study provides real-world data on the frequency and anatomical distribution of BM in patients with lung cancer and highlights the importance of histological subtype in the occurrence of intracranial metastatic disease. Further multicenter prospective studies incorporating standardized brain imaging, molecular characteristics, disease stage, and multivariable statistical modeling are warranted to clarify the independent determinants of BM and to determine whether primary tumor location contributes meaningfully to metastatic risk.

In conclusion, in this cohort, BM occurred in approximately one-fifth of patients with primary lung cancer and was more frequent in SCLC than in NSCLC. Among NSCLC patients, adenocarcinoma showed a higher frequency of BM than squamous cell carcinoma. Multiple intracranial lesions were common, with the parietal lobes, cerebellum, and frontal lobes representing the most frequently involved regions. Although most BM cases occurred in patients with left-sided primary tumors, this finding reflected the predominance of left-sided tumors in the overall cohort and did not establish an increased risk associated with tumor laterality. Larger prospective studies with comprehensive clinical and molecular data are needed to determine the independent factors associated with BM development and distribution.

Acknowledgements

None.

Ethical Approval

It is a retrospective study, thus does not require ethical approval.

Conflict of Interest

The authors declare no conflict of interest.

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