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Original Research

Patterns of Cranial Metastases in Primary Lung Cancer: A Study from a Tertiary Cancer Center in Northwestern India

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Background: Brain metastases (BM) are the most common intracranial neoplasms in adults and are a frequently occur in the course of lung carcinoma. This study aims to assess the possible correlation between the site and histology of lung cancer and the likelihood of metastatic disease spreading to brain.

Materials and Methods: A retrospective study was conducted at our institute over a period of three years (January 2021 to December 2023) to evaluate the relationship between the site and histology of primary lung malignancy and the incidence of BM. Patients were categorized into two groups: those with brain metastases at the time of diagnosis (whether solitary or multiple) and those who developed BM during treatment and follow-up. The variables analysed included the site and pathological type of primary tumour in correlation with the location and frequency of cranial metastases.

Results: A total of 496 patients with primary lung cancer were enrolled into the studied. Out of which 94.35% (n=468) patients had Non-Small Cell Lung Carcinoma (NSCLC), while 5.65% (n=28) patients had Small Cell Lung Carcinoma (SCLC). 97 patients (19.56%) had BM, out of which 89.69% (n=87) patients having NSCLC and 10.31% (n=10) patients having SCLC histology. Among patients with unilateral primary tumour on the left side, BM was observed in 65.98% (n=64) patients, of which 90.63% (n=58) patients had NSCLC and 9.37% (n=6) patients SCLC respectively. In contrast, for patient with primary tumour on the right side, BM occurred in 25.77% (n=25) patients with 88% (n=22) patients having NSCLC and 12% (n=3) patients SCLC respectively. Among patients with bilateral lung cancer, BM was observed in 8.25% (n=8) patients of which 75% (n=6) patients having NSCLC and 25% (n=2) patients having SCLC respectively. Predictive factors of brain metastases included small-cell lung cancer, followed by left-side adenocarcinoma.

Conclusion: This study highlights the high incidence of BM in patients with primary left-side NSCLC. Overall, small cell carcinoma, followed by adenocarcinoma is more frequently associated with symptomatic BM. However, the underlying cause of the correlation between frequency of BM and primary tumour site remains unclear and requires further investigation

to establish a causal relationship.

Introduction

Brain metastases (BM) is one of the most common types of intracranial neoplasms in adults [1, 2]. In the United-states, an estimated 170,000 new cases of BM are diagnosed annually [3]. In a population-based study conducted by Barnholtz et al., from the Metropolitan Detroit Cancer Surveillance System collected data from 16,210 patients diagnosed with BM from various primary tumours between 1973 and 2001 and then revealed that lung cancer is the primary tumour found in 40 to 50 % with brain metastases [4]. Among lung cancer patients, 16-20% developed brain metastases. Lung carcinomas have been classified into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) based on histopathological subtypes. Of the various types of lung cancer, SCLC and adenocarcinoma are the most commonly identified sources of brain metastases. Approximately 10% of newly diagnosed patients with advanced NSCLC have BM. It has been reported in various studies regarding the pathophysiology of brain metastases that it is a complex multistage process, mediated by molecular mechanisms. However, to date, No study has been documented, regarding preferential sites with histology of primary lung for BM. This retrospective study was conducted on 496 patients with lung cancer to assess the frequency distribution of BM according to the primary tumour site and different histology.

Materials and Methods

This study excluded lung cancer with a second primary malignancy. The diagnosis of all primary lesions was confirmed by pathological or imaging examination based on the criteria as set by the World Health Organization (WHO) for primary cancers, while the detection of brain metastases was based on contrast enhanced MRI.

This retrospective study was conducted in the Department of Radiation Oncology at Acharya Tulsi Regional Cancer Treatment and Research Institute (ATRCTRI), Bikaner. Data was retrieved from January 2021 to December 2023. All patients underwent detailed history taking, physical examination, and routine investigations as per institution protocol. The male-to- female ratio was 8:1. The age of presentation ranged from 25 to 86 years, of which the majority of cases were encountered in the fifth and sixth decades of life. For all suspected lung cancer patients, a contrast-enhanced computed tomography (CECT) scan of thorax was performed, followed by biopsy. Data regarding the site of the primary that is right or left lung involvement and histology of the primary was noted. All primary lung cancer patients were divided into two groups, first lung cancer patients who have BM at the time of diagnosis and second who developed BM during treatment and follow up. It is found that contrast-enhanced MRI is highly sensitive in detecting small brain metastases. We performed CEMRI brain when there is suspicion of brain metastases. Most of the patients were non-alcoholic, and the proportions of smokers and non-smokers were equal.

There are chances that numerous metastatic lesions present in a particular region. The distribution of brain metastatic lesions was recorded as per the different regions of the brain involved. We classified the regions of brain metastases into the right/left (frontal, parietal, temporal, and occipital) lobe, cerebellum, and brain stem. While comparing the distribution of brain metastases, we recorded one metastatic lesion per region of the brain, regardless of the number of lesions in that region. Therefore, we focused on the incidence of brain metastases in a region, rather than the number of metastatic lesions.

MRI Examinations

We ensured that all patients underwent conventional contrast-enhanced MRI (CEMRI) examination. The sequences collected using conventional MRI included coronal, sagittal, and axial T2-weighted and T1-weighted images, fluid-attenuated inversion recovery (FLAIR) sequence, diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps, and T1-weighted enhanced images. All the results were confirmed by experienced radiologists.

Results

A total of 496 patients with lung cancer were studied. As mentioned in Table 1, 94.35% (n=468) patients had non-small cell carcinoma (NSCLC), while 5.65% (n=28) patients had small cell carcinoma (SCLC).

	Total	NSCLC	SCLC
Lung cancer patients	496	468(94.35%)	28 (5.65 %)
		Left 316 (67.52%)	Left 15 (53.57%)
		Right 117 (25%)	Right 8 (28.57%)
		Bilateral 35(7.48%)	Bilateral 5(17.86%)
BM according to presentation	97	87 (89.69%)	10 (10.31%)
At diagnosis	9	7 (8.05%)	2 (20%)
Consequently	88	80 (91.95%)	8 (80%)
BM according to primary site	n = 97		
Left primary	64 (65.98%)	58 (90.63%)	6 (9.37%)
Right primary	25 (25.77%)	22 (88.0%)	3 (12.0%)
Bilateral	8 (8.25%)	7 (87.5%)	1 (12.5%)

Table 1. Distribution of Brain Metastases According to Lung Cancer Site.

When analysing the distribution of the primary tumour according to site of lung, NSCLC was observed in 67.52% (n=316) of cases in the left lung, 25% (n=117) in the right lung, and 7.48% (n=35) bilaterally. Similarly, SCLC was found in 53.57% (n=15) of cases in the left lung, 28.57% (n=8) in the right lung, and 17.86% (n=5) bilaterally. The most common histological subtype of NSCLC (n=468) was adenocarcinoma, affecting 75.85 % (n=355) patients followed by squamous cell carcinoma, affecting 24.15% (n=113) patients.

Most of the patients with brain metastases (BM) presented with symptoms of raised intracranial pressure (ICP), including headaches and vomiting, followed by seizures in decreasing order of frequency. In total 19.56% (n=97) patients had BM, with 89.69% (n=87) of cases occurring in patients with NSCLC and 10.31% (n=10) in those with SCLC.

Among patients with a unilateral primary tumour on the left side, BM was observed in 65.98% (n=64) of patients, with 90.63% (n=58) occurring in NSCLC and 9.37% (n=6) in SCLC. For those with a primary tumour on the right side, BM was seen in 25.77% (n=25) of patients, with 88% (n=22) in NSCLC and 12% (n=3) in SCLC respectively. Among patients with bilateral primary tumours, BM was seen in 8.25% (n=8) of patients, with 87.5% (n=7) occurring in NSCLC and 12.5% (n=1) in SCLC. BM was present at the time of presentation in 8.05% (n=7) of NSCLC patients, while it subsequently developed in 91.95% (n=80) of patients. In SCLC, 20% (n=2) of patients had BM at the time of presentation, whereas 80% (n= 8) developed BM during treatment and follow-up. Although the total number of NSCLC patients was higher than SCLC, the frequency of BM was greater in SCLC (BM in 10 out of 28 SCLC patients,35.71%) compared to NSCLC (87 out of 468 patients,18.59%) (Table 1).

Among NSCLC subtypes, patients with adenocarcinoma had a higher incidence of cranial metastases- 73 out of 355 (20.56%), compared to Squamous cell carcinoma, which had 14 out of

113 cases (15.82%).

Solitary brain metastases was observed in 14.43% (n=14) of patients, while multiple metastatic lesions were present in 85.57% (n=83) patients. The most frequently involved regions were the cerebellum (47.42%, n=46), right parietal lobe (52.58%, n=51) and left frontal lobe (41.24%, n=40). Among patients with BM with lung adenocarcinoma (n=73), the right frontal lobe was affected in 43.8% (n= 32), the left frontal lobe in 52.05% (n=38), and the cerebellum in 57.53 (n= 42). In small-cell carcinoma (n=10), the cerebellum (60%,n=6) and right frontal lobe (40%, n=4) were most commonly affected sites. For squamous cell carcinoma with cranial metastases (n=14), the cerebellum was the predominant site (66.28%, n=9).

Factors predictive of brain progression included small-cell lung carcinoma, followed by left-sided adenocarcinoma.

Discussion

BM is frequently discovered in cancer patients and is said to be significantly more common than primary brain tumours. Approximately 25% of cancer patients who die are found to have CNS metastases upon autopsy [5]. Around 10% of lung cancer patients present with brain metastases at the time of diagnosis and an estimated 40% will eventually develop brain metastases during the course of disease [4], most of which occurs within 2 years with a median survival of 4 to 5 months [6]. Graf AH et al. show that there is an increased frequency of large cell carcinoma of the lung to the occipital lobe and squamous cell carcinoma of the lung to the cerebellum. Metastases of SCLC in the lung were found equally distributed in all regions of the brain. This study suggested the possibility that specific cell surface properties of metastasizing tumour cells and particular properties of the vascular endothelium of the target organs of metastases are responsible for the location of metastases [7].

According to H Popper, there are two different mechanisms by which tumour cells migrate, in single-cell or small-cell clusters as it is seen in SCLC as well as undifferentiated NSCLC and movement by large clusters of organized cells such as in acinar adenocarcinoma or some cases of squamous cell carcinoma [8]. The specific sites of brain metastases were previously explained using the “Paget’s theory” or “seed and soil theory”: According to this theory, the microenvironment nurtures fertile “soil” supporting the growth of malignant cells under specific conditions [9]. The microenvironment of the parietal lobe, cerebellum, and frontal lobe offers appropriate conditions that supports the development of brain metastases. Further, high blood profusions in this area are another potential explanation that explains favorable conditions for metastases, colonization, homing, and outgrowth of tumor cells in the brain parenchyma [10-12].

Keeping the increasing incidence and mortality associated with lung cancer with brain metastases, we undertook this observation to summarize the experience concerning the site and histology of primary lung cancer and the occurrence of BM.

In conclusion, lung carcinoma and its metastases to the brain have many mechanisms and also many genes/ proteins are involved. There are complementing factors hidden that can suggest preferential metastatic sites with primary lung carcinoma and vice versa. We are highlighting the observation of the high incidence of BM with primary left-side NSCLC. Overall small-cell lung cancer followed by adenocarcinoma is a frequent histological type in symptomatic BM patients. The cause of the frequency of BM according to the primary site is not established. It needs further study to prove the causal relationship.

Acknowledgments

Statement of Transparency and Principals

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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