Magnetic Resonance (MR) Patterns of Brain Metastasis in Lung Cancer Patients

Correlation of Imaging Findings with Symptom

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Introduction: Asymptomatic brain metastasis in lung cancer patients, if detected early have been reported to show survival benefit with treatment. These asymptomatic metastasis have been found to be smaller and less in number than those with symptoms. We however observed that many lung cancer patients bear a significant metastatic load in the brain irrespective of the stage or neurologic symptoms at the time of initial presentation.

Material and Methods: A retrospective study was conducted on 175 patients of proven non-small cell lung cancer to assess the patterns of brain metastasis in the two groups of patients, with and without neurologic symptoms. All patients had undergone screening magnetic resonance imaging for brain metastasis as an initial staging protocol. The patients with brain metastasis were divided into two groups: asymptomatic (group I) and symptomatic (group II). The lesions were studied with regards to the number, size, site, nature (solid with and without necrosis), and presence of perilesional edema and intralesional hemorrhage in both the groups in various stages of disease.

Results: Brain metastasis was seen in 62 (31.3%) patients of whom 46.7% were neurologically asymptomatic. Patients (90.3%) with brain metastasis were in stage IV at the time of presentation. No statistically significant correlation was found between the two groups regarding the number of lesions ($p = 0.554$), size of lesion ($p = 0.282$), site of lesion ($p = 0.344$), nature of lesion ($p = 0.280$), presence of perilesional edema ($p = 0.404$), and presence or absence of intralesional hemorrhage ($p = 0.09$). In our study, brain metastases were present only in stages III and IV disease with no statistically significant difference in the lesion patterns.

Conclusion: The study reveals almost equal number of patients with brain metastasis in the symptomatic and asymptomatic groups with no significant difference in lesion patterns. We therefore conclude that although imaging surveillance of the brain for metastasis will detect asymptomatic metastasis early for early institution of appropriate therapy the prognosis in these patients would not solely depend on the presence or absence of symptoms and the pattern of lesion may have an influence on the patients' response to therapy and survival benefit specially for those asymptomatic patients with equally large metastatic load.

Key Words: Asymptomatic brain metastasis, MR patterns, NSCLC.

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Brain is one of the common sites of distant metastasis as well as initial recurrence in patients of lung cancer with an incidence of 20% at diagnosis and upto more than 50% at autopsy.[1–3] Non-small cell lung cancer (NSCLC) does not have a set of clinical pattern of metastasis and brain metastasis may exist in neurologically asymptomatic patients. Several studies have documented the incidence of asymptomatic brain metastasis and have stressed upon the importance of screening magnetic resonance (MR) imaging of brain in patients with lung cancer to detect occult brain metastasis so as to provide survival benefit by allowing earlier treatment of brain.

Demange et al.[4] reported better survival for patients in good neurologic condition at the time metastasis was discovered in patients with resectable NSCLC. Kim et al.,[5] in their study, observed that patients with less number of lesions survived better. In a follow-up study of brain with computed tomography (CT) in patients with resected lung cancer, Kohei Yokoi et al.[6] reported that asymptomatic metastasis were small in number and size (measuring less than 2.5 cm).

In our clinical setting, however, we observed patients of NSCLC with large metastatic load in brain at the time of initial presentation, were neurologically asymptomatic. This prompted us to study whether imaging pattern of brain metastasis is in any way different in the symptomatic and asymptomatic patients.

MATERIALS AND METHODS

This study was approved by our Institutional Review Board. Database search of the cases attending a medical oncology clinic of our institute identified 175 patients of proven NSCLC (age group 32–80 years, male-to-female ratio 152:23) who were treated between 2003 and 2006. Only those patients who underwent MR imaging of the brain as part of initial staging work up, besides the routine clinical,

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hematological examinations and other staging procedures (including CT scan of the chest and upper abdomen, Tc 99m Methylene Di-phosphonate bone scan) were included in the study. These patients' records including radiology, pathology, clinical notes, and discharge summaries were reviewed by the medical oncologist for presence/absence of neurologic symptoms. The medical oncologist was blinded as regards the presence or absence of brain metastasis on MR imaging, while reviewing the files. The staging was done by the medical oncologist according to the international system for T, N, and M staging of lung cancer without considering the findings on MR brain. MR imaging of brain was done on 1.0 T MR System (MAGNETOM EXPERT, Siemens, Germany) in all the cases. Imaging protocol included Fluid attenuation inversion recovery, and T1 Spin echo sequences (with Magnetization transfer suppression) in axial and coronal planes. Postcontrast T1 SE images were obtained after administration of 0.1 mmol/kg body weight of gadobenate dimeglumine. An additional axial Gradient-recalled echo sequence to detect magnetic susceptibility effect was taken to rule out any old hemorrhage in the lesion. In all cases, slice thickness was 5 mm with 10% interslice gap and matrix size of 256 × 256.

The MR imaging were analyzed by two different radiologists independently, unaware of the patients neurologic status and stage of disease, for the number and size of the lesion, the site of lesion (supratentorial [ST]/infratentorial [IT]), nature (solid with and without necrosis), presence of perilesional edema, intralesional hemorrhage, and finding taken in consensus was included for analysis. Interobserver agreement was excellent with [*kappa*] coefficient of 0.89 for MR findings.

Patients, who had brain metastasis shown by MR imaging at initial staging, were divided into two groups; group I included neurologically asymptomatic patients and group II included patients who had neurologic symptoms. The neurologic symptoms which were considered were headache, seizures, sensory or motor deficit. Patients with osseous metastasis having neurologic deficit because of extradural cord compression were not included in the study. The largest dimension in any plane on postcontrast axial or coronal images was taken into consideration. The nonenhancing area of altered signal intensity beyond the enhancing component was considered as perilesional edema.

p Value was calculated for these parameters using the Pearson's χ^2 test (using SPSS (Department of Biostatistics, AJIMS, New Delhi, India) version 10) to assess the level of significance of presence of these features with patients' symptom.

RESULTS

Demographic information of the two study groups is listed in Table 1. Of the 175 patients, 62 (35.4%) patients had brain metastasis of which 29 (46.7%) patients were neurologically asymptomatic (group 1). Thirty-three (53.2%) patients with brain metastasis had neurologic symptoms (group 2) at the time of initial presentation. The probability of finding symptomatic and asymptomatic metastasis in patients with lung cancer is almost same.

TABLE 1. Demographic Distribution of Patients with Lung Cancer

	Total	Asymptomatic	Symptomatic
Age range (yr)	32–80	32–78	34–75
Mean age (yr)	60	59	56
Male	152	23	28
Female	23	6	5

TABLE 2. Stage Wise Distribution of Patients with NSCLC*

		BM (n = 62)		
Stage	Total Patients (n = 175)	Asymptomatic, Group I (n = 29)	Symptomatic, Group II (n = 33)	No BM
I	2	0	0	2
IIa	5	0	0	5
IIb	10	0	0	10
IIIa	15	0	1	14
IIIb	23	4	1	18
IV	120	25	31	64

*Staging of the patients has been done according to the international system of staging lung cancer without considering the MR brain findings.

NSCLC, non-small cell lung cancer; BM, brain metastasis.

The stage-wise distribution of patients in the asymptomatic and symptomatic groups is depicted in Table 2. Patients (68.5%)were in stage IV at presentation. Of our 62 patients 56 (90.3%) with brain metastasis were already in stage IV, of which, 44.6% were asymptomatic at presentation. Six patients had stage III disease, of which, four were asymptomatic. None of our stage I and II patients (n = 17) had brain metastasis.

Table 3 shows the distribution of neurologic symptoms in patients with brain metastasis. Most common symptom encountered was seizure,[7] followed by headache.[8]

Table 4 shows the distribution of the lesion patterns on MR imaging among the symptomatic and asymptomatic groups.

Eighteen patients had a solitary focus of metastasis of which 11 (61%) were symptomatic. Although four patients in each group (groups I and II) had considerable lesion load in brain with more than 10 lesions, 75.8% of asymptomatic

TABLE 3. Distribution of Symptoms with and without Brain Metastasis

Symptom	Metastatic (33)	Nonmetastatic (7)
Headache	4	1
Vomiting	4	3
Headache and vomiting	7	0
Neurological deficit	7	0
Seizures	8	1
Visual	3	1
Sensorium	5	1
Ataxia	1	0

TABLE 4. Distribution of Lesion Pattern in Both Groups

	Asymptomatic (29)	Symptomatic (33)	*p*
No. of lesions			0.410
Solitary	7	11	
Multiple	22	22	
10+	4	4	
Size of lesions			0.282
<1	9	6	
1–2.5	13	14	
≥2.5	7	13	
Mean lesion size (cm)	1.8	2.2	
Maximum size (cm)	5.4	5.0	
Oedema			0.404
+	23	30	
−	6	3	
Hemorrhage			0.1
+	7	12	
−	22	21	
Solid with and without necrosis			0.280
Solid without necrosis	23	23	
Solid with necrosis	6	10	
Site			0.344
ST	15	19	
BO	14	11	
IT	0	3	

ST, supratentorial; BO, both; IT, infratentorial; +, present; −, absent.

patients had multiple brain metastases (Figures 1 and 2). There was no statistically significant difference in the number of lesions in the two groups ($p = 0.410$). Although, of the 15 patients with lesion size <1 cm, six patients (40%) were neurologically symptomatic, seven patients (35%) with lesion size >2.5 cm were found asymptomatic. Twenty-seven of 62 (43.5%) patients had maximum lesion size varying from 1 to 2.5 cm. Mean lesion size was 2.2 cm in symptomatic group and 1.8 cm in the asymptomatic group. The largest lesion size in asymptomatic group was 5.4 cm (Figure 3). There was no significant difference in the size of lesion in symptomatic and asymptomatic groups (p value = 0.282).

Patients (36.8%) having lesions associated with hemorrhage were without any symptoms (Figure 4). Fifty-three of the 62 patients who had associated perilesional edema, 43.4% patients were asymptomatic (Figure 3). Although, 30 of 53 (56.6%) patients with edema related to brain metastasis were clinically symptomatic, 23 of 29 (79%) asymptomatic patients had associated perilesional edema. There was no significant difference in the number of patients in both the groups as regards the presence or absence of perilesional edema (p value = 0.404) and hemorrhage within the lesions ($p = 0.1$).

Fifty percentage of the solid lesions were asymptomatic. Lesions with necrosis were present in 16 patients of which six (37.5%) were without neurologic symptoms with no statistically significant difference ($p = 0.280$).

Lesions were present in both ST and IT compartments in 25 patients of which 56% (14 of 25) were asymptomatic. Thirty-four patients had lesions confined to the ST compartment of which 44.1% (15 of 34) patients were asymptomatic. All the three patients having lesions confined to IT compartment in this study were found symptomatic. The number of patients with lesions in the IT compartment is too less for any statistical calculation.

Table 5 shows the stage-wise distribution of lesion patterns. In our study, none of the patients in stages I and II had brain metastasis. We found no significant difference in the lesion pattern in patients with stage III and stage IV disease.

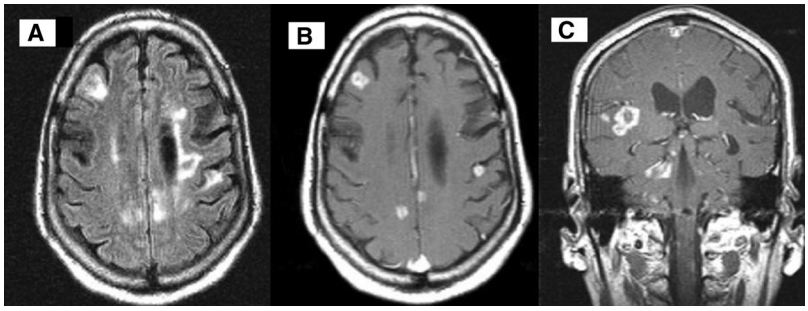

FIGURE 1. *A*, Axial FLAIR. *B*, Axial postcontrast T1W. *C*, Coronal postcontrast T1W. A 62-year-old neurologically asymptomatic man with NSCLC of the left lung with multiple metastasis in both supra and infratentorial compartments and associated perilesional edema.

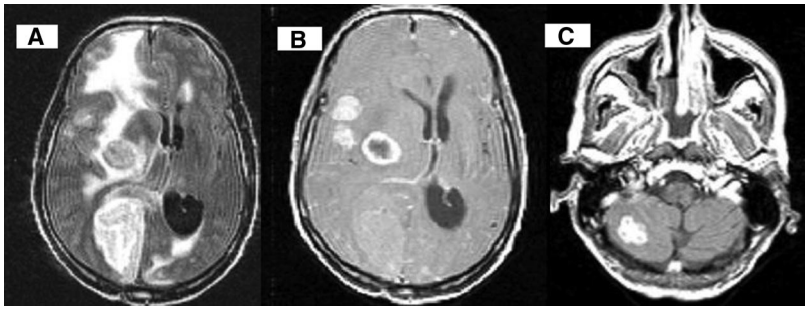

FIGURE 2. *A*, Axial FLAIR. *B* and *C*, Postcontrast T1W. A 48-year-old neurologically asymptomatic man with adenocarcinoma of the right lung—stage IV disease with osseous, hepatic, and pulmonary metastasis and multiple lesions in both supra and infratentorial compartments of brain.

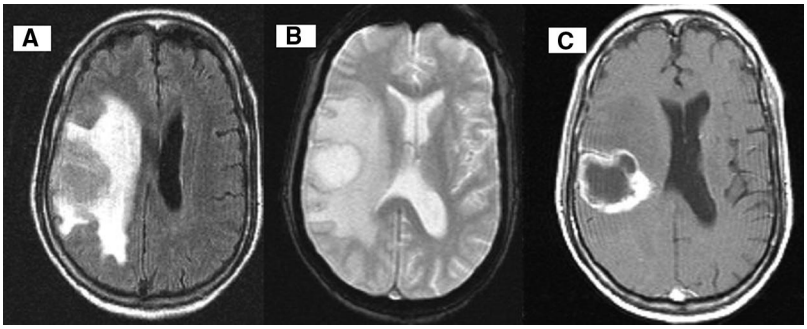

FIGURE 3. Axial (*A*) FLAIR, (*B*) FLASH 2d, (*C*) postcontrast T1W. A 64-year-old neurologically asymptomatic man with stage IV NSCLC of the left lung with solitary hemorrhagic and necrotic metastasis in the right parietal lobe measuring 4.4 cm.

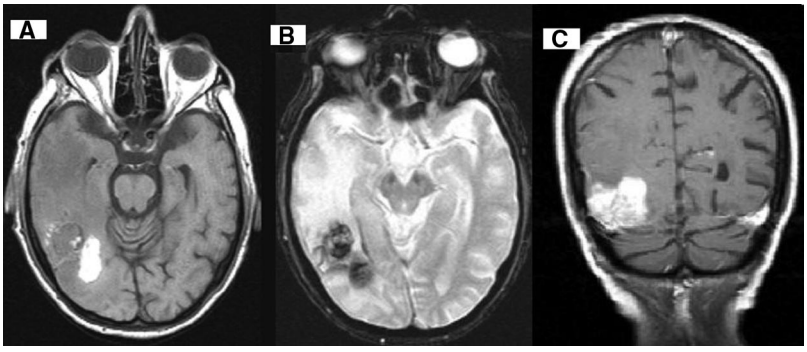

FIGURE 4. Axial (*A*) FLAIR, (*B*) FLASH 2d, (*C*) Coronal postcontrast T1W. A 71-year-old neurologically asymptomatic man with adenocarcinoma of the left lung in stage IV with multiple hemorrhagic metastases largest in the right temporo-occipital region measuring 3.9 cm.

TABLE 5. Stage Wise Distribution of Lesion Patterns in Both Groups

Stage of Disease	I	II (6)	III	IV (56)	*p*
No. of lesions					1.0
Solitary	0	0	2	16	
Multiple	0	0	4	40	
10+	0	0	1	8	
Size of lesions					0.61
<1	0	0	2	11	
1–2.5	0	0	3	26	
≥2.5	0	0	1	19	
Mean lesion size (cm)	0	0	1.7	2.1	
Maximum size (cm)	0	0	4.5	5.4	
Oedema					0.25
+	0	0	4	48	
−	0	0	2	8	
Hemorrhage					0.66
+	0	0	1	18	
−	0	0	5	38	
Solid with and without necrosis					1.0
Solid without necrosis	0	0	5	40	
Solid with necrosis	0	0	1	16	
Site					0.75
ST	0	0	4	30	
BO	0	0	2	23	
IT	0	0	0	3	

ST, supratentorial; BO, both; IT, infratentorial; +, present; −, absent.

DISCUSSION

Approximately 25 to 30% of patients with lung cancer develop brain metastasis at some stage and the incidence at the initial work up has been reported to be between 12% and 18%.[5,7,8] Hochstenbag et al.[9] in 2003, and Kim et al.[5] in 2005, have documented incidence of brain metastasis in patients with lung cancer to be 14% and 18.9%, respectively. In our study, 35.4% patients with newly diagnosed lung cancer had brain metastasis on MR imaging at the time of initial staging. This is probably because we had a large number of patients (68.5%) in stage IV. Although none of our patients with stages I and II had brain metastasis, only 6 of 38 patients with stage III disease had brain metastasis. It corroborates with the fact that the incidence of brain metastasis increases with advancing stage of the disease.[5,9]

The prognosis for patients with brain metastasis who go untreated is extremely poor (about 1 month after diagnosis),[2] whereas patients with NSCLC who are treated with radiation therapy survive for about 8 months.[10] Improvements in systemic and local therapies can improve the long-term survival of cancer patients, which means that early and accurate diagnosis of BM has become crucial to improving quality of life and poor survival rates of cancer patients.

In our study, asymptomatic brain metastasis was found in about 16.5% of lung cancer patients which was in agreement with previous studies.[5,9] Patients (44.6% of stage IV) and 66.6% of stage III patients with brain metastasis were asymptomatic at presentation. However, we did not find any statistically significant difference between symptom and stage of disease ($p = 0.308$). This is in concordance with the findings of Shi et al.[11] stating that the patient symptom is independent of the stage of disease at presentation.

The prognosis of patients with symptomatic brain metastasis is substantially worse than those in which metastasis are asymptomatic.[4] Several reports in the past have emphasized screening of the brain for early detection of brain

metastasis with survival benefit in those who are in good neurologic condition at presentation. Kim et al.[5] in 2005, reported better survival in patients who had less than three metastatic foci with a statistically significant difference in the median survival in patients with 1 to 3 and >3 foci. However, their study does not mention the distribution of these metastatic foci in symptomatic and asymptomatic groups.

In our study, we found no statistically significant difference ($p = 0.554$) in the number of lesions in both groups of patients. Equal numbers of symptomatic and asymptomatic patients were found to harbor a sizeable metastatic load. Asymptomatic patients with a large metastatic load may not have survival benefit over those symptomatic patients with a smaller load. Kim et al.,[5] also reported that there was no statistically significant difference in the survival rate in symptomatic and asymptomatic patients. They, however, reasoned it probably to be because of early and aggressive treatment in both groups of patients with and without symptoms.

In a follow-up study of brain with CT in patients with resected lung cancer, Kohei Yokoi et al.[6] found asymptomatic metastasis in 63.6% of their cases and reported that the number of metastasis in all asymptomatic patients was small and maximum size of almost all lesions were less than 25 mm. We have found no statistically significant association between presence of symptom and size of the lesion ($p = 0.282$) with an overlap in lesion size between the two groups of patients. The disparity could be because of the modality used (CT instead of MR imaging) and limited number of patients in their study ($n = 11$). Moreover, the largest lesion in their study (lesion size 3.7 cm) was not associated with any symptoms and equal number of patients with and without symptoms ($n = 2$) harbored lesions measuring 2.5 cm. Also, no overall correlation was found between the site of lesion and symptoms ($p = 0.344$) though all three IT lesions were symptomatic in our study. Shi et al., also found similar observation as regards the number and distribution of brain metastasis.[10]

We did not find any reported studies that mention influence of other contributory factors (viz presence of edema, hemorrhage, and necrosis within the lesions) on patients' symptoms at presentation. We found no association between presence of perilesional edema and symptoms ($p = 0.027$) and 41.8% of patients with perilesional edema were silent at presentation. Although 63.1% of patients with intralesional hemorrhage were symptomatic at presentation, 24.1% of asymptomatic patients had associated hemorrhage ($p = 0.09$). We also did not find any statistically significant difference in the two groups as regards to nature of lesions with and without necrosis.

CONCLUSION

The incidence of asymptomatic brain metastasis in our study was 16.5% with almost equal number of symptomatic and asymptomatic metastasis in lung cancer patients. Hence, imaging surveillance of the brain for metastasis is worthwhile to detect asymptomatic metastasis early for early institution of appropriate therapy. In our study, we have found no significant difference between the neurologically symptomatic and asymptomatic patients as regards the various lesion parameters (viz., size, number, site, presence or absence of edema, hemorrhage, and necrosis) and asymptomatic patients had an equally large metastatic load. These asymptomatic patients may not have survival benefit over those symptomatic patients with a smaller load. Hence, we would like to state that the prognosis in patients with brain metastasis would not solely depend on the presence or absence of symptoms as has been described previously in literature and the pattern of lesion may have an influence on the patients' response to therapy and hence the survival benefit. Because our study lacks survival data because of poor follow-up of patients, further work is needed to study the influence of lesion pattern on the patients' response to therapy and assess the exact survival benefit.

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