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ORIGINAL RESEARCH

To study the clinical and demographic profile of the patients with brain metastases in a tertiary care centre in north India

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ABSTRACT

Aim: To study the clinical and demographic profile of the patients with brain metastases in a tertiary care centre in north India.

Material and methods: This Observational and cross sectional study was conducted among patients attending the outpatientmedicine/radiotherapy department or admitted in Government Medical College, Jammu. Total number of 100 patients was taken. The study group comprised of patients with clinical and radiological signs of brain metastasis.

Results: Maximum subjects were from the age group of 51-60 years (41%) followed by 41-50 as well as >60 years (20%). Statistically significant difference was found among the subjects having brain metastasis w.r.t age group as p<0.05. Females and male comprised of 56% and 44% of the subjects respectively. Left and right side of the brain in brain metastasis was found among 33% and 28% of the subjects respectively while bilateral involvement was revealed in 39% of the subjects. Frontal, parietal, temporal occipital and cerebellar was reported among 19%, 53%, 11%, 15% and 2% of the subjects respectively. Supratentorial and infratentorial location of tumour was found among 96% and 4% of the subjects respectively. Hence dominating location of tumour was supratentorial with statistically significant difference as p<0.05. Most common symptom was headache (69%) followed by vomiting (58%) and neurological deficit (40%). Least common reported symptom was cerebellar sign (4%) followed by visual symptoms (24%) and seizures (27%). According to ECOG grading, fully active status was not found in any of the subject. ECOG grade 1, 2, 3 and 4 was reported among 11%, 42%, 33% and 14% of the subjects respectively.

Conclusion: It can be concluded from our results that brain metastases are disease of elderly people with slight female dominance in this area. Lung and breast are the most common primary sources throwing metastases in brain. Most of the patients had multiple lesions at the timeof diagnosis.

Keywords: Brain metastases, Clinical profile, Demographic profile

INTRODUCTION

Brain metastases are the most common type of intracranial neoplasm, with the total number

diagnosed annually outnumbering all other intracranial tumors combined. Brain metastases increases morbidity and mortality in cancer patients.[1] They outnumber primary brain tumors by a ratio of 10:1 and occur in about 25% of all patients with cancer. Conservative estimates suggest that 100,000-170,000 new cases of brain metastases are diagnosed every year in the United States. Between 20% and 40% of all patients with metastatic cancer will have brain metastases at autopsy.[2]

The majority of patients who develop brain metastases have a known primary cancer (metachronous presentation). Most brain metastases originate from lung (40-50%), breast (15-25%), melanoma (5-20%) and kidney (5-10%).[3] No primary site of cancer is detected in 5- 10% of patients with brain metastases. Brain metastases are located in the cerebral hemispheres in about 80%, in the cerebellum in 15% or in the brainstem in 5% of patients Up to two-third of all, brain metastases are symptomatic at some point during life and one-third may escape detection during life of cancer patient .[4]

Several processes are required for metastasis to the CNS to develop from distant loci. This involves malignant cells that escape from the primary tumor, degradation of the extracellular matrix, intravasation into blood vessels, and survival of cells in hematogenous dissemination.[5] This is followed by entry of the cells into the cerebral circulation, extravasation into the brain parenchyma, and finally proliferation and survival of the tumor cells in the cerebral microenvironment. The cells are able to remain in a state of latency for a prolonged period and are able to establish neovascularization processes by induction of vascular endothelial growth factors (VEFG). The hematogenous entry explains the topographic distribution of the metastases; 80% are located in the hemispheres specifically in Middle and Posterior Cerebral Artery territories.[6]

BM are located especially in the gray-white matter junction (GWMJ) due to the change in the caliber of the vessels or their spiral shape that act as a trap for the cells. Another mechanism involved is the sowing of cancer by direct extension to the meninges adjacent to the base of the skull, a common mechanism in osteo-affinity neoplasms such as breast and prostate cancer. One of the endpoints of tumor growth causing mass effect, edema, and obstruction of cerebrospinal flow is intracranial hypertension (IH) which may lead to brain structure herniation and eventual death.[7]

There are 3 varieties of BM: intraparenchymal tumors, leptomeningeal carcinomatosis, and milliary metastases. Intraparenchymal tumors are the most common variety and may be single or multiple. Macroscopically, the lesions lie within the GWMJ and are superficial, well-circumscribed, surrounded by edema, with margins that compress neighboring tissues. Microscopically, there may be a histologic similarity with the primary tumor or it may be undifferentiated.[8] The majority of cases show considerable anaplasia with foci of hemorrhage, necrosis, and mitosis. In general, they tend to have well-demarcated edges with adjacent reactive brain tissue. However, tumors such as melanomas and small-cell metastatic lung carcinomas tend to infiltrate adjacent tissues. Colorectal adenocarcinomas are associated with extensive necrosis, sometimes with a thin border of viable tumor. Melanoma, renal cell carcinoma, and choriocarcinoma have metastatic tumors that classically cause hemorrhage. Leptomeningeal carcinomatosis is relatively frequent and are present in around 10% of patients with CM. This variety of CM is common in patients with primary cancer of pulmonary origin, lymphomas, leukemias, breast cancer, and melanoma and causes a picture of hydrocephalus, cranial nerve palsy, or infiltration of spinal roots. Milliary metastasis is very rare and will not be discussed in this document.[9]

Clinical history, physical examination, and laboratory values guide the diagnosis of BM with the imaging for confirmation. It is recommended as a screening only in patients with small cell lung cancer.[10] Contrast Computed tomography (CT) is the preferred initial diagnostic modality for patients with neurological deficits and suspected metastasis due to its high

availability, tolerance, and ability to rapidly diagnose serious pathologic states such as hemorrhage, hydrocephalus, and IH.

Biopsy or surgical resection is indicated to confirm the diagnosis, especially in patients with single lesions without diagnosis of cancer or metastatic disease. The diagnosis of BM can be made with neuroimaging, but if there is uncertainty as to the etiology of the tumor, the histological diagnosis becomes necessary either with biopsy or resection and CSF cytology in special cases. The differential diagnosis includes glioblastoma multiforme which requires many times a directed study with biopsy for the correct diagnosis. Other less frequently occurring differential diagnosis are primary CNS lymphoma and brain abscess that simulate metastatic lesions in the neuroimage.[11]

Radiographically, metastases are ring enhancing lesions, often located at grey-white matter junction and surrounded by significant edema arterial hematogenous spread result in tumor emboli growth at the gray-white junction. Metastatic lesions rarely involve the corpus callosum or cross midline. The radiological differential diagnoses are primary brain tumor, inflammatory lesion, abscess and brain hemorrhage or infarction.[12] This study is aimed to evaluate the demographic as well as clinical profile of patients with brain metastases.

MATERIAL AND METHODS

This Observational and cross sectional study was conducted among patients attending the outpatient medicine/radiotherapy department or admitted in Government Medical College, Jammu. Total number of 100 patients was taken. This study has been approved by the Institutional Ethics Committee of the hospital. Written Informed consent was taken from all the subjects, who were included in the study after explaining to them the nature and purpose of the study. The study group comprised of patients with clinical and radiological signs of brain metastasis.

INCLUSION CRITERIA

1. Patients with Clinical and radiological signs of brain metastasis
2. Both Male and female patients of any age group

EXCLUSION CRITERIA

1. Pregnant patients
2. Unwilling patients
3. Patients with associated primary brain cancer

METHODOLOGY

The data was collected by a preformed structured interviewer-administered questionnaire that was pretested with modifications made prior to its use in the study. The patients were interviewed that requests for the demographic, socioeconomic status, medical history and previous history of taking any medications and supplements. Clinical examination including neurological evaluation; fundoscopy and perimetry, Complete blood count, Liver and kidney function test, Imaging – CT/MRI scan of the brain and other different imaging studies (chest X-ray posterior-anterior view, ultrasonography whole abdomen, CECT scan of chest, CECT scan of the abdomen and pelvis, CECT of the face and neck), which were done to detect the primary and Histopathological biopsy of the primary site as well as intracranial SOL were studied.

STATISTICAL ANALYSIS

Data so collected was tabulated in an excel sheet, under the guidance of statistician and statistical analysis was done using SPSS version 22.0.

RESULTS

Table 1: Age distribution among the study groups.

Age Group (in years)	N	%	p value
10-20	2	2	
21-30	4	4	
31-40	13	13	
41-50	20	20	
51-60	41	41	
>60	20	20	<0.01*
Total	100	100	

***: statistically significant**

Maximum subjects were from the age group of 51-60 years (41%) followed by 41-50 as well as >60 years (20%). Minimum subjects were in the age group of 10-20 years (2%) followed by 21-30 years (4%). Statistically significant difference was found among the subjects having brain metastasis

w.r.t age group as $p<0.05$ (table 1).

Table 2: Gender distribution among the study subjects.

Gender	N	%	p value
Male	44	44	0.63
Female	56	56	
Total	100	100	

Table 2 shows the gender distribution among the study subjects. Females and male comprised of 56% and 44% of the subjects respectively.

Table 3: Occupation distribution among the study subjects.

Occupation	N	%	p value
None	5	5	
Clerk	1	1.0	
Contractor	1	1.0	
Engineer	1	1.0	
Ex Servicemen	3	3.0	
Farmer	8	8.0	
House Wife	28	28.0	
Laborer	12	12.0	
Lecturer	1	1.0	
Own Business	7	7.0	
Police	1	1.0	0.23
Servicemen	11	11.0	
Shopkeeper	3	3.0	
Student	2	2.0	
Tailor	1	1.0	
Teacher	2	2.0	
Other	13	13.0	
Total	100	100.0	

As the present study consisted of more females, therefore 28% of the study subjects were housewife. 12%, 11% and 8% of the subjects were laborer, servicemen and farmer respectively (table 3).

Table 4: Socioeconomic status among the study subjects.

SES	N	%	p value
Upper	29	29	
Upper Middle	17	17	
Lower Middle	14	14	
Upper Lower	18	18	
Lower	22	22	0.24
Total	100	100	

Table 4 shows the socioeconomic status (SES) among the study subjects. Upper, upper middle, lower middle, upper lower and lower SES wasreported among 29%, 17%, 14%, 18% and 22% of the subjects respectively with statistically insignificant difference.

Table 5: Distribution of patients according to brain side involved.

Side	N	%	p value
Left	33	33	0.37
Right	28	28	
Bilateral	39	39	
Total	100	100	

Left and right side of the brain in brain metastasis was found among 33% and 28% of the subjects respectively while bilateral involvement was revealed in39% of the subjects (table 5).

Table 6: Distribution of patients according to site of lesion in brain.

Site	N	%	p value
Frontal	19	19	
Parietal	53	53	
Temporal	11	11	
Occipital	15	15	0.03*
Cerebellar	2	2	
Total	100	100	

Table 6 the distribution of patients according to site of lesion in brain. Frontal, parietal, temporal occipital and cerebellar was reported among 19%, 53%, 11%, 15% and 2% of the subjects respectively.

Table 7: Distribution of patients according to location of tumour.

Location	N	%	p value
Supratentorial	96	96	<0.01*
Infratentorial	4	4	
Total	100	100	

Supratentorial and infratentorial location of tumour was found among 96% and 4% of the subjects respectively. Hence dominating location of tumour was supratentorial with statistically significant difference as $p<0.05$ (table 7).

Table 8: Distribution of patients according to type of lesion (single vs.multiple).

Type	N	%	p value
Single Metastasis	27	27	<0.01*
Multiple Metastasis	73	73	
Total	100	100	

Table 8 shows the distribution of patients according to type of lesion (single vs. multiple). Single and multiple metastasis was revealed in 27% and 73% of the subjects respectively. Hence multiple metastasis was found moreas compared to single metastasis with statistically significant difference as $p<0.05$.

Table 9: Distribution of patients according to clinical symptoms.

Symptoms	N	%
Headache	69	69
Vomiting	58	58
Neurological Deficit	40	40
Seizures	27	27
Cerebellar Signs	4	4
Visual Symptoms	24	24

Table 9 shows the distribution of patients according to clinical symptoms. Most common symptom was headache (69%) followed by vomiting (58%) and neurological deficit (40%). Least common reported symptom was cerebellar sign (4%) followed by visual symptoms (24%) andseizures (27%).

Table 10: Distribution of site of primary giving rise to metastasis.

Site	N	%	p value
Lung	56	56	
Breast	32	32	
Oesophagus	2	2	
Kidney	2	2	
Ovary	3	3	
Urinary Bladder	1	1	
Unknown Primary	4	4	<0.01*

As observed carcinoma of the lung was the commonest primary site that metastatizes to brain (56%) followed by breast (32%). In 4% of patients, theprimary was unknown, but they had evidence of metastases in lymph node/lung, which were proved on cytology/biopsy (table 10).

Table 11: Time Progression to metastasis (months)

Time in Months	N	%
0 to 6	39	39.0
12 to 18	25	25.0
18 to 24	21	21.0
>24	15	15.0
Total	100	100.0

Table 11shows the time progression to metastasis (months) amongthe study subjects. 0 to 6, 12 to 18, 18 to 24 and >24 month for progression to metastasis was reported among 39%, 25%, 21% and 15% of the subjectsrespectively.

Table 12: Distribution of patients according to ECOG performancestatus.

ECOG	N	%
1	11	11
2	42	42
3	33	33
4	14	14

According to ECOG grading, fully active status was not found in any of thesubject. ECOG grade 1, 2, 3 and 4 was reported among 11%, 42%, 33% and
14% of the subjects respectively (table 12).

DISCUSSION

Brain metastases are the commonest type of intracranial neoplasm, with an annual incidence of about 1,70,000 to 2,00,000 cases every year in united states. The ratio of metastatic brain tumors to primary neoplasm of brain is 10:1 and occur in about 25% of all patients with

cancer.[13] About 20% to 40% of all patients with metastatic cancer will have brain metastases at autopsy. Brain metastases are associated with significant morbidity and mortality and quality of life deteriorate as well. The common primaries causing brain metastases are: lung cancer (40-50%), breast cancer(15-25%), melanoma (15-20%) and kidney (5-10%).[14] In 5% to 10% of the patient's brain metastases were from unknown primary. Brain metastases from extracranial primaries are multiple in two- third to three-fourth of patients. Cerebral hemispheres are involved in about 80% of patients followed by cerebellum 15% and brainstem in 5%. Parietal and frontal lobes are most commonly involved. Treatment of brain metastases is multidisciplinary with radiation forming the cornerstone of treatment.[15] In Indian literature, scant data are available regarding clinical profile of patients with brain metastases. This study is aimed to evaluate the demographic as well as clinical profile of patients with brain metastases.

AGE GROUP

In this study, maximum subjects were from the age group of 51-60 years (41%) followed by 41-50 as well as >60 years (20%). Minimum subjects were in the age group of 10-20 years (2%) followed by 21-30 years (4%). Statistically significant difference was found among the subjects having brainmetastasis w.r.t age group as $p<0.05$. Study by **Victor TS *et al*., (2011)** showed that about 60% of patients of brain metastasis are aged between 50 and 70 years.[16] **TakokuraK *et al*., (1982)** viewed that the age of onset of brain metastases inmale is 56 years and in females 40 years.[17] In a study by **Saha A *et al*., (2013)**, 44.44% of patients were in the 6th decade and 22.22% of patients were in 5th decade of life; which correlates with above study. The incidence of brain metastasis was also uncommon up to 3rddecade.[18] These studies findings are similar to our study.

GENDER

Females and male comprised of 56% and 44% of the subjects respectively inour study. Hence females were comparatively more as compared to males, though statistically insignificant. Similarly, **Saha A *et al*., (2013)** in their study found that there is almost equal distribution of sex male versus female (52.78% vs. 47.22%).[18] **Ghosh M *et al*., (2017)** in their study revealed similar results too i.e. female preponderance was seen constituting 68.69% whereas male constituted 31.31%.[19] **Victor TS *et al*., (2011)** showed that although melanoma spreads to the brainmore commonly in males than in females, gender does not affect the overallincidence of brain metastases.[16]

OCCUPATION

As the present study consisted of more females, therefore 28% of the study subjects were housewife. 12%, 11% and 8% of the subjects were laborer, servicemen and farmer respectively. However, in a study by **Saha A *et al*., (2013)**, 29.2% of patients were day laborer followed by service holder and farmer both constituting 20.8%.[18] **Debnath H *et al*., (2008)** in their study too showed that the highest occupational group were day laborers (31.43%) followed by service-holders (22.85%) and farmers (20%).[20] This difference in findings in compare with our study may be due to the difference in study area.

SOCIO ECONOMIC STATUS

In our study; upper, upper middle, lower middle, upper lower and lower SES was reported among 29%, 17%, 14%, 18% and 22% of the subjects respectively with statistically insignificant difference. There was no significant difference in distribution of patients according to socio‑economic status by modified Kuppuswamy scale as mentioned by **Kumar N *et al*., (2012)**.[21] Nearly 27.8% were in upper socio‑economic status and 23.6%

were in the lower socio‐ economic status as stated by **Saha A *et al*.,(2013)**in their study.[18]

SIDE INVOLVEMENT

Left and right side of the brain in brain metastasis was found among 33% and 28% of the subjects respectively while bilateral involvement was revealed in 39% of the subjects in our study. **Saha A *et al.*, (2013)** in their study revealed that out of total 72 patients 40.3% had bilateral involvement in brain. In 34.7% of patients only left side of the brain was involved compared with 25% of patients where only right side of the brain was involved.[18]

SITE OF LESION

Frontal, parietal, temporal occipital and cerebellar was reported among 19%, 53%, 11%, 15% and 2% of the subjects respectively in the present study. Hence most common site was parietal region. **Saha A *et al.*, (2013)** in their study reported that parietal lobe was the commonest site of involvement constituting 48% of all lesions.[18]

LOCATION OF TUMOUR

In the present study; supratentorial and infratentorial location of tumour was found among 96% and 4% of the subjects respectively. Hence dominating location of tumour was supratentorial with statistically significant difference as $p<0.05$. In a study by **Saha A *et al.*, (2013)**, supratentorial involvement (97.2%) was much more common than infratentorial involvement (2.8%).[18]

TYPE OF LESION (SINGLE VS. MULTIPLE)

In this study; single and multiple metastasis was revealed in 27% and 73% of the subjects respectively. Hence multiple metastasis was found more as compared to single metastasis with statistically significant difference as $p<0.05$. Multiple secondaries predominant over solitary metastasis, which was opined by **Posner JB *et al.*, (1995).**[22] Studies using CT scan data indicated thatmetastases to the brain are multiple in more than 50% of cases as shown by **Delattre *et al.*, (1988)** Recent experience with MRI indicates that proportion of multiple metastasis is higher and in the range of two-third to three-fourth of patients with brain metastases.[12] In a study by **Saha A *et al.*, (2013)**, 77.8% of patients had multiple lesion and 22.2% had single lesion, which strongly correlates with above studies.[18]

CLINICAL SYMPTOMS

Most common symptom was headache (69%) followed by vomiting (58%) and neurological deficit (40%). Least common reported symptom was cerebellar sign (4%) followed by visual symptoms (24%) and seizures (27%) in our study. In a study by **Saha A *et al.*, (2013)**, headache (66.7%) was the most common symptom followed by vomiting (54.16%), neurological deficit (36.11%) andseizure (25%).[18] Symptoms are usually related to the location of the tumor. Clinical symptoms or presentation of a patient with brain metastases have been described by **Posner JB *et al.*, (1995).** In his series, headache was the commonest clinical presentation observed in 49% of patients followed by mental changes in 32%, focal weakness in 30% and seizures in 18% of patients.[2] **Victor TS *et al.*, (2011)** found that headache (42%) and seizure (21%) are the 2 most common presenting symptoms. In addition, 35% of patients havecognitive dysfunction and 30% have motor dysfunction.[16]

PRIMARY GIVING RISE TO METASTASIS

As observed carcinoma of the lung was the commonest primary site that metastases to brain (56%) followed by breast (32%). In 4% of patients, the primary was unknown, but they had evidence of metastases in lymph node/lung, which were proved on cytology/biopsy.

Metastasis is not common in children; accounts for 6% of all CNS tumor in children. Leukemia accounts for most metastatic CNS lesions in young patients – followed by lymphoma, osteogenic sarcoma and rhabdomyosarcoma. Germ cell tumors are common in adolescents and youngadults between 15 and 21 years. **LassmanAB *et al*., (2003)** reviewed nine studies and found the following variation in reported percentages of patients developing brain metastases for specific primary histologies: 18-64% (lung cancer), 2-21% (breast cancer), 2-12% (colorectal cancer), 4-16% (melanoma), 1‑8% (kidney), 1-10% (thyroid) and 1-18% (unknown primary).[23] In 2700 cases from the Memorial Sloan-Kettering Cancer Center in New York, **Victor TS *et al*., (2011)** showed the distribution of primary cancers as follows: 48% lung, 15% breast, 9% melanoma, 1% lymphoma (mainly non-Hodgkin), 3% gastrointestinal (GI) (3% colon and 2% pancreatic), 11% genitourinary (21% kidney, 46% testes, 5% cervix, 5% ovary), 10% osteosarcoma, 5% neuroblastoma and 6% head and neck tumor.[16] According to **Takokura K *et al*., (1982)** most common primary producing brain metastases are ca lung (48%), carcinoma breast (25%), GI tract (8%), genitourinary tract (6%), melanoma (6%) and others (13%).[17] Similarly in a study by **Saha A *et al*., (2013)**, carcinoma of the lung was the most common primary that metastatizes to brain (51.4%), followed bycarcinoma breast (30.6%). In 4.2% of patients, the primary was unknown.[18]

ECOG GRADING

Fully active status was not found in any of the subject. ECOG grade 1, 2, 3 and 4 was reported among 11%, 42%, 33% and 14% of the subjects respectively in the present study. Similarly, **Andleeb A *et al*., (2016)** in their study found that at the time of diagnosis, most of the patients had ECOG performance score of 2 and 3.[24] The present study highlights that the incidence of brain metastasis is commonin elderly population and mostly due to primary lung.

CONCLUSION

It can be concluded from our results that brain metastases are disease of elderly people with slight female dominance in this area. Lung andbreast are the most common primary sources throwing metastases in brain. Majority of the patients become symptomatic at some point during disease and symptoms are the same as any space-occupying lesion of the brain, which include mainly headache, seizures, and vomiting. Supratentorial lesions outnumber infratentorial. Most of the patients had multiple lesions at the time of diagnosis. Brain metastases are a bad prognostic sign in any malignancy with a median survival of only 3 months after its detection.

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