Original Article

Brain metastases: A single institute experience

Asifa Andleeb, Mohammad Ashraf Teli, Mohammad Maqbool Lone, Fir Afroz, Hakim Irfan Ahmad[1], Kaneez Fatima

Department of Radiotherapy and [1]Department of Medical Oncology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India

ABSTRACT

Background: Brain metastases represent an important cause of morbidity for cancer patients. Its incidence has increased overall overtime as a consequence of improved detection by magnetic resonance imaging (MRI). However, in Indian literature, scant data are available. At this moment, we have analyzed our data from a single tertiary care center in North India. The purpose of the study was to analyze the clinical profile of patients with brain metastases. A retrospective study from a single tertiary care center. **Patients and Methods:** A retrospective review of records of all patients who were registered in hospital-based cancer registry and developed brain metastases from June 2011 to June 2013 yielded 95 patients for analyses. **Results:** Majority of cases were seen in the 6th decade of life. Lung cancer was the most common primary followed by breast. On imaging (computed tomography or MRI), multiple lesions were more common than single. Most of the patients presented with a headache (37.9%). Supratentorial involvement was seen in 87.3% against 12.6% infratentorial involvement. Median time interval from diagnosis of primary and development of brain metastases was 13.8 months. A median survival of only 3 months was seen after development of brain metastases. **Conclusion:** The present study highlights that brain metastases occur mainly in elderly people with lung being the most common primary malignancy. It is a deadly event with a median survival of only 3 months.

Key words: Brain metastases, common symptoms, primary malignancy

INTRODUCTION

Brain metastases are the most common form of intracranial tumor. They exceed the number of primary brain tumors by at least 10 times and occur in about 25% of all patients with cancer. Most brain metastases originate from lung (40–50%), breast (15–25%), melanoma (15–20%), and kidney (5–10%). Brain metastases are located at cerebral hemispheres in 80%, cerebellum in 15%, and brainstem in 5%.[1] 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.[2,3] The clinical presentation of brain metastases is similar to any intracranial mass lesion and includes headache (70%), seizures (30–60%), cognitive impairment (30%), papilledema (8%), and miscellaneous focal neurological deficits.[4] High-performance status, solitary brain metastasis, absence of systemic metastases, controlled primary tumor, and younger age (<60–65 years) are the most important favorable prognostic factors.[5,6] Based on these factors, the radiation therapy oncology group (US) has classified patients into three categories as recursive partitioning analysis (RPA) I, II, and III. The overall survival duration for patients in RPA Class 1, defined as those with Karnofsky performance status (KPS) score > 70, age < 65 years, controlled primary tumor, and no extracranial sites of disease, was 7.1 months. The median survival duration was only 2.3 months for patients in RPA Class 3, defined as all patients with KPS score <70. The median survival duration for the remaining RPA Class 2 was 4.2 months. Neurocognitive functions are prognostically important as well.[7,8] The prognosis is similar for patients with both known and unknown primary tumors.[9] In recent years, there is an apparent increase in cases of brain

Address for correspondence: Dr. Asifa Andleeb, Room No 229, Department of Radiotherapy, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India. E-mail: andleebasifa@yahoo.com

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.182054

Cite this article as: Andleeb A, Teli MA, Lone MM, Afroz F, Ahmad HI, Fatima K. Brain metastases: A single institute experience. Clin Cancer Investig J 2016;5:213-7.

secondary due to increasing incidence of lung cancer, improved detection by more sensitive imaging techniques, and development in anticancer treatment resulting in prolonged survival.[10]

Advances in imaging technology have contributed greatly to the diagnosis and management of patients with suspected neoplastic diseases of the central nervous system. Contrast-enhanced computed tomography (CECT) is used widely because of its easy accessibility and low cost. Contrast-enhanced magnetic resonance imaging (MRI) is more sensitive than enhanced CT scanning in detecting brain metastases, particularly small lesions or metastases situated in the posterior fossa.[11,12] MRI is particularly recommended either for patients with an apparently single metastasis on a CT or for patients with limited disease (i.e., lung tumors) in whom the detection of asymptomatic brain metastases would alter the therapeutic management.[13] Radiographically, metastases are ring-enhancing lesions, most often located at the gray-white matter junction surrounded usually by significant edema.

Depending on the patient's age, functional status, extent of systemic disease, and number of metastases, median survival ranges from 2.3 to 13.5 months.[14] Supportive care addresses brain edema, seizures, deep vein thrombosis, gastrointestinal complaints, psychiatric complications, and side effects of treatment.[15] Definitive therapy is intended to restore neurological function, improve quality of life, and extend survival. Therapeutic modalities may be used singly or in combination included surgery, stereotactic radiosurgery, whole brain radiotherapy (WBRT), and chemotherapy.

Being a tertiary care center, we get an average of 60–70 patients of brain metastases per year and majority of them have lung and breast as primary. With this study, we primarily intend to observe the clinical profile of patients who developed brain metastases over 2 years and retrospectively analyze the data of our cases in comparison with the available literature.

PATIENTS AND METHODS

The study is based on the observations made in 95 patients who developed brain metastasis between June 2011 and June 2013. Diagnosis of brain metastasis was made either by CT (computerized tomography) scan, MRI scan of the brain, or brain lesion histopathology (wherever available). Brain imaging was obtained either as a routine staging procedure (in patients of small cell lung) or in the evaluation of a suspicious symptomology. Observations were based on thorough analysis of all patients and their records. The details included were demographic characteristics, site of primary tumors, time between diagnosis of primary and development of brain metastasis, presenting complaint, performance score, area of the brain involved, method of diagnosis, number of metastatic lesions, whether received WBRT, presence of extracranial metastases, and survival from development of brain metastases. Survival was measured from the time of diagnosis of brain metastases until death or the last patient contact. Only the cases with complete information were considered for the study. The data were tabulated, analyzed, and compared with the available literature.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 16.0 for Windows 7 program (IBM Corporation) was used for statistical analysis to evaluate the results. In addition to the descriptive statistics (median, mean, standard deviation, frequency), Chi-square test was used for qualitative data. A $P < 0.05$ was set as the limit for statistical significance. Kaplan–Meier survival analysis was used for survival analyses and the log-rank test was used for comparing survival data.

RESULTS

A total of 130 patients developed brain metastases between June 2011 and June 2013, and only 95 were considered for analysis because of incomplete information details in 35 patients. Majority of patients were in the 6th decade of life and no sex difference was seen with a male to female ratio of 1.06:1 [Table 1]. Among different malignancies, lung was the most common primary that metastasized to brain, i.e., 51.57%, (nonsmall cell in 34.73% and small cell in 16.87%) followed by breast 15.7%, gastrointestinal tract (GIT) 14.73% (esophagus 7, stomach 2, colon 1, and rectum 4 patients), malignant melanoma 5.3%, unknown primary 7.3%, and others 5.3% (carcinoma nasopharynx 1, renal cell carcinoma 1, testis 1, and carcinoma ovary 2 patients). Time to progress from the diagnosis of primary to development of brain metastasis varied significantly, with a median interval of 13.8 months [Table 2]. Initially, only 90 patients (94.7%) out of 95 were symptomatic for brain pathology; however, later, all patients developed varying

Table 1: Age and gender distribution of patients

	Number of patients	Percentage
Age (years)		
31-40	6	6.3
41-50	25	23.7
51-60	35	36.8
61-70	29	30.5
Mean age	51.66	
Gender		
Male	49	51.6
Female	46	48.4

degree of symptoms. Most of the patients had a headache as presenting symptom followed by others [Table 3]. Brain metastases were an incidental finding in 5 patients of small cell carcinoma lung where brain MRI was done as a routine at initial staging workup. Cerebrum was involved in 87.3% of patients, followed by cerebellum in 9.5%, brainstem in 3.1% of patients, and among the different lobes of cerebrum, parietal lobe was commonly involved [Table 4]. We could not find any side predilection of cerebral hemispheres. The right side was involved in 28 patients, left in 25 patients, and 30 patients had bilateral involvement. At the time of diagnosis, most of the patients had ECOG performance score of 2 and 3 [Table 5]. Patients were diagnosed mainly by the brain imaging (CECT 66 and MRI 26), and histology of brain lesion was available in 3 patients who presented with CT/MRI documented brain lesion and were operated for the same; later, histology was suggestive of metastatic deposits of adenocarcinoma. After further evaluation, two patients had primary in lung and in the third, it was stomach. Lesions were single in 44.2% of patients and multiple (range 2–10) in 55.8% of patients. All patients received varying doses (2 mg BD to 8 mg TID) of dexamethasone depending on symptom severity. WBRT was received by only 76.8% of patients, and 23.2% of patients were managed with best supportive care, in view of very poor general condition and minimal expected survival because of disease *per se* and diffuse extracranial metastases. Extracranial metastases were seen in 52.6% of patients. With WBRT, a survival benefit of nearly 1 month was observed [Figure 1]. Survival was measured from the time of diagnosis of brain metastases to the death of patient or the last patient contact, and a median survival of 3 months was observed [Table 6].

DISCUSSION

Brain metastases are frequent complication of systemic cancer and can affect 24% of patients with cancer,[16] particularly those with lung and breast cancer.[4] Up to two-third of all, brain metastases are symptomatic at some time during life.[2] The most common symptoms of brain metastases are headache, altered mental status, and focal weakness occurring in up to half of patients. The next most common symptoms include seizures and gait ataxia which are seen in approximately 10–20% of patients.[4] MRI studies suggest that single metastasis accounts for one-third to one-quarter of patients with brain metastases.[17] Treatment of brain metastases is multidisciplinary with radiation forming cornerstone of treatment.[18,19] Johnson and Young observed that patients are diagnosed with brain metastases

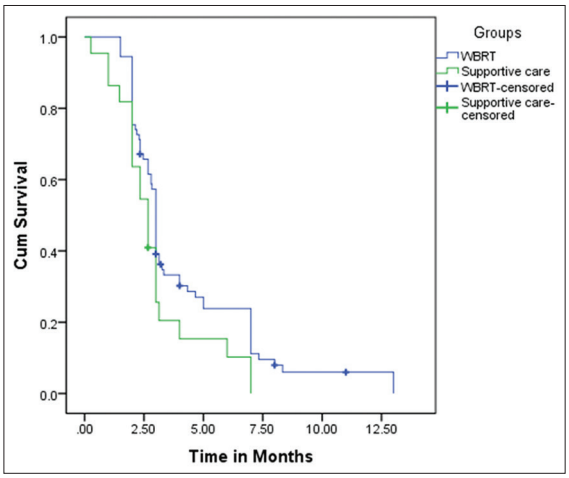

Figure 1: Kaplan–Meier survival analysis

Table 2: Time of progression to brain metastases

Time in months	*n* (%)
0-6	22 (23.1)
6-12	17 (17.8)
12-18	28 (29.4)
18-24	15 (15.7)
>24	13 (13.6)
Median (13.8 months)	

Table 3: Symptoms/signs of metastatic brain disease*

Presenting symptom/sign	*n* (%)
Headache	36 (37.9)
Seizures	21 (22.1)
Vomiting	18 (18.9)
Impaired speech	6 (6.3)
Visual impairment	5 (5.3)
Impaired memory	11 (11.6)
Weakness	17 (17.9)
Ataxia	10 (10.5)

*Many patients presented with more than one symptoms/signs. *n*: Number of patients, %: Percentage of patients

Table 4: Frequency of cerebral lobes involved

Cerebral lobe involved	*n* (%)
Frontal	24 (25.3)
Occipital	37 (38.9)
Temporal	42 (44.2)
Parietal	66 (69.5)

n: Number of patients, %: Percentage of patient

Table 5: Eastern Cooperative Oncology Group performance status of patients

ECOG*	*n* (%)
1	10 (10.5)
2	39 (41.1)
3	29 (30.5)
4	17 (17.9)

*ECOG: Eastern Cooperative Oncology Group performance status, *n*: Number of patients, %: Percentage of patients

Table 6: Survival of patients

Survival (month)	Mean±SE	Median
WBRT group	4.151±0.357	3.00
Supportive group	2.957±0.4	2.667
Overall	3.874±0.293	3.00

SE: Standard error, WBRT: Whole brain radiotherapy

usually in the 5th to 7th decade of life.[20] In the present study, most of the patients were in the 6th and 7th decade of life and only a few patients were below 40 years. The present study showed a slight male preponderance though not statistically significant, i.e., 51.6% males versus 48.4% females. Brain metastases demonstrate the same predilection for gender as that of primary tumors; lung cancer is the most common source of metastases in male patients whereas breast is the most common source in female patients.[21] In the present study, different primaries which spread to brain were lung (51.57%) including nonsmall cell of 34.7% and small cell of 16.8% followed by breast (15.7%), GIT (14.73%), malignant melanoma (5.3%), others (5.3%), and unknown primary (7.3%). Our observation was broadly consistent with Chason *et al*.[22] They conducted their study in 200 patients and observed lung as the most common source in 61% of patients, followed by breast in 16%, colorectal in 4%, melanoma 5%, and kidney 4%. A study done by Posner and Chernik[23] and various other studies have shown that there is substantial proportion of cases from unknown primary ranging from 0 to 24%. However, in the present study, patients with unknown primary were 7.3%. Although any primary malignancy may metastasize to the brain, lung has been identified as the universally most common malignancy going to brain in several clinical studies,[24-28] ranging from 18% to 64%. The next most common cancers in descending order were breast (2–21%), melanoma (4–16%), and colorectal cancers (2–11%).[4,6,22-29] Patients of brain metastases have varying degree of signs and symptoms depending on site of the brain involved. In this study, headache was the most common symptom observed in 37.9% of patients followed by seizures which was seen in 22.1%. Other symptoms were vomiting (18.9%), weakness (17.9%), memory impairment (11.6%), ataxia (10.5%), speech impairment (6.3%), and visual impairment (5.3%). Clouston *et al*. observed in their study that patients with a primary diagnosis and neurological symptoms will have brain metastases 45% of the time.[30] Data from the independent studies done by Zimm *et al*.,[29] Nussbaum *et al*.,[4] and Posner[31] on 1013 patients of presenting clinical features with brain metastasis have shown that the relative frequency of different signs and symptom as cognitive or mental status change in 34%, headache 31%, weakness 24%, seizure 19%, ataxia 11%, visual change 5%, nausea or vomiting 4%, other (includes bulbar symptoms, dizziness, and syncope) 4%, sensory change 2%, papilledema 0.5%, and none 9%. In the present study, cerebrum was involved in 83 patients (87.3%), cerebellum in 9 patients (9.4%), and 3 patients had brainstem involvement (3.1%). These observations correlate with the results of Patchell[32] according to whom anterior circulation accounts for approximately 80% of parenchymal metastases compared to 20% for the lower flow posterior circulation (15% cerebellum, 5% brainstem). In the present study, both cerebral hemispheres were affected equally with no side predilection. All lobes of cerebrum were involved either alone or in various combinations and parietal lobe was most common 69.5%), followed by temporal lobe (44.2%), then occipital (38.9%), and finally frontal (25.3%). Metastatic lesions may be solitary or multiple. In this study, it was solitary in 44.2% of cases and multiple in 55.8% of cases. Results from a clinical study of Nussbaum *et al*.,[4] imaging study of Delattre *et al*.,[1] and autopsy study of Posner and Chernik[23] have shown that approximately half of brain metastasis are solitary and half are multiple, which is consistent with our observation.

It proved a very deadly disease with a rapid progression to death. Only 7.4% of patients were alive at the time of closure of study and continued with follow-up. Median survival was only 3 months. Langer and Mehta[33] have observed that median survival from detection of brain metastases rarely exceeds 1 month without treatment. Zimm *et al*.[29] reviewed the records of 191 patients with an antemortem diagnosis of intracerebral metastasis made from August 1974 to November 1978. They observed a median survival time after diagnosis of an intracerebral metastasis was 3.7 months for the entire series. Lagerwaard *et al*.[6] reviewed 1292 patients for identification of prognostic factors in patients with brain metastases; the overall median survival was about 1.6 months in patients treated with steroids only, 3.6 months in patients treated with radiotherapy, and 8.9 months in patients treated with neurosurgery followed by radiotherapy.

CONCLUSION

Brain metastases are disease of elderly people with no sex predilection. Lung and breast 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. Arch Neurol 1988;45:741-4.
2. Cairncross JG, Kim JH, Posner JB. Radiation therapy for brain metastases. Ann Neurol 1980;7:529-41.
3. Plotkin SR, Wen PY. Brain metastases. In: Samuels MA, Feske SK,

editors. Office Practice of Neurology. 2nd ed. Philadelphia: Churchill Livingstone; 2003. p. 1101-6.
4. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. Cancer 1996;78:1781-8.
5. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, *et al.* Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997;37:745-51.
6. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: A review of 1292 patients. Int J Radiat Oncol Biol Phys 1999;43:795-803.
7. Murray KJ, Scott C, Zachariah B, Michalski JM, Demas W, Vora NL, *et al.* Importance of the mini-mental status examination in the treatment of patients with brain metastases: A report from the Radiation Therapy Oncology Group protocol 91-04. Int J Radiat Oncol Biol Phys 2000;48:59-64.
8. Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, *et al.* Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: Results of a randomized phase III trial. J Clin Oncol 2004;22:157-65.
9. Rudà R, Borgognone M, Benech F, Vasario E, Soffietti R. Brain metastases from unknown primary tumour: A prospective study. J Neurol 2001;248:394-8.
10. Auchter RM, Lamond JP, Alexander E, Buatti JM, Chappell R, Friedman WA, *et al.* A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. Int J Radiat Oncol Biol Phys 1996;35:27-35.
11. Davis PC, Hudgins PA, Peterman SB, Hoffman JC Jr. Diagnosis of cerebral metastases: Double-dose delayed CT vs contrast-enhanced MR imaging. AJNR Am J Neuroradiol 1991;12:293-300.
12. Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. J Neurooncol 1999;44:275-81.
13. Suzuki K, Yamamoto M, Hasegawa Y, Ando M, Shima K, Sako C, *et al*. Magnetic resonance imaging and computed tomography in the diagnoses of brain metastases of lung cancer. Lung Cancer 2004;46:357-60.
14. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 2000;47:1001-6.
15. El Kamar FG, Posner JB. Brain metastases. Semin Neurol 2004;24:347-62.
16. Posner JB. Neurologic Complications of Cancer. Philadelphia: F.A. Davis; 1995.
17. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, *et al.* A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322:494-500.
18. Mintz A, Perry J, Spithoff K, Chambers A, Laperriere N. Management of single brain metastasis: A practice guideline. Curr Oncol 2007;14:131-43.
19. Chang JE, Robins HI, Mehta MP. Therapeutic advances in the treatment of brain metastases. Clin Adv Hematol Oncol 2007;5:54-64.
20. Johnson JD, Young B. Demographics of brain metastasis. Neurosurg Clin N Am 1996;7:337-44.
21. Adams RD, Victor M, editors. Intraspinal tumors. In: Principles of Neurology. 2nd ed. New York: McGraw-Hill; 1981. p. 638-41.
22. Chason JL, Walker FB, Landers JW. Metastatic carcinoma in the central nervous system and dorsal root ganglia. A prospective autopsy study. Cancer 1963;16:781-7.
23. Posner JB, Chernik NL. Intracranial metastases from systemic cancer. Adv Neurol 1978;19:579-92.
24. Baker AB. Metastatic tumors of the nervous system. Arch Pathol 1942;24:495-537.
25. Globus JH, Meltzer T. Metastatic tumors of the brain. Arch Neurol Psychiatry 1942;482:163-226.
26. Tom MI. Metastatic tumours of brain. Can Med Assoc J 1946;54:265-8.
27. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma; analysis of 1000 autopsied cases. Cancer 1950;3:74-85.
28. Hunter KM, Rewcastle NB. Metastatic neoplasms of the brain stem. Can Med Assoc J 1968;98:1-7.
29. Zimm S, Wampler GL, Stablein D, Hazra T, Young HF. Intracerebral metastases in solid-tumor patients: Natural history and results of treatment. Cancer 1981;48:384-94.
30. Clouston PD, DeAngelis LM, Posner JB. The spectrum of neurological disease in patients with systemic cancer. Ann Neurol 1992;31:268-73.
31. Posner JB. Brain metastases: 1995. A brief review. J Neurooncol 1996;27:287-93.
32. Patchell RA. Brain metastases. Neurol Clin 1991;9:817-24.
33. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. J Clin Oncol 2005;23:6207-19.