RESEARCH ARTICLE

Brain Metastases from Solid Tumors: an Institutional Study from South India

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Abstract

Background: Brain metastases are the most common intra-cranial neoplasms. The incidence is on a rise due to advanced imaging techniques. Aims: The objective of the study was to analyse the clinical and demographic profile of patients with brain metastases from primary solid tumors. Materials and Methods: This is a retrospective single institutional study covering 130 consecutive patients with brain metastases from January 2007 to August 2014. Results: Some 64.6% of the patients were females. The majority were in the sixth decade of life. The site of the primary tumor was the lungs in 50.8% of the cases. The overall median time from the diagnosis of the primary malignancy to detection of brain metastases was 21.4 months. Survival was found to be significantly improved in patients with solitary brain lesions when compared to patients with multiple brain metastases, and in patients undergoing surgical excision with or without cranial irradiation when compared to whole brain irradiation alone. The majority of the cases belonged to the recursive partitioning analysis class II group. Whole brain radiation therapy was delivered to 79% of the patients. Conclusions: Most of the patients with brain metastases in the study belonged to recursive partitioning analysis classes II or III, and hence had poor prognosis. Most of the patients in the Indian context either do not satisfy the indications for surgical excision or are incapable of bearing the high cost associated with stereotactic radiosurgery. Treatment should be tailored on an individual basis to all these patients.

Keywords: Intra-cranial neoplasms- adenocarcinoma - recursive partitioning analysis

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Introduction

Brain metastases account for the most number of intracranial tumors, outnumbering all other primary brain tumors combined (Sawaya et al., 1994). Brain metastases occur in 25-50% of all cancer patients. In adults, the most important causes of brain metastases are lung carcinoma (50-60%), followed by breast cancers (15-20%), melanomas (5-10%) and other tumors like tumors of the gastrointestinal tract and renal cell carcinomas (Johnson et al., 1996).

There is an increased rate of brain metastases in recent times mostly due to advanced imaging techniques. Survival in brain metastases patients have been determined by various factors. Three prognostic groups of patients with significant differences in survival were identified using recursive partitioning analysis (RPA) derived from various Radiation Therapy Oncology Group (RTOG) trials [Table 1] (Gaspar et al., 1997).

Therapeutic approaches to intracranial metastases include whole brain radiation therapy, surgery, stereotactic radiosurgery and chemotherapy in selected patients. The efficacy of whole brain radiotherapy along with chemotherapy was found to be higher than whole brain radiotherapy alone in brain metastasis from non-small cell lung cancers and breast cancers (Liu et al., 2012; Fang et al., 2014; Cai et al., 2013; Erten et al., 2013).

The objective of the present study was to analyse retrospectively the clinical and demographic profile of patients with brain metastases from solid tumors.

Materials and Methods

This is a retrospective study of 130 patients done from January 2007 to August 2014 in the Department of Radiotherapy in our institution. Patients with brain metastasis, who were treated in the institute were only included in the study. MRI was done along with contrast enhanced CT in all patients to identify the brain lesions. All data were gathered from the computerised hospital information system and the standard case sheets of our hospital. Patients with inadequate data available for the study, were excluded. Lymphomas, leukemias and meningeal tumors were excluded from the study. The institutional ethical committee permission was taken.

Statistical analysis

Data was tabulated in Microsoft Excel 2013 and

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Table 1. Median Duration of Survival According to the RPA Class for Patients Treated with WBRT (9)

CRPA Class	Clinical Characteristics	Median duration of survival
1	KPS score ≥ 70 and age < 65 and controlled primary tumor and no extra-cranial metastases	7.1 months
2	KPS score ≥ 70 and age ≥ 65 or uncontrolled primary tumor or extra-cranial metastases	4.2 months
3	KPS score < 70	2.3 months

*RPA - Recursive Partitioning Analysis; WBRT – Whole Brain Radiation Therapy; KPS – Karnofsky Performance Status.

analysed using Statistical Package for the Social Sciences Software Version 21. P<0.001 was taken to be statistically significant in this study. Survival analysis was done by using Kaplan-Meier method and log-rank test.

Results

Brain metastases is the most common type of intra-cranial neoplasm and occurs ten times more commonly than primary brain tumors (Delattre, et al., 1988). Demographically, most of the patients with brain metastasis in our study were females which were mostly due to breast and lung cancer related brain metastasis, which is similar to that found in a study from Tabriz (Miabi, 2011). A higher proportion of lung cancer patients in the study were females due to a relatively higher incidence of smoking and exposure to smoke while cooking in our female population. Most of the studies have shown brain metastases to occur more commonly in patients aged between 50 and 70 years (Saha et al., 2013; Fabi et al., 2011). The median age of patients with brain metastases in our study is about 59.1 years, which is a bit on the higher side, as brain metastases occur more commonly in younger patients with breast as well as lung cancers. This may be attributed to the fact that most of our patients were illiterate and were unaware of their exact age.

According to most of the available literature, lung cancer is the leading cause of brain metastases, with 50% of the brain metastases arising from primary lung cancers (Johnson JD et al., 1996) which is in concordance with our study result. Extra-cranial disease was seen in 93.8% of the patients, which is similar to that reported in literature (Fabi et al., 2011). In 73.8% patients, the primary tumor was uncontrolled during the time of brain metastases, which is nearly similar to other reported studies (Saha et al., 2013).

In the present study, the histology of the primary tumor in 46.1% of the patients was adenocarcinoma, followed by small cell carcinoma in 20% patients and squamous cell carcinoma in 18.5% patients. Similar results were also found in earlier studies (Saha et al., 2013; Jin et al., 2011). Available literature states that histology of the primary tumor remains unknown in 3-4% of the patients with brain metastases (Delattre et al., 1988). In the current study, 7.7% of the primary tumor histology was unknown.

According to literature, 80% of the metastatic brain lesions are found in the cerebrum, 15% in the cerebellum and 5% in the brainstem (Delattre et al., 1988), which correlates with the present study. In the present study 81.5% of the patients had supratentorial metastatic brain lesions. The metastatic intra-cranial lesions are most commonly found in the frontoparietal cerebral tissue, which is supplied by the middle cerebral artery (Subramanian et al., 2002). In the current study, 49.2% of the metastatic brain lesions were found in the parietal lobe. In general, lung carcinomas and melanomas more commonly present with multiple brain metastases rather than single metastatic lesion (Delattre et al., 1988). In the current study, single metastatic brain lesion was found in 34% patients and most of them were from breast malignancies. 40% of the patients in the present study had more than three intra-cranial metastatic lesions, and most of them were from non-small cell lung cancers.

Few studies have reported headache as the most common symptom in patients with brain metastases (Saha et al., 2013; Miabi , 2011; Jin et al., 2011). In the present study, 66.1% patients had headache and another 47.7% patients presented with vomiting along with other associated symptoms. Neurocognitive impairment was absent in 56.9% of the patients. Magnetic resonance imaging is more sensitive than computed tomography in the detection of brain metastases (Jin et al., 2011). In a large retrospective study with 1292 patients of brain metastases, the median interval between diagnosis of the primary tumor and brain metastases was 8.5 months (Lagerwaard et al., 1999). But, this median time to brain metastases varies in different studies, as every study has a mixed set of primary tumors, and primary disease is a major factor correlated with this time interval. In a study by Fabi et al., median time to brain metastases was found to be 25 months. Tumor-specific time to brain metastases was 9 months for non-small cell lung cancers and 46 months for breast carcinomas (Fabi et al., 2011). In the current study, the median time from diagnosis of the primary tumor to brain metastases was 21.4 months. The tumor-specific median time to brain recurrence was 10.7 months for lung cancers and 36.9 months for breast cancers. Significant survival advantage has been demonstrated in literature for patients with <3 metastatic brain lesions when compared to those with >3 lesions (Song et al., 2013). In the present study, a significant survival advantage was seen in patients with solitary brain metastasis when compared to those with multiple brain metastases. The Recursive Partitioning Analysis (RPA) was the first prognostic score developed for patients with brain metastases in 1997 (Gaspar et al., 1997). Larger series have previously demonstrated that majority of the patients with metastatic brain lesions are classified as RPA-RTOG Class II (Fabi et al., 2011). Similarly, 66.2% of the patients with brain metastases in the current study belonged to RPA-RTOG Class II, while 27.7% of the

Table 2. Clinical and Demographic Profile of Patients

Total Patients	130 (100%)
Gender	
Male	46 (35.4%)
Female	84 (64.6%)
Age in years	
≤ 50	6 (4.6%)
>50 - 60	54 (41.54%)
>60 - 70	64 (49.23%)
>70	6 (4.6%)
Primary Tumor Histology	
Adenocarcinoma	60 (46.1%)
Squamous cell carcinoma	24 (18.5%)
Small cell carcinoma	26 (20%)
Melanoma	10 (7.7%)
Unknown histology	10 (7.7%)
Primary Tumor	
Lung	66 (50.8%)
Breast	36 (27.7%)
Melanoma	10 (7.7%)
Unknown primary	10 (7.7%)
Colorectal	6 (4.6%)
Esophagus	2 (1.5%)
Brain site involved	
Cerebrum	106 (81.5%)
Cerebellum	18 (13.8%)
Brainstem	6 (4.6%)
Presence of extra-cranial disease	
Yes	122 (93.8%)
No	8 (6.2%)
Uncontrolled primary tumor	
Yes	96 (73.8%)
No	34 (26.2%)
Relation of the lesions to tentorium	
Supratentorial	106 (81.5%)
Infratentorial	24 (18.5%)
Lobes of the brain involved mainly	
Parietal	64 (49.2%)
Temporal	16 (12.3%)
Frontal	26 (20%)
Cerebellar	18 (13.8%)
Brainstem	6 (4.6%)
Neurocognitive impairment (MMSE)	
Yes	56 (43.1%)
No	74 (56.9%)
Number of lesions in the brain	
≤3	78 (60%)
>3	52 (40%)
RPA-RTOG Classes	
I	8 (6.2%)
II	86 (66.2%)
III	36 (27.7%)

Table 3. Survival Time for Different Primary Tumor Types in the 130 Patients with Brain Metastases

Primary Site of Tumor	Time from Diagnosis to Metastasis (Months)	Time from Metastasis to Death (months)
Lung	10.7	1.8
Breast	36.9	4.3
Melanoma	25.6	4.1
Unknown Primary	24.7	4.3
Colorectal	30.2	4.7
Esophagus	37	5
Total	21.4	3.05

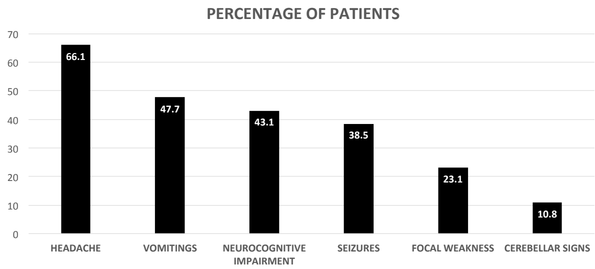

Figure 1. Clustered Column Chart Showing the Distribution of the Percentage of Patients with Different Clinical Symptoms

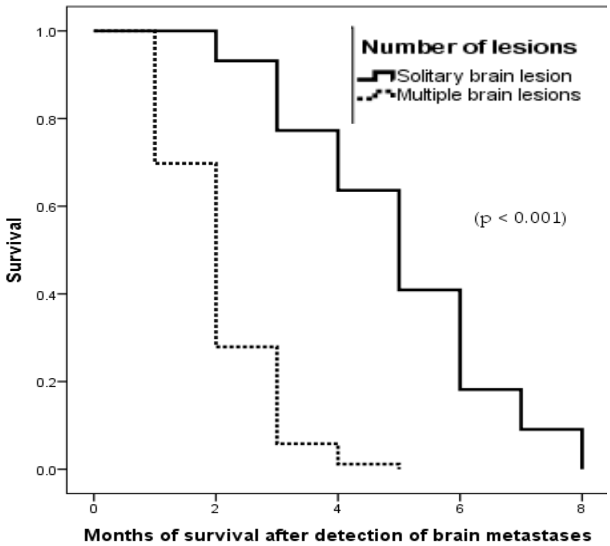

Figure 2. Kaplan-Meier Survival Curves Showing that the Length of Time from the Detection of Brain Metastasis to Death was Significantly Shorter (Log Rank Test, P<0.0001) in the 42 Patients with Multiple Brain Metastases (Dashed Line) than in the 23 Patients with solitary metastatic brain lesion (normal line)

patients belonged to Class III.

The major treatment options in patients with brain metastasis include surgical resection, stereotactic radiosurgery, whole brain radiation therapy and chemotherapy in selected patients. Overall survival has been demonstrated to be higher in patients with brain metastasis who have been treated with surgical excision with cranial irradiation when compared to those treated with whole brain irradiation alone (Akhavan et al., 2014). Surgery for brain metastases is generally limited to patients with single metastatic brain lesion with good performance status and controlled extra-cranial disease. Here, the term controlled extra-cranial disease includes controlled primary tumor along with controlled extra-cranial metastatic disease. Though oligometastasis were present in 60% of the patients in the present study, surgical resection was offered to only 14 out of 65 patients, as many patients had uncontrolled extra-cranial disease and in some other patients, surgical debulking was not

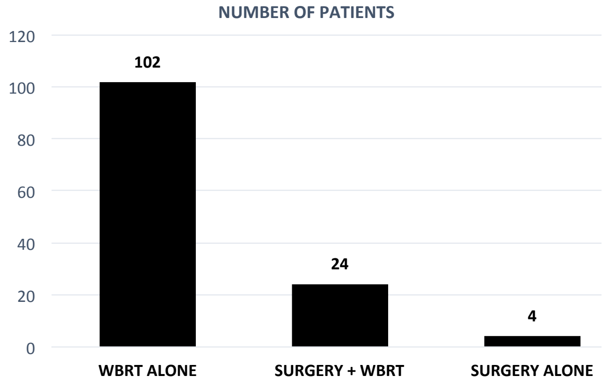

Figure 3. Bar Chart Showing the Distribution of the Modalities of Treatment Delivered in the Patients with Metastatic Brain Lesions

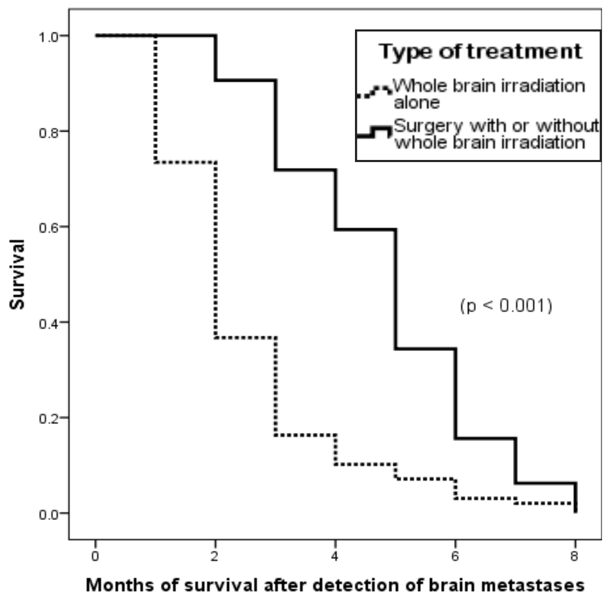

Figure 4. Kaplan-Meier Survival Curves Demonstrating that the 14 Patients who Underwent Surgery with or without whole Brain Irradiation (Normal Line) Survived Significantly Longer (Log Rank Test, P<0.0001) than the other 51 Patients who Underwent whole brain Radiation Therapy alone for the Treatment of Brain Metastases (Dashed Line)

considered due to the close proximity of the tumor to vital structures or due to the morbidity associated with the resection. Poor performance status further added to the inoperability in these patients. So surgery alone was performed in only 3% of the patients, while surgery followed by whole brain radiation therapy was delivered in 18% of the patients. Whole brain radiation therapy alone with 30 Gy in 10 fractions, was delivered in 79% of the patients. Stereotactic radiotherapy, when combined with whole brain irradiation had lower local recurrence rate and new brain metastasis rate when compared to stereotactic radiotherapy alone. On the other hand, patients undergoing stereotactic radiotherapy alone had better neurological function and quality of life when compared to stereotactic radiosurgery combined with whole brain irradiation (Duan et al., 2014). A multi-institutional study from Japan demonstrated a 10.8 months mean survival in patients with two to ten metastatic brain lesions with stereotactic radiosurgery alone. The survival of patients with five to ten metastatic brain lesions with stereotactic radiosurgery alone was non-inferior to that in patients with two to four metastatic brain lesions (Yanamoto et al., 2014). Stereotactic radiosurgery was not available in the institute. The patients who were deemed to be fit for stereotactic radiosurgery, did not opt for the treatment at some other place due to financial constraints.

Most of the patients with brain metastases in our scenario, present quite late in the disease process and belong to the RPA-RTOG Class II or III. Though treatment with surgery or stereotactic radiosurgery has better results when compared to whole brain irradiation alone, most of the patients in Indian context either do not satisfy the indications of surgical excision or are incapable of bearing the high cost associated with stereotactic radiosurgery. The overall prognosis of the patients with brain metastases in Indian scenario, remain poor due to the late detection, advanced RPA-RTOG Class presentations and poor socioeconomic status of the patients. Treatment should be tailored on an individual basis to all patients belonging to the RPA-RTOG Class I and II, even in patients with controlled extra-cranial disease.

Discussion

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