Original Article

Treatment outcomes in patients with multiple brain metastases: A prospective randomized study

Animesh Saha, Sajal Kumar Ghosh[1], Chhaya Roy[2], Priyanjit Kayal[3]

Departments of Radiotherapy, Tata Medical Center, [1]IPGMER and SSKM Hospital, [2]RG Kar Medical College, [3]Calcutta National Medical College, Kolkata, West Bengal, India

ABSTRACT

Context: There is controversy regarding the radiotherapeutic dose fractionation in brain metastases (bm). **Aims:** The aim of this study is to analyze the treatment outcomes in patients with multiple bm. **Settings and Design:** Prospective, randomized study. **Subjects and Methods:** Patients with multiple bm with Eastern Cooperative Oncology Group performance status ≤2 were included. In arm-A patient received whole brain radiotherapy (WBRT) 30 GY in 10# over 2 weeks and in arm-B patients received 20 GY in 5# over 1 week. Assessment of improvement in clinical symptoms was done using Barthel's adjusted daily live (ADL) score. Assessment of radiological response was done using magnetic resonance imaging scan of brain after 3 months of completion of external beam radiation therapy. Acute radiation toxicity was assessed using Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer acute radiation morbidity scoring. **Statistical Analysis Used:** Chi-square test was used to compare categorical variables between groups. Overall survival was computed by Kaplan-Meier survival analysis and Log-Rank test used for comparison of survival plots. For change in quality-of-life during treatment and follow-up, repeated measures ANOVA were used. **Results:** In both arms, there was a significant improvement in ADL score after treatment, but when two arms were compared, no significant difference was found between the two treatment arms. There was no statistically significant difference in response or morbidity between the two treatment arms. Median survival was 29 weeks in arm-A compared to 25.86 weeks in patients arm-B. Kaplan-Meier Survival curve analysis shows no significant difference in survival between the two arms. **Conclusions:** 20 GY in 5 fractions is equally effective with that of the 30 GY in 10 fractions for WBRT in bm. In the palliative setting short duration of treatment with minimum discomfort to the patient is desirable. Hence, we can opt for 20 GY in 5 fractions in poor performance status patients and 30 GY in 10 fractions in patients with good performance status.

Key words: Brain metastases, quality of life, whole brain radiotherapy

INTRODUCTION

Brain metastases (bm) are the most common type of intracranial neoplasm, with the total number diagnosed annually outnumbering all other intracranial tumors combined.[1] Bm increases morbidity and mortality in cancer patients. Surveillance epidemiology and end result programme data suggest that there will be 23,130 new cases of brain tumor in 2013.[2] Bm outnumber primary brain tumors by a ratio of 10:1 and occur in about 25% of all patients with cancer.[3] Between 20% and 40% of all patients with metastatic cancer will have bm at autopsy.[4]

The majority of patients who develop bm have a known primary cancer (metachronous presentation). Most bm 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 bm.[5] Bm are located in the cerebral hemispheres in about 80%, in the cerebellum in 15%, or in the brainstem in 5% of patients.[6]

In recent years, there is an apparent increase in cases of brain secondaries because of increasing incidence of lung cancer, improved detection by more sensitive imaging

Access this article online	
Quick Response Code:	Website: www.ccij-online.org
	DOI: 10.4103/2278-0513.134467

Address for correspondence: Dr. Animesh Saha, 2/1A Kalinath Munsli Lane, Kolkata - 700 036, West Bengal, India.
E-mail: mesh.vicky@gmail.com

techniques, development in anticancer treatment resulting in prolonged survival.[7-9]

The clinical presentation of bm is similar to any intracranial mass lesion and include headache (70%), seizures (30-60%), cognitive impairment (30%), papilledema (8%), and miscellaneous focal neurological deficits.[4,10]

Advances in neuroradiology have contributed greatly to the diagnosis and management of patients with suspected neoplastic diseases of central nervous system (CNS). Contrast-enhanced computed tomography (CT) is used widely due to its easy accessibility and low cost. Contrast-enhanced magnetic resonance imaging (MRI) is more sensitive than enhanced CT scanning in detecting bm, particularly small lesions or metastases situated in the posterior fossa.[11,12] MRI is particularly recommended 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 bm would alter the therapeutic management.[13] Radiographically, metastases are ring-enhancing lesions, most often located at the grey-white matter junction surrounded usually by significant edema. Unlike primary brain tumors, metastatic lesions rarely involve the corpus callosum or cross the midline. The radiographic appearance of bm is nonspecific and may mimic other processes, such as infection. Tissue confirmation is necessary in patients even with a history of prior cancer, in those whose history of cancer is remote, and in those for whom clinical or neuroimaging features may suggest an alternative diagnosis, such as a primary brain tumor.

A comprehensive approach to managing a patient with bm includes therapies that (1) reduce mass effect and increased intracranial pressure; (2) provide treatment for medical complications, such as seizures, venous thrombosis, and side-effects from medication; and (3) offer definitive treatments that prolong survival and quality of life.

Treatment of bm is multidisciplinary with radiation forming the cornerstone of treatment.[14,15] Further studies defining optimal role of conventional treatments and future advances in the use of chemotherapy, neurosurgery, radiosurgery, and more novel cancer therapies may lead to further increases in effectiveness of treatments for bm.

Whole brain/external beam radiotherapy (WBRT/EBRT) has traditionally been the standard treatment for patients with bm since 1950. WBRT has been shown to effectively improve neurologic symptoms and function for patients with minimum radiation induced toxicity. However, controversy exits regarding the demographic profile, radiotherapeutic dose fractionation in bm, which require further evaluation.

In view of challenging role of radiotherapy in management of intracranial neoplasms, the aim of this study is to analyze the treatment outcomes in patients with multiple bm.

SUBJECTS AND METHODS

It was a prospective, interventional randomized open labeled study done from January 2011 to June 2013. Inclusion criteria for treatment was (1) brain secondaries diagnosed based on MRI scan with multiple metastases in a case of known primary and in case of unknown primary after confirmation by histopathological biopsy, (2) patient having Eastern Cooperative Oncology Group performance status[16] 0, 1, 2, (3) no prior RT to brain. MRI scan of the brain was repeated after 3 months of completion of radiotherapy to assess the treatment response. Follow-up of patients was done initially every 6 weeks for 3 months, followed by every 3 months up to 1 year and every 4 months thereafter until the end of study, based on clinical status including a detailed neurological evaluation, complete blood count, biochemical tests, radiological parameters, and questionnaires. EBRT to whole brain was given with megavoltage equipment with cobalt-60 ATC-C9, with 80 cm source skin distance. In arm-A patient received 30 GY in 10# over 2 weeks and in arm-B patients received 20 GY in 5# over 1 week. Target volume was whole brain. Field arrangement was done using bilateral parallel opposing field with dose prescription at the center of interfield distance. Radiation portal-ANTERIOR: Dose fall-up in the air along metopic suture, POSTERIOR: Dose fall-up in the air along occipital bone, SUPERIOR: Dose fall-up in the air along sagittal suture, INFERIOR: Lines drawn from supraorbital ridge across the tip of mastoid. The lower border is extending up to the lower border of C2 vertebra. During treatment gantry was tilted 5° posteriorly to prevent divergence of treatment beams through the contralateral lens. In patients with metastases of inferior aspects of frontal and temporal region, a line from infraorbital ridge across the external auditory meatus is drawn with lens block to both eyes. Both fields were treated daily. Head rest with three clamp thermoplastic mask was used for immobilization. Assessment of improvement in clinical symptoms was done using Barthel's adjusted daily live (ADL) score,[17] before treatment, just after treatment and 6 week of treatment and improvement analyzed. Assessment of radiological response was done using MRI scan (with contrast) of brain after 3 months of completion of EBRT, by using Response Evaluation Criteria in Solid Tumors criteria.[18]

Dexamethasone 8 mg BD was given either in tablet form or injection at the beginning of treatment and tapered to 4 mg/day. Antiemetics, hematinics and proton pump inhibitors were given to all patients throughout the treatment period. Periodic blood transfusions were given

whenever Hb% levels become <10 g%. Patients who present with seizures or who develop seizures during therapy was started on antiseizure medications. In the absence of seizure, antiseizure prophylaxis was given to patient with bm in highly eliptogenic areas or in patients with tumors that frequently involve the cortex, such as melanomas. Acute toxicity of the patient was assessed during treatment and the follow-up (up to 90 days post EBRT) period using clinical status, laboratory investigations and radiological test and graded according to Radiation Therapy Oncology Group (RTOG/European Organization for Research and Treatment of Cancer) acute radiation morbidity scoring.[19] Chi-square test or Fisher's exact test was used to compare categorical variables between groups. All tests were two-sided with $P < 0.05$ taken to be statistically significant. Overall survival was computed by Kaplan-Meier survival analysis and Log-Rank test used for comparison of survival plots. For change in quality-of-life during treatment and follow-up, repeated measures ANOVA were used. Statistical analysis was performed using MEDCALC version 11 software.

RESULTS

The study was prospective, interventional randomized open labeled study, conducted between January 2011 and June 2013. A total of 58 patients with multiple brain metastasis were randomized after fulfilling the eligibility criteria. Two patients were excluded from analysis, out of which one did not receive allotted treatment and other died of nononcological cause. Hence, at the end of study, we have 56 evaluable patients for analysis with 30 patients in arm-A and 26 patients in arm-B arm. Patient's characteristics in both the arm were quite comparable as shown in Table 1. The Barthel ADL score before treatment, just after treatment and after 6 weeks of treatment were documented and symptomatic improvement analyzed using repeated measures ANOVA test. In both arms, there was a significant improvement in ADL score after treatment, that is, improvement in clinical symptoms and quality of life, but when two arms were compared, no significant difference (*P* value not significant) was found between the two treatment arms [Table 2 and Figure 1]. Pretreatment Barthel index score was 77.69 ± 18.50 for arm-B and 77.17 ± 14.24 for arm-A patients. Posttreatment scores were increased in both groups, arm-B showing a mean score of 91.54 ± 13.17 against arm-A mean score of 95.17 ± 9.05. Observations measured at 6th week posttreatment showed mean scores of 91.54 ± 13.17 for arm-B patients against 93.17 ± 12.70 for arm-A patients. Patients were evaluated for the response to treatment after 3 months by doing MRI scan of the brain. There was no statistically significant difference in response between two treatment arms [Table 3 and Figure 2]. The acute radiation toxicity observed during treatment was graded according to RTOG acute toxicity criteria; analysis is given in Figures 3a and b. There were no significant differences in treatment morbidity between the two treatment arms. Median survival was 29 weeks in patients treated with 30 GY compared with 25.86 weeks in patients who were treated with 20 GY to whole brain. Kaplan-Meier survival curve analysis shows no significant difference in survival between the two arms. "Log-Rank test" *P* value 0.9555 (not significant), hazard ratio of 0.9842, 95% confidence interval 0.5541-1.7484 [Figure 4].

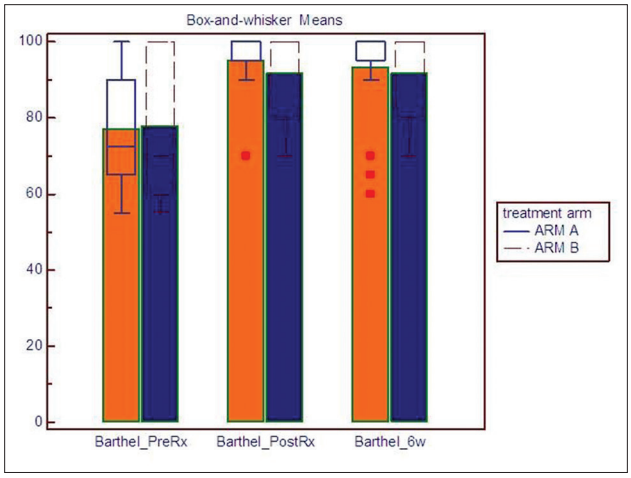

Figure 1: Clustered multiple variable graph showing box and whisker plot of pretreatment Barthel adjusted daily live (ADL) score, posttreatment Barthel ADL score and Barthel ADL score 6 weeks after treatment, compared between two treatment arm

DISCUSSION

In this study, 56 patients with multiple metastasis were randomized to two treatment arms, that is, arm-A (30 patients) and arm-B (26 patients).

Study by Victor[20] showed that about 60% of patients of bm are aged between 50 and 70 years. Metastasis is not common in children; accounts for 6% of all CNS tumor in children. Leukemia accounts for most metastatic CNS lesions in

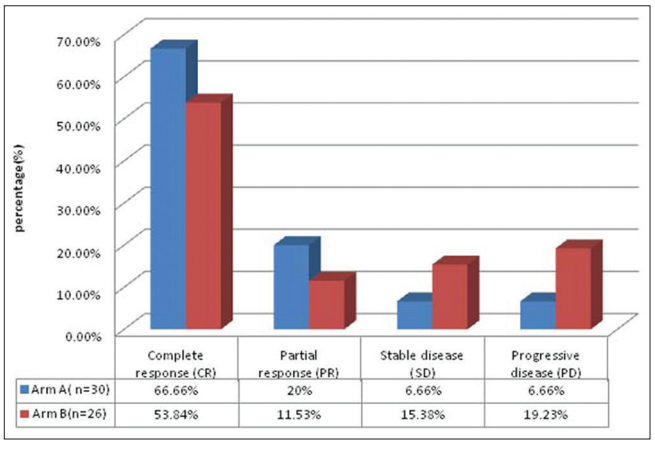

Figure 2: Bar diagram showing response rate on magnetic resonance imaging scan after 3 months

Table 1: Patients characteristics

Patient's characteristics	Variables	Arm-A (*n*=30)		Arm-B (*n*=26)		*P* value
		Number	Percentages	Number	Percentages	
Age group (years)	<40	2	6.66	8	30.77	0.0054
	≥40–<50	12	40	2	7.69	
	≥50–<60	15	50	12	46.15	
	≥60	1	3.34	4	15.38	
Sex	Female	14	46.66	13	50	0.9847
	Male	16	53.34	13	50	
Occupation	Day laborer	12	40	5	19.23	0.4029
	Service-holder	5	16.67	7	26.92	
	Farmer	5	16.67	4	15.38	
	Professional	4	13.33	3	11.54	
	Others	4	13.33	7	26.92	
SE status	Lower	7	23.33	7	26.92	0.3764
	Lower middle	7	23.33	2	7.69	
	Upper	6	20	9	34.61	
	Upper lower	4	13.33	5	19.23	
	Upper middle	6	20	3	11.54	
Primary	Breast	10	33.33	8	30.77	0.4688
	Colorectum	1	3.33	0	0	
	Kidney	0	0	1	3.84	
	Lung	17	56.66	14	53.84	
	Ovary	0	0	2	7.69	
	Unknown	2	6.66	1	3.84	
ECOG status	0	11	36.66	8	30.77	0.7304
	1	13	43.33	14	53.84	
	2	6	20	4	15.38	
RPA class	1	21	70	17	65.38	0.8355
	2	4	13.33	5	19.23	
	3	5	16.67	4	15.38	
Histology of primary	Adenocarcinoma	12	40	13	50	0.8820
	Squamous cell carcinoma	8	26.66	6	23.07	
	Others-specify	8	26.66	6	23.07	
	Unknown	2	6.66	1	3.84	
Controlled primary	Yes	9	30	9	34.6	0.9347
	No	21	70	17	75.4	
Brain side involved	Bilateral	16	53.33	13	50	0.9341
	Left	9	30	9	34.6	
	Right	5	16.67	4	15.38	
Supra/infratentorial	Supratentorial	29	96.67	25	96.16	0.5361
	Infratentorial	1	3.33	1	3.84	
Symptoms	Headache	20	66.7	19	73.1	
	Vomiting	14	46.7	17	65.4	
	Neurodeficit	11	36.7	10	38.5	
	Visual symptoms	10	33.3	3	11.5	
	Seizure	10	33.3	4	15.4	
	Cerebellar sign	0	0	2	7.7	
Site of brain involved	Fronal	19	24.67	13	19.69	
	Parietal	40	51.95	31	46.97	
	Temoral	3	3.89	10	15.15	
	Occipital	15	19.48	10	15.15	
	Cerebellar	0	0	2	3.03	

ECOG: Eastern Cooperative Oncology Group, RPA: Recursive partitioning analysis

young patients - followed by lymphoma, osteogenic sarcoma, and rhabdomyosarcoma. Germ cell tumors are common in adolescents and young adults between 15 and 21 years. Takokura *et al*., viewed that the age of onset of bm in the male is 56 years and in females 40 years.[21] Victor[20] showed that although melanoma spreads to the brain more commonly in males than in females, gender does not affect the overall incidence of bm. Debnath *et al.*,[22] showed that the highest occupational group were day laborers (31.43%) followed by service-holders (22.85%) and farmers (20%). Debnath *et al.*,[22] in their study showed that in the majority of patients with bm histology of the primary was adenocarcinoma (40.00%) followed by small cell carcinoma of lungs (28.57%) and squamous cell carcinoma (22.86%).

Approximately 80% of lesions found in the cerebrum, 15% in the cerebellum, and 5% in the brainstem as opined by Nussbaum *et al.*,[23] and Delattre *et al.*,[3] Multiple secondaries predominant over solitary metastasis, which was opined by Posner.[10] Studies using CT scan data indicated that metastases to the brain are multiple in more than 50% of cases as shown by Delattre *et al.*,[3] Recent experience with

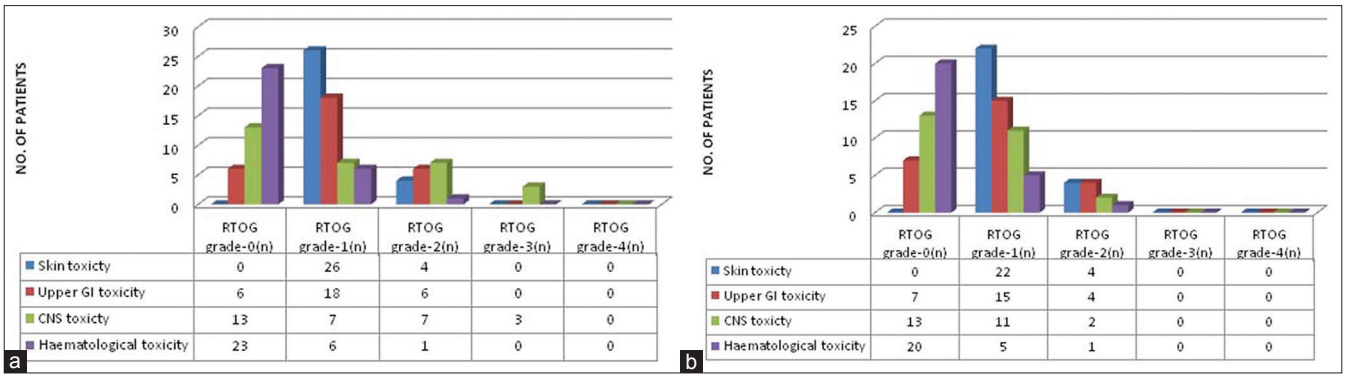

Figure 3: a) Bar diagram showing acute toxicity arm-A, b) Bar diagram showing acute toxicity arm-B

Table 2: Barthel index score pretreatment and posttreatment and at 6 weeks follow-up

Arm	Pretreatment	Posttreatment	At 6 weeks
Arm-B			
Mean	77.6923	91.5385	91.5385
Standard deviation	18.50572	13.17340	13.17340
Minimum	55.00	70.00	70.00
Maximum	100.00	100.00	100.00
Median	70.0000	100.0000	100.0000
Arm-A			
Mean	77.1667	95.1667	93.1667
Standard deviation	14.24438	9.04808	12.69560
Minimum	55.00	70.00	60.00
Maximum	100.00	100.00	100.00
Median	72.5000	100.0000	100.0000
Total			
Mean	77.4107	93.4821	92.4107
Standard deviation	16.20861	11.19739	12.82721
Minimum	55.00	70.00	60.00
Maximum	100.00	100.00	100.00
Median	70.0000	100.0000	100.0000

Table 3: Response rate on CT scan after 3 months

Response criteria	Arm-A (*n*=30)		Arm-B (*n*=26)	
	No.	Percentage	No.	Percentage
Complete response	20	66.66	14	53.84
Partial response	6	20	3	11.53
Stable disease	2	6.66	4	15.38
Progressive disease	2	6.66	5	19.23

P=0.2904. CT: Computed tomography

MRI indicates that proportion of multiple metastasis is higher and in the range of two-third to three-fourth of patients with bm.[24] Lassman and DeAngelis[25] reviewed nine studies and found the following variation in reported percentages of patients developing bm 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). In 2700 cases from the Memorial Sloan-Kettering Cancer Center in New York, Victor 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, and 5% ovary), 10% osteosarcoma, 5% neuroblastoma, and 6% head and neck tumor.[20] According to Takokura *et al.*,[21] the most common primary producing bm are cancer lung (48%), carcinoma breast (25%), GI tract (8%), genitourinary tract (6%), melanoma (6%), and others (13%). Approximately, 60% of patients with bm have sub-acute symptoms. Symptoms are usually related to the location of the tumor. Clinical symptoms or presentation of a patient with bm have been described by Posner.[25] In his series, headache was the most common clinical presentation observed in 49% of patients followed by mental changes in 32%, focal weakness in 30%, and seizures in 18% of patients. In their study, Victor[20] they found that headache (42%) and seizure (21%) are the two most common presenting symptoms. In addition, 35% of patients have cognitive dysfunction, and 30% have motor dysfunction. Victor *et al.*,[20] showed that the maximum number of brain secondaries found in patients whose primary disease was not controlled at the time of presentation. Borgelt *et al.*,[26] showed that there was an improvement in relief of symptoms such as convulsion 90%, headache 82%, and neurological deficit about 74% of bm patients treated with WBRT. Plotkin and Wen[27] showed that WBRT produces symptomatic improvement in 75-80% of patients with bm. In our study, the Barthel ADL score before treatment, just after treatment and after 6 weeks of treatment were documented and symptomatic improvement analyzed using repeated measures ANOVA test. In both arms, there was a significant improvement in ADL score after treatment, that is, improvement in clinical symptoms and quality of life, but when two arms were compared, no significant difference (*P* value not significant) was found between the two treatment arms. Pretreatment Barthel index score was 77.69 ± 18.50 for arm-B and 77.17 ± 14.24 for arm-A patients. Posttreatment scores were increased in both groups, arm-B showing a mean score of 91.54 ± 13.17 against arm-A mean score of 95.17 ± 9.05. Observations measured at 6th week posttreatment showed mean scores of 91.54 ± 13.17 for arm-B patients against 93.17 ± 12.70 for arm-A patients.

Radiation Therapy Oncology Group 6901 and RTOG 7361, involving more than 1800 patients, found complete or partial

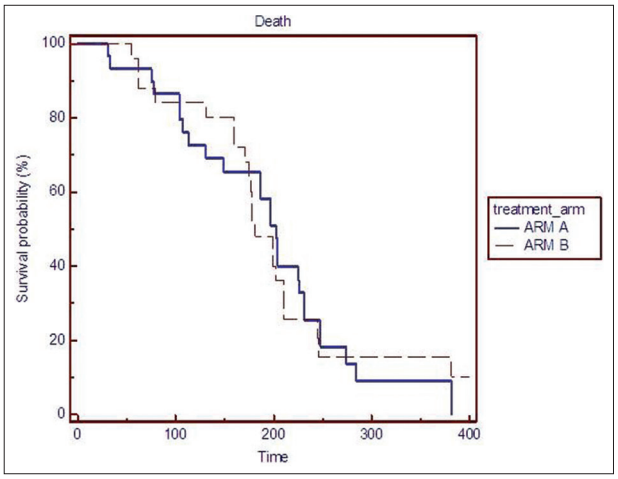

Figure 4: Kaplan-Meier survival curve analysis shows no significant difference in survival between the two arms. "Log-Rank test" P value 0.9555 (not significant), hazard ratio of 0.9842, 95 confidence interval 0.5541-1.7484. Median survival in arm-A and arm-B are 29 weeks and 25.86 weeks, respectively

clinical responses in 60-90% of symptomatic patients, with a median duration of improvement 10-12 weeks, and with 75-80% of remaining survival time spent in an improved or stable neurologic state.[26,28] In the present study, 66.66% patients in arm-A and 53.84% patients in arm-B had a complete response and 20% patients in arm-A and 11.53% patients in arm-B had a partial response.

The acute side-effects of WBRT are unpleasant and include hair loss (88%), fatigue (95%), memory impairment (72%), poor concentration (61%), and depression (54%).[29] In our study, acute morbidity (skin, CNS, upper GI, hematological) during radiotherapy were graded according to RTOG acute toxicity criteria. There were no significant differences in treatment morbidity between the two treatment arms.

Borgelt *et al.*,[26] in RTOG 7361 trail showed that median survival was 4 month in 20 GY in 5# and 3.7 months in 30 GY in 10# arm. Komarnicky *et al.*,[30] in RTOG 7916 trail showed that median survival following 30 GY in 10# WBRT was 4.5 months. In RTOG 7606 trail Kurtz *et al.*,[31] randomly assigned 255 patients to receive either 30 GY in 10# or 50 GY in 20# and the median survival was 4.5 months and 4.2 months, respectively. In our study, median survival following WBRT in arm-A (30 GY in 10#) was 29 weeks and in arm-B (20 GY in 5#) was 25.86 weeks. Comparing our study with above studies, the median survival is slightly higher in our study, but there is no significant difference between two arms.

CONCLUSION

Radiotherapy is the mainstay of treatment to relieve the symptoms in patients with multiple bm, which was observed through the ADL score. There is a definite improvement in the relief of symptoms and quality of life with the addition of radiotherapy. 20 GY in 5 fractions is equally effective with that of the 30 GY in 10 fractions. In the palliative setting short duration of treatment with minimum discomfort to the patient is desirable. Hence, we can opt for 20 GY in 5 fractions in poor performance status patients and 30 GY in 10 fractions in patients with good performance status.

ACKNOWLEDGMENT

The authors are gratefully acknowledged the cooperation of patient's relatives for supplying the reports, etc., for our study.

REFERENCES

1. Sawaya R, Ligon BL, Bindal RK. Management of metastatic brain tumors. Ann Surg Oncol 1994;1:169-78.
2. SEER Stat Fact Sheets: Brain and Other Nervous System Cancer. National Cancer Institute. Available from: http://www.seer.cancer.gov/statfacts/html/brain.html. [Last accessed on 2014 May 10].
3. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. Arch Neurol 1988;45:741-4.
4. Sawaya R, Bindal RK, Lang FF, Abi-Said D. Metastatic brain tumors. 2nd ed. New York: churchill Livingstone; 2001.
5. 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.
6. Patchell RA. Metastatic brain tumors. Neurol Clin 1995;13:915-25.
7. 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.
8. Cherryman G, Golfieri R. Comparison of spin echo T1-weighted and FLASH 90 degrees gadolinium-enhanced magnetic resonance imaging in the detection of cerebral metastases. Br J Radiol 1990;63:712-5.
9. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, *et al*. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 1996;78:1470-6.
10. Posner JB. Brain metastases: 1995. A brief review. J Neurooncol 1996;27:287-93.
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. Mintz A, Perry J, Spithoff K, Chambers A, Laperriere N. Management of single brain metastasis: A practice guideline. Curr Oncol 2007;14:131-43.
15. Chang JE, Robins HI, Mehta MP. Therapeutic advances in the treatment of brain metastases. Clin Adv Hematol Oncol 2007;5:54-64.
16. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.

17. Mahoney FI, Barthel DW. Functional evaluation: The barthel index. Md State Med J 1965;14:61-5.
18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
19. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiati on Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) Int J Radiat Oncol Biol Phys 1995;31:1341-6.
20. Victor TS. Brain metastasis. Medscape Reference. Available from: http://www.emedicine.medscape.com/article. [Last updated on 2011 Oct 07].
21. Takokura K, Sarok HO. Metastatic tumour of CNS. Tokyo Egarku, Shoal; 1982.
22. Debnath H, Barua KK, Hossain MA, Khair MA, Islam MA. Outcome and prognosis of metastatic brain tumour: A study of 35 cases. Bangladesh J Neurosci 2008;24:17-23.
23. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. Cancer 1996;78:1781-8.
24. Sze G, Milano E, Johnson C, Heier L. Detection of brain metastases: Comparison of contrast-enhanced MR with unenhanced MR and enhanced CT. AJNR Am J Neuroradiol 1990;11:785-91.
25. Lassman AB, DeAngelis LM. Brain metastases. Neurol Clin 2003;21:1-23, vii.
26. Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, *et al*. The palliation of brain metastases: Final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 1980;6:1-9.
27. 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.
28. Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: Final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 1981;7:1633-8.
29. Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Radiosurgery with or without whole-brain radiotherapy for brain metastases: The patients' perspective regarding complications. Am J Clin Oncol 2005;28:173-9.
30. Komarnicky LT, Phillips TL, Martz K, Asbell S, Isaacson S, Urtasun R. A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). Int J Radiat Oncol Biol Phys 1991;20:53-8.
31. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: A randomized clinical trial by the radiation therapy oncology group. Int J Radiat Oncol Biol Phys 1981;7:891-5.

Cite this article as: Saha A, Ghosh SK, Roy C, Kayal P. Treatment outcomes in patients with multiple brain metastases: A prospective randomized study. Clin Cancer Investig J 2014;3:269-75.

Source of Support: Nil, **Conflict of Interest:** None declared.