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A PROSPECTIVE INTERVENTIONAL STUDY TO COMPARE THE TREATMENT OUTCOMES IN PATIENTS WITH TWO DIFFERENT FRACTIONATION SCHEDULE OF WHOLE BRAIN RADIOTHERAPY WITH MULTIPLE BRAIN METASTASES

Oncology/Radiotherapy

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ABSTRACT

Purpose of study : To compare the treatment outcomes in patients with brain metastasis treated with two different fractionation schedules of whole brain radiotherapy. **Materials and methods:** A prospective randomised study was carried out on newly diagnosed cancer patients with MRI diagnosis of brain metastasis. Patients with multiple bm with Eastern Cooperative Oncology Group performance status 0-4 were included. In Arm A, patients received whole brain radiotherapy (WBRT) of total dose 30 GY , 3Gy/fraction/10# over 2 weeks ,whereas , in Arm-B patients received total dose of 20 GY in 4Gy/fraction/5# over 1 week. Assessment of improvement in clinical symptoms was done using **BARTHEL'S ADJUSTED DAILY LIVE (ADL)14** Score before treatment, just after treatment and 6 week of treatment and improvement was analysed. At three months follow up , radiological response was carried out by MRI scan of brain. Acute toxicities were assessed during treatment and follow up (up to 90 days post EBRT) using clinical status, laboratory investigations and radiological test and graded according to RTOG/EORTC criteria. **Results:** Significant improvement in terms of ADL score was observed in both arms , however when both arms were compared , no significant difference was found out. There was no statistically significant difference in response or morbidity between the two treatment arms. **Conclusions:** In the palliative setting short duration of treatment with minimum discomfort to the patient is desirable. 20 Gy in 5 fractions is equally effective as 30 Gy in 10 fractions, with slight advantage in terms of toxicity. Thus 20 Gy in 5 fractions can be preferred in brain metastasis patients, especially those with poor performance status.

KEYWORDS

INTRODUCTION

Brain metastases (BM) are the most common kind of intracranial neoplasm that is ahead in terms of count among all the other intracranial tumors diagnosed annually increasing morbidity and mortality in cancer patients.[1] The patients presenting with Brain metastases versus primary neoplasm is 10:1.[2]

Of all the patients with metastatic cancer , 20-40% are diagnosed with brain metastasis at autopsy.[3] Exact incidence is unknown, however, the incidence of BM according to population-based studies range from 8.3 to 14.3 per 100,000 people.[4]

The majority of patients who develop BM have a known primary cancer (metachronous presentation). Most BM have been found to have association with malignancy of lung (40-50%), breast (15-25%), melanoma (5-20%), and kidney (5-10%).[2] Brain metastasis with unknown primary is detected in 5-10% of patients.[5] The uncommon primary site for brain metastasis includes non-melanoma skin cancer, adenocarcinoma of prostate, squamous cell carcinoma of oropharynx.

Around 80% of brain metastases are found to be located in the cerebrum ,whereas, around 15% in the cerebellum ,and in the brainstem in 5% of patients.[5] In recent years, the apparent increase in cases of brain secondaries has been attributed to increased incidence of lung cancer, improved detection by more sensitive imaging techniques, development in anticancer treatment resulting in prolonged survival.[6-8]

The symptomatic presentation of patient with BM is quite similar to symptoms due to any intracranial mass lesion ,including headache (70%), seizures (30-60%), cognitive impairment (30%), papilledema (8%), and miscellaneous focal neurological deficits.[3,9]

The advancing neuroradiology has contributed tremendously to the diagnosis and management of patients with suspected neoplastic diseases of central nervous system (CNS). Although contrast-enhanced magnetic resonance imaging (MRI) is more sensitive than enhanced computed tomography scan in detecting BM, particularly small lesions or metastases situated in the posterior fossa, there is an inclination towards use of CECT due to its easy accessibility and low cost.[10,11]

Patients diagnosed with brain metastases have several potential management options and treatment regimens are dependent on the patient's performance status, age, control of primary cancer, presence of extracranial disease, number of brain metastases, size of brain metastases, and location of brain metastases. Corticosteroids are used to decrease cerebral edema. Dexamethasone is the preferred steroid because of its low mineralocorticoid activity and lesser risk of infection or cognitive impairment. In general, patients with brain metastases have a poor outlook and survive an average of 1 to 2 months when treated with steroid therapy alone. Seizures are treated with anticonvulsant therapy. The lowest effective doses are recommended to minimize possible drug toxicities.

Surgery should be considered for patients who have controlled primary cancer and an expected survival time of at least 3 to 4 months. Radiation therapy has been the foundation of treatment for brain metastasis for decades. The primary goal of radiation therapy is local control of the tumor, symptomatic relief, and possible prolongation of life. Early treatment generally produces a better outcome. 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. WBRT takes advantage of differences in radiobiology between tumor cells and nervous tissue by targeting rapidly dividing tumor cells in all areas of the brain, while minimizing damage to the adjacent brain tissue.[12]

The patients with favorable prognosis, such as a single and small brain metastasis; controlled or no extracranial disease good performance status, and younger age hence good outcome. Acute radiation reactions include skin erythema, headache, hair loss, and general weakness. Possible late radiation complications are neurocognitive deterioration, dementia, leukoencephalopathy, atrophy, and rarely radiation necrosis and hypothyroidism.[2,13]

In view of challenging role of radiotherapy in management of intracranial neoplasms, the aim of this study is to compare the treatment outcomes in patients with two different fractionation schedule of Whole Brain Radiotherapy with multiple brain metastases.

Objectives

- To compare the proportion of cases with clinical symptoms in both groups and pre and post interventional comparison in both groups as per BARTHEL (ADL) criteria.
- To compare toxicities as per the RTOG criteria in both comparison groups and comparison in pre and post interventional group.
- To compare the radiological response as per RECIST criteria in both comparison groups.

METHODS

Study Population

This is a prospective randomised study conducted on newly diagnosed cancer patients with MRI diagnosis of brain metastasis.

The patients included in the study had brain metastases diagnosed based on MRI in case of known primary, an ECOG performance status 0 to 4 and the patients were willing to give informed written consent.

Patients who were excluded from the study were those who had received previous radiotherapy to brain and patients with brain metastases with unknown primary not confirmed by histo/ cytopathological examination.

Radiation Technique

All patients were treated by External beam Radiotherapy on teletherapy Co-60 Machine by 2 lateral opposed fields.

Target volume included whole brain .

All the patients in study arm received a total dose of 20Gy at the rate of 4Gy/# to the whole brain for 5 days a week (Monday-Friday) over 1 week .

Patients in control arm received a total dose of 30 Gy at the rate of 3Gy/# to the whole brain for 5 days a week (Monday-Friday) over 2 weeks .

Medical Management

- Dexamethasone 8mg BD/TDS was given in the form of tablet/ injectable in the beginning of treatment.
- Antiemetics , proton pump inhibitors were given to all patients throughout the treatment period.
- Anti-seizure medication started in patient who presented with seizure or who developed seizure during therapy were started on anti-seizure medications.

Evaluation After Completion Of Treatment And Follow-up

Assessment of improvement in clinical symptoms was done using **BARTHEL'S ADJUSTED DAILY LIVE (ADL)**[14] Score before treatment, just after treatment and 6 week of treatment and improvement was analysed.

Acute toxicities were assessed during treatment and follow up (up to 90 days post EBRT) using clinical status, laboratory investigations and radiological test and graded according to RTOG/EORTC criteria.

RESULTS

The purpose of the study was to evaluate the treatment outcomes in patients of brain metastases with two different fractionation schedules of WBRT. A total of 60 patients were included in the study. Patients' characteristics have been defined in Table 1.

The Barthel ADL score before treatment, just after treatment and after 6 weeks of treatment were documented and symptomatic improvement analysed 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. A 6 weeks follow up Barthel Index was more in control group (92.27) as compared to the study arm (89.27) , but this difference was not found to be statistically significant (p value>0.05). The Pre-treatment Barthel Index mean scores varied in both arms . It was 81.8 ± 10.18 in study arm , whereas , it was 80.53 ± 11.64 in control arm.

The post-treatment Barthel Index scores had increased in both arms , with slightly higher increase in control arm. It was 89.9 ± 8.59 in study arm , and in control arm it was 92.43 ± 6.78.

At 6 weeks follow up , Barthel Index mean scores were found to be slightly elevated in control arm, but statistically insignificant.

At 3 months follow up , radiological response in patients in both arms was assessed by MRI scan of brain. The complete response was almost similar in both arms (~53%). The partial response was seen more in patients of control group in comparison to study arm. The progression of disease was more common in study arm. Though, this difference rate among the two study groups was not statistically significant (p value >0.05)

The acute radiation toxicities were graded according to RTOG criteria , analysis is given in Figure 1-3 . 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.

Table 1 : Patients Characteristics

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Patient's characteristics	Variable	Arm-A (n=30)		Arm-B (n=26)	
		Number	Percentages	Number	Percentages
Age group (years)	<40	6	20	2	6.7
	³40–<50	8	26.7	16	53.3
	³50–<60	12	40	11	36.7
	³60	4	13.3	1	3.3
Sex	Female	13	43.3	16	53.3
	Male	17	56.7	14	46.7
Occupation	Day laborer	8	26.7	10	33.3
	Service-holder	7	23.3	6	20
	Farmer	4	13.3	3	10
	Professional	6	20	6	20
	Others	5	16.7	5	16.7
SE status	Upper	5	16.7	2	6.7
	Upper middle	7	23.33	1	3.3
	Middle	5	16.7	9	30
	Upper lower	6	20	11	36.7
	Lower	7	23.3	7	23.3
Primary	Lung	19	63.33	17	56.7
	Breast	9	30	11	36.7
	Ovary	1	3.3	1	3.3
	Colorectal	1	3.3	0	0
	Kidney	0	0	1	3.3
Histology of primary	Adenocarcinoma	16	53.3	15	50
	Squamous cell carcinoma	9	30	7	23.3
	Others-specify	3	10	5	16.7
	Unknown	2	6.66	3	10
Brain side involved	Bilateral	16	53.33	16	53.3
	Left	7	23.3	12	40
	Right	7	23.3	2	6.7
Supra/infratentorial	Supratentorial	29	96.67	29	96.66
	Infratentorial	1	3.33	1	3.33
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	6.7
Site of brain involved	Frontal	13	24.67	20	66.7
	Parietal	20	51.95	19	63.3
	Temporal	7	3.89	7	23.3
	Occipital	12	19.48	13	43.3
	Cerebellar	0	0	2	3.03

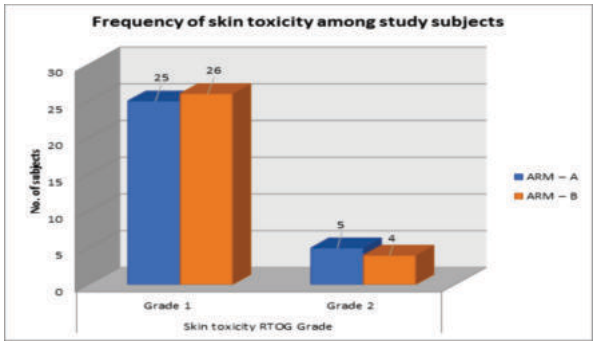

Figure 1: Skin toxicity grading as per RTOG criteria

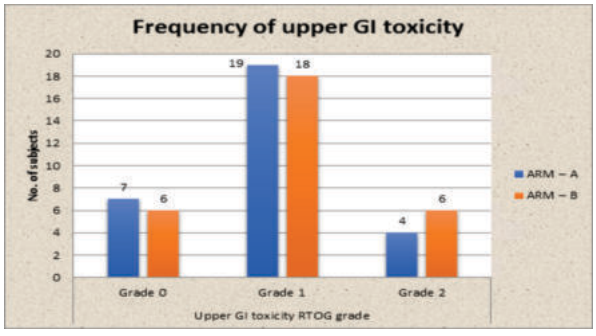

Figure 2: Upper GI toxicity as per RTOG criteria

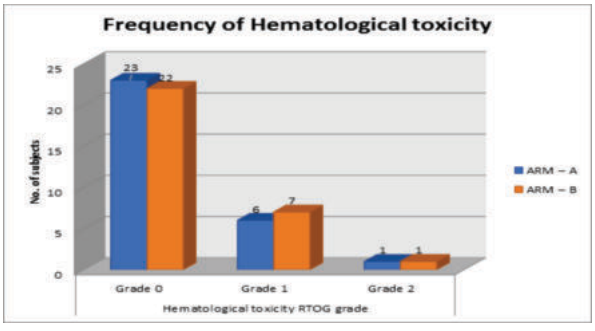

Figure 3 : Haematological toxicity as per RTOG criteria

DISCUSSION

In this study, 60 patients were randomised in two treatment arms . In present study most of the study subjects were aged 40 – 49 years (40%) followed by 50 – 59 years (38.4%). The mean age of subjects in ARM-A was 50.27 ± 9.22 years, while mean age of subjects in ARM-B was 48.57 ± 6.9. Elaimy AL et al[15] however observed that the median patient age was 60 years (29 years to 86 years) at the time of diagnosis. Study by Victor[16] 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 young patients - followed by lymphoma, osteogenic sarcoma, and rhabdomyosarcoma. Germ cell tumors are common in adolescents and young adults between 15 and 21 years.

Among all the patients with metastatic brain tumor included in this study, most common primary was in lung (56.6%), followed by breast (31.7%). Other rare primary tumors were ovary (3.3%), colorectal (1.7%) and kidney (1.7%). In 3 (5%) patients, primary was unknown. Elaimy A L et al [15] observed that non-small-cell lung cancer (NSCLC) was the most common primary tumor histology. Saha A et al [17] found that carcinoma of the lung was the commonest primary that metastasizes to brain i.e. 51.4%, followed by breast.

Among all patients with metastatic brain tumor, frontal lobe involvement was seen in 55% patients, while patietal lobe involvement was seen in 65% patients. Occipital lobe involvement (41.7%) and temporal lobe involvement (23.3%) were relatively less common. Cerebellar involvement was rare (3.3%). No significant difference was seen in any site of involvement among the two study arms. Ghosh M et al [18] observed the distribution of single brain metastases as follows parietal 50.98%, frontal 25.49%, temporal 19.6%, occipital 17.64%, cerebellar 13.72% and others (suprasellar, thalamus) 3.92% . Prajapati J. A. et al [19] observed single metastatic lesion among majority (67%). The anatomical sites of metastatic lesions in brain were cerebrum (78.91%), cerebellum (14.06%), both cerebrum and cerebellum in (6.25%) and skull vault (0.78%). In the cerebrum, most common site was frontal (21.13%) followed by parietal (19.14%), occipital (20.79%) and temporal (17.85%).

Among all patients with metastatic brain tumor, headache (70%) was the most common symptom, followed by vomiting (55%) and neuro-deficit features (36.7%). Visual symptoms were noted in 21.7% patients, while seizure occurred in 23.3% patients. Cerebellar sign was rare (3.3%). Saha et al [17] found that headache was the most common symptom followed by vomiting and neurological deficit. Shatarupa Dutta et al [20] found that headache (73%) and motor weakness were most common presenting symptoms.

In our study, the Barthel ADL score before treatment, just after treatment and after 6 weeks of treatment were documented and symptomatic improvement analysed using repeated measures ANOVA test. This difference was however not statistically significant.The pre-treatment Barthel index was similar in both the groups. Post treatment, Barthel index improved more in ARM B (92.43) as compared to ARM A (89.9).

Radiation Therapy Oncology Group 6901 and RTOG 7361, involving more than 1800 patients, found complete or partial 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.[21,22] In our study , complete response was slightly higher in ARM B (56.6%) as compared to ARM A (53.4%) . Similarly partial response was also higher in ARM B (20%) vs than in ARM A (13.3%) .

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, haematological) during radiotherapy were graded according to RTOG acute toxicity criteria. There were no significant differences in treatment morbidity between the two treatment arms .

CONCLUSION

Radiation treatment is the mainstay for the treatment of patients with symptomatic brain metastases. In the palliative setting short duration of treatment with minimum discomfort to the patient is desirable. 20 Gy in 5 fractions is equally effective as 30 Gy in 10 fractions, with slight advantage in terms of toxicity. Thus 20 Gy in 5 fractions can be preferred in brain metastasis patients, especially those with poor performance status

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