



Effect of Whole-Brain Radiotherapy in Alleviating Symptoms and Improving Quality of life in Patients with Brain Metastases – A Prospective Study

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Abstract

Background and Objectives: Brain metastases are a common complication of cancer, and a cause of significant patient morbidity and mortality. 20-40% of cancer patients will develop metastases to brain in the course of their illness, making them the most common intracranial neoplasm in adults. A prospective observational study was done in the Department of Radiotherapy, Government Medical College Thrissur, with the primary objective of evaluating the symptom burden of the patients with brain metastasis before and after whole brain radiotherapy.

Methods: 64 patients of radiologically proven brain metastasis who satisfied the inclusion criteria were given whole brain radiotherapy with a dose of 30 Gy in 10 fractions over 2 weeks with Cobalt-60 unit. Patients were made to fill a symptom check list comprising of 10 items before radiation and during post radiation follow up at one month.

Conclusion: External beam radiotherapy with dose of 30 Gy in 10 fractions over 2 weeks achieved good palliation in terms of symptom improvement, improvement in performance status, neurological status and quality of life, especially in patients with good performance status and neurological status at presentation.

Keywords: Brain metastasis; whole brain radiotherapy; quality of life.

Introduction

Brain metastases are a common complication of cancer, and a cause of significant patient morbidity and mortality. An estimated 20-40% of cancer patients will develop metastases to brain in the course of their illness,¹ making them the most common intracranial neoplasm in adults. Frequency of brain metastases appears to be on the rise, which may be attributed to superior

imaging modalities, early detection and longer survival after a primary cancer diagnosis due to effective treatment.

The majority of brain metastases originate from one of three primary malignancies: lung cancer (40%–50%), breast cancer (15%–25%), and melanoma (5%–20%).² Their distribution generally parallels blood flow, with 80% occurring in the cerebral hemispheres, 15% in the

cerebellum, and 5% in the brainstem.^{3,4} Common clinical manifestations are headache, vomiting and seizures. Cognitive impairment can be demonstrated in as high as 65% of the patients,^{5,6} which may be due to destruction or displacement of brain tissue by expanding tumor, peritumoral edema leading to further disruption of surrounding white matter tracts, increased intracranial pressure, and/or vascular compromise.

Objectives of the Study

The primary objective of this study is to prospectively evaluate the symptom burden of the patients with brain metastasis before and after whole brain radiotherapy.

Secondary objectives:

1. To assess observer-rated changes in performance and neurological status after whole brain radiotherapy.
2. To assess the quality of life of the patients before, during and after radiotherapy.

Materials and Methods

Study Design: Single arm prospective observational study

Study Setting: Hospital based observational study conducted in the Department of Radiotherapy, Medical College Chest Hospital, Thrissur.

Study Population

Inclusion Criteria

1. Radiologically diagnosed brain metastases using brain CT or MRI
2. Signed informed consent to participate in the study

Exclusion Criteria

1. Non consenting patients
2. Significant speech or cognitive impairment preventing the patient from completing the questionnaire
3. Previous whole brain radiotherapy
4. Brain metastases from haematological malignancies

Study Period: One and a half year

Sample Size

Sample size was calculated using the formula $4pd/d^2$ at significance level 0.05 and power 80%.

p is the percentage of patients who achieved symptomatic improvement in a study conducted by Bilimaga et al. in the department of radiotherapy, M.S Ramaiah medical College, Bangalore.

$q = 100-p$, $d=20\%$ of p (20% is the maximum allowed error)

Considering p in terms of improvement in presenting symptoms, $p = 88\%$, $n = 18$. Additional 10 was included to allow for expected dropouts because of the poor prognosis in these patients.

After the target accrual was achieved, patients were again recruited until the completion of study period to improve precision. Total of 64 patients who fulfilled the inclusion criteria were included in the study.

Study Tools

- Proforma
- Informed consent
- CT/MRI for diagnosis of brain metastasis
- ECOG performance scale
- Medical Research Council (MRC) neurological function evaluation scale
- ECOG QLQ – C30 questionnaire
- ECOG QLQ – BN 20 questionnaire

Methodology

Patients who meet the inclusion criteria will be made to fill a symptom checklist consisting of 10 items (appendix 1) before the start of radiation. 8 items (headache, nausea, vomiting, leg weakness, arm/hand weakness, balance problems, difficulty of walking, and speech disorders) are expected side effects of increased intracranial tension.

Radiotherapy

Whole brain radiotherapy was given by external beam radiation with megavoltage beams on telecobalt machine using two opposing lateral fields with a total dose of 30 Gy in 10 fractions, 2 Gy per fraction, 5 fractions per week.

Simulation was done in supine position with a neck rest. Immobilization is achieved using a custom mask.

All patients were given steroids and anti-edema measures which were gradually tapered and stopped. Anti seizure medications and other supportive measures were given as required.

At the one month follow up visit after radiotherapy, patients were asked to complete the same symptom checklist. Performance and neurological status will be assessed. Values before and after radiation were compared.

Data Analysis: Data will be analyzed statistically.

Results and Analysis: Of the patients with brain metastases who underwent Whole Brain

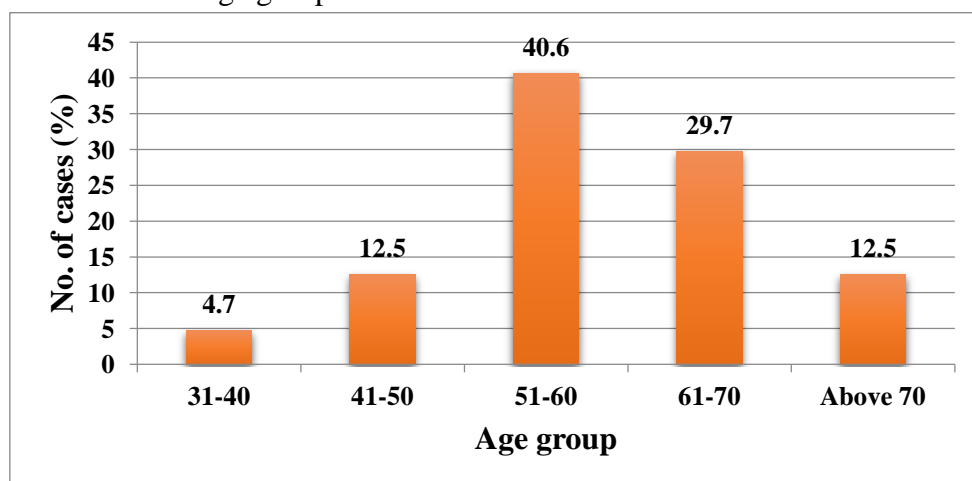
Radiotherapy in the Department of Radiotherapy, Government medical College Thrissur during the 1.5 years of study period, 64 patients satisfied the inclusion criteria and was included in the study with their consent.

Of the total 66 patients recruited, 62 patients completed the planned treatment. 2 patients died during RT. 2 patients died before the one month follow up.

Personal Profile

Age: Age of the patients ranges in between 32 to 90 with mean age 59.06 and standard deviation 11.52. Age wise distribution is shown in the table. Majority of the patients were in the age group of 51-60 (40.6%).

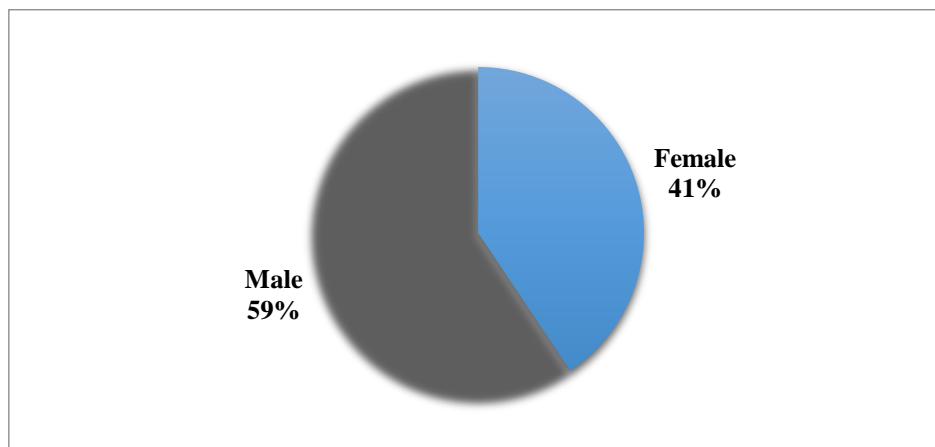
Figure 1 Distribution based on age group



Gender

In the study group, 38 patients were males (59.4%) and 26 patients were females (40.6%).

Figure 2 Gender wise Distribution



Performance Status

Among the study population, 8 patients (12.5%) belonged to ECOG performance status 4, 19 patients (29.6%) belonged to ECOG performance status 3, 30 patients (46.8%) belonged to performance status 2, 5 patients (7.8%) belonged to ECOG performance status 1 and 2 patients (3.12%) belonged to ECOG performance status 0.

Performance status

ECOG PS	Frequency	Percent
0	2	3.12
1	5	7.8
2	30	46.8
3	19	29.6
4	8	12.5
Total	64	100.0

Primary tumour

Most common site of primary tumour among the study population was Lung (43.8%), followed by breast (31.3%). Other primary sites were colon (9.3%), rectum (4.7%), stomach (3.1%), RCC (1.6%), Melanoma (1.6%), and Larynx (1.6%). In 2 patients (3.1%), the primary site was unknown.

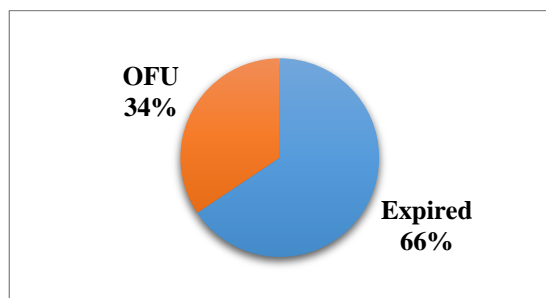
Primary tumour

Primary	Frequency	Percent
Lung	28	43.8
Breast	20	31.3
Colon	6	9.3
Rectum	3	4.7
Stomach	2	3.1
Unknown primary	2	3.1
RCC	1	1.6
Larynx	1	1.6
Malignant Melanoma	1	1.6
Total	64	100.0

Present status

In the total study population, 42 subjects died and 22 were alive at the time of closure of study.

Figure 3 Status



OFU – On follow up

Improvement in Symptoms

1. Headache

Severity	Before RT		After RT	
	Freq	Per cent	Freq	Per cent
0	26	43.3	45	75.0
1	14	23.3	11	18.3
2	17	28.3	4	6.7
3	3	5.0		
Total	60	100	60	100

Of the 60 patients who completed treatment and were available for post RT follow up, 34 patients (57 %) had headache, making it the most common presenting symptom. 12 patients (23.3%) had mild headache, 17 patients (28.3%) had moderate headache and 3 patients (5%) had severe headache.

At the one month post RT follow up, 28 patients (82%) had improvement in their symptoms.

2. Nausea

Severity	Before RT		After RT	
	Freq	Per cent	Freq	Per cent
0	30	50.0	47	78.3
1	18	30.0	9	15.0
2	8	13.3	4	6.7
3	4	6.7		
Total	60	100	60	100

Of the 60 patients who completed treatment and were available for post RT follow up, 30 patients (50%) had nausea on presentation. 18 patients (30 %) had mild nausea, 8 patients (13.3%) had moderate nausea and 4 patients (6.7%) had severe nausea.

At one month post RT follow up, 25 patients (83%) had improvement in nausea.

3. Vomiting

Severity	Before		After	
	Freq	Per cent	Freq	Per cent
0	29	48.3	55	91.7
1	19	31.7	5	8.3
2	11	18.3		
3	1	1.7		
Total	60	100	60	100

Of the 60 patients who completed treatment and were available for post RT follow up, 31 patients (51.7%) had vomiting on presentation. 19 patients

(31.7%) had mild vomiting, 11 patients (18.3%) had moderate vomiting and 1 patient (1.7%) had severe vomiting.

At one month post RT follow up, 26 patients (84%) had improvement in vomiting

4. Seizures

Severity	Before RT		After RT	
	Freq	Per cent	Freq	Per cent
0	37	61.7	52	86.7
1	15	25.0	7	11.7
2	8	13.3	1	1.7
Total	60	100	60	100

Of the 60 patients who completed treatment and were available for post RT follow up, 23 patients (38.3%) had seizures on presentation. 15 patients (25%) had mild symptoms and 8 patients (13.3%) had moderate symptoms.

At one month post RT follow up, 18 patients (78%) had improvement in the severity of seizures.

5. Visual problems

Of the 60 patients who completed treatment and were available for post RT follow up, 8 patients (13.3%) had seizures on presentation. 1 patient (1.7%) had mild symptoms and 7 patients (11.3%) had moderate symptoms.

At one month post RT follow up, 7 patients (87.5%) had improvement in the visual problems.

6. Leg Weakness

Of the 60 patients who completed treatment and were available for post RT follow up, 13 patients (21.6%) had weakness of legs on presentation. 8 patients (13.3%) had moderate weakness and 5 patients (8.3%) had severe weakness.

At one month post RT follow up, 2 patients (25%) had improvement in the severity of symptoms.

7. Arm Weakness

Of the 60 patients who completed treatment and were available for post RT follow up, 7 patients (11.6%) had weakness of arms on presentation. 4 patients (6.7%) had moderate weakness and 3 patients (5%) had severe weakness.

At one month post RT follow up, 3 patients (43%) had improvement in the severity of symptoms.

8. Balance problems

Of the 60 patients who completed treatment and were available for post RT follow up, 4 patients (6.6%) had balance problems on presentation. 3 patients (5%) had moderate symptoms and 1 patient (1.7%) had severe symptoms.

At one month post RT follow up, 3 patients (75%) had improvement in the severity of symptoms.

9. Walking Difficulty

Of the 60 patients who completed treatment and were available for post RT follow up, 14 patients (23.3%) had difficulty in walking due to various reasons on presentation. 9 patients (15%) had moderate symptoms and 5 patients (8.3%) had severe symptoms.

At one month post RT follow up, 3 patients (21.4%) had improvement in the severity of symptoms.

10. Speech Problems

Of the 60 patients who completed treatment and were available for post RT follow up, 3 patients (5%) had speech problems on presentation. 1 patient (1.7%) had moderate symptoms and 2 patients (3.3%) had severe symptoms.

At one month post RT follow up, 1 patient (33%) had improvement in the severity of symptoms.

11. Neurological status

60 patients completed treatment and were available for post RT follow up. Among them, 39 patients had neurological dysfunction at presentation. After RT, 25 patients (64%) had improvement in the neurological status.

12. Performance status

60 patients completed treatment and were available for post RT follow up. Among them, 58 patients had impaired performance status at presentation. After RT, 39 patients (67.2%) had improvement in the performance status.

Improvement in Symptoms vs. Primary Cross Tabulation

Primary	No. of Subjects	Improvement		No Improvement	
		Freq	Per cent	Freq	Per cent
Lung	25	13	52	12	48
Breast	20	18	90	2	10
Colon	5	5	100	-	-
Rectum	3	3	100	-	-
Stomach	2	1	50	1	50
Unknown primary	2	2	100	-	-
RCC	1	1	100	-	-
Larynx	1	1	100	-	-
Malignant Melanoma	1	1	100	-	-
Total	60	45	75	15	25

- Of the 25 subjects who had a lung primary, 13 subjects (52%) had improvement in symptoms post RT.
- Of the 20 subjects who had a breast primary, 18 subjects (90%) had improvement in symptoms post RT.
- Of the 2 subjects who had a stomach primary, 1 subject (50%) had improvement in symptoms post RT.
- Subjects with all other primary diseases were observed to have some improvement with RT

Improvement in Symptoms vs. Performance status

Percentages of patients who attained symptomatic improvement of patients in each ECOG performance status are:

- PS 0: 100%
- PS 1: 100%
- PS 2: 96.6%
- PS 3: 52.9%
- PS 4: 0%

Improvement in Symptoms vs. MRC Grade

Percentages of patients who attained symptomatic improvement of patients in each MRC Grade are:

- 1: 100%
- 2: 81%
- 3: 61.5%
- 4: 0%

Quality of Life Assessment

Comparison of global health status (QL2) before, during and after RT

Dimension	Before		During		After		Chi square value
	Mean	SD	Mean	SD	Mean	SD	
QL2	7.57 ^a	1.59	7.57 ^b	1.59	8.55 ^c	2.48	48.8**

The global health status remained the same mostly during treatment followed by an increase after treatment. p value of the comparison between pre

and post treatment being <0.01 indicates that there is significant increase in the global health status after treatment.

Comparison of physical functioning (PF2) before, during and after RT

Dimension	Before		During		After		Chi square value
	Mean	SD	Mean	SD	Mean	SD	
PF2	12.32 ^a	4.62	12.32 ^b	4.62	11.92 ^c	4.79	26.5**

There is as a significant improvement in the physical functioning of the patients after RT. Worsening of the physical functioning during RT could be prevented, probably due to the use of anti

edema measures during RT. p value of the comparison between pre and post treatment being <0.01 indicates that there is significant increase in the physical functioning after treatment.

Comparison of role functioning (RF2) before, during and after RT

As expected, there is a decline in the role functioning during radiotherapy. However the general trend is of an improved role functioning after radiation. p value of the comparison between pre and post treatment being <0.01 indicates that there is significant increase in the role functioning after treatment.

Comparison of emotional functioning (EF) before, during and after RT

As with role functioning, there is a decline in the emotional functioning during radiotherapy, which is expected. However the general trend is of an improved emotional functioning after radiation. p value of the comparison between pre and post treatment being <0.01 indicates that there is significant increase in the emotional functioning after treatment.

Comparison of cognitive functioning (CF) before, during and after RT

Worsening of cognitive functioning during RT was prevented in general, by the use of anti edema measures and other supportive medications. There was a general improvement in the cognitive functioning post RT, which was significant with a p value <0.01

Comparison of social functioning (SF) before, during and after RT

Social functioning also showed a significant improvement post RT with a p value of less than 0.01

Comparison of fatigue (FA) before, during and after RT

Fatigue was increased among patients during radiotherapy and decreased post RT. The values were significant with a p value <0.01

Comparison of nausea and vomiting (NV) before, during and after RT

There was a significant improvement of nausea and vomiting during RT, probably due to the use of anti edema measures and anti emetic drugs. As a general trend, nausea and vomiting showed further improvement in post RT follow up.

Comparison of pain (PA) before, during and after RT

There was no significant difference in pain during or after RT. The slight decrease accounts for the control of head ache, but that was not significant, as the treatment did not alter the primary disease status, which was the major cause of pain in majority of the patients.

Comparison of dyspnoea (DY) before, during and after RT

There was no significant change in dyspnoea during or after RT.

Comparison of sleep (SL) before, during and after RT

Patients in general had sleep disturbances during radiotherapy which improved after RT. In general, patients had better sleep post RT compared to the pre RT status.

Comparison of appetite (AP) before, during and after RT

In general, patients had increased appetite during RT, which further improved after RT, which may be due to the symptomatic relief with RT.

Comparison of constipation (CO) before, during and after RT

There was no significant change in constipation among patients.

Comparison of diarrhoea (DI) before, during and after RT

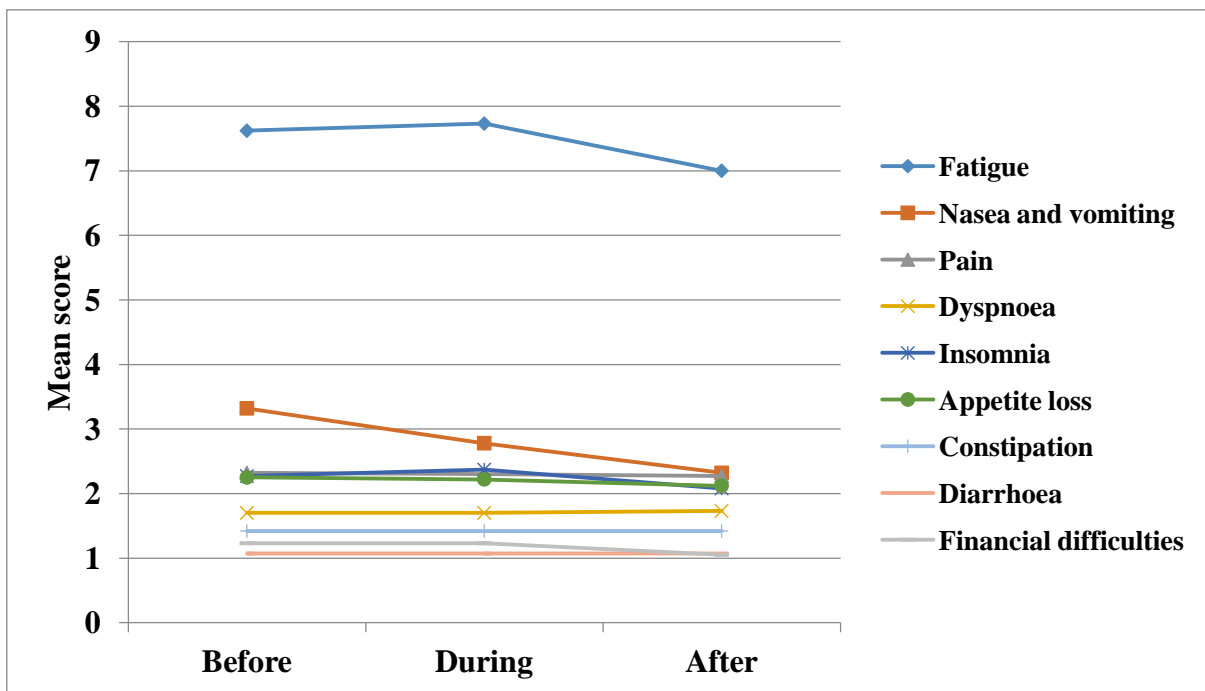
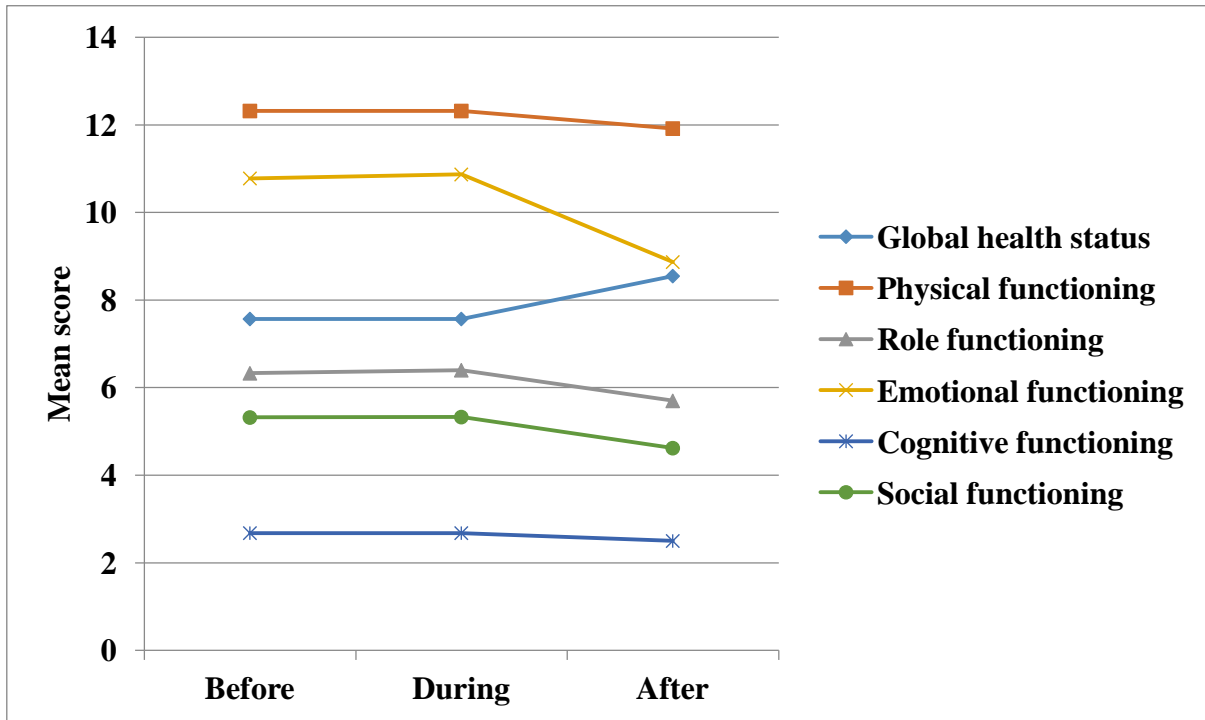
There was no significant change in constipation among patients.

Comparison of financial difficulties (FI) before, during and after RT

Since most of the patients were offered treatment under government provided schemes, there was not a significant increase in financial difficulties during treatment in general. Once the hospital stay finished, most of the patients had decreased financial difficulties probably due to a decrease in symptoms.

For the comparisons of dimensions of QL between different measurements was done by using Friedman's test followed by Wilcoxon signed rank test.

Comparison functional status before, during and after RT



Disease Specific Quality of Life Assessment
Comparison of future uncertainty (BNFU)
before, during and after RT

Feeling of future uncertainty increased during treatment as expected which improved post RT. In general, the post RT values show significant improvement compared to the pre RT values.

Dimension	Before		During		After		Chi square value	p-value
	Mean	SD	Mean	SD	Mean	SD		
BNFU	11.38 ^a	1.37	11.45 ^a	1.44	10.63 ^b	1.63	44.17**	< 0.01

Comparison of visual disorder (BNVD) before, during and after RT

Visual disorders in general remained the same during treatment which showed a significant improvement after radiotherapy, with a significant p value of <0.01

Comparison of motor dysfunction (BNMD) before, during and after RT

Motor disorders also showed improvement in general, post RT, although to a lesser extent when compared to other parameters which showed improvement.

Comparison of communication deficit (BNCD) before, during and after RT

WBRT failed to produce any significant improvement in the communication deficit in the study subjects during RT or at the 1 month post RT follow up.

Comparison of headache (BNHA) before, during and after RT

Headache, which was the most common symptom among the study subjects showed a significant improvement during RT. Further improvement was seen during the 1 month post RT follow up.

Dimension	Before		During		After		Chi square value	p-value
	Mean	SD	Mean	SD	Mean	SD		
BNHA	1.68 ^a	0.77	1.22 ^b	0.49	1.12 ^c	0.37	51.93**	< 0.01

Comparison of seizures (BNSE) before, during and after RT

Seizures also showed an improvement during RT, which was further improved on the post RT follow up.

Dimension	Before		During		After		Chi square value	p-value
	Mean	SD	Mean	SD	Mean	SD		
BNSE	1.50 ^a	0.81	1.10 ^b	0.30	1.10 ^c	0.30	34.00**	< 0.01

Comparison of drowsiness (BNDR) before, during and after RT

Drowsiness was increased during radiation as expected but was later improved significantly by

the time of first follow up, with a significant p value of <0.01

Dimension	Before		During		After		Chi square value	p-value
	Mean	SD	Mean	SD	Mean	SD		
BNDR	1.45 ^a	0.50	1.58 ^a	0.50	1.22 ^c	0.42	26.57**	< 0.01

Comparison of itchy skin (BNIS) before, during and after RT

Itchy skin was seen during RT as a complication in most of the patients. Although it decreased post

RT, the symptom was significantly higher when compared to the pre RT status.

Dimension	Before		During		After		Chi square value	p-value
	Mean	SD	Mean	SD	Mean	SD		
BNIS	1.00 ^a	0.00	1.77 ^b	0.43	1.28 ^c	0.45	67.61**	< 0.001

Comparison of hair loss (BNHL) before, during and after RT

Hair loss, which is an acute complication of WBRT occurred in most of the patients during and

after RT, the occurrence being significant with a p value of <0.01

Dimension	Before		During		After		Chi square value	p-value
	Mean	SD	Mean	SD	Mean	SD		
BNHL	1.82 ^a	0.39	2.93 ^b	0.31	2.03 ^c	0.61	90.62**	< 0.01

Comparison of weakness of legs (BNWL) before, during and after RT

Weakness of legs failed to show any significant improvement among subjects who underwent WBRT.

Dimension	Before		During		After		Chi square value	p-value
	Mean	SD	Mean	SD	Mean	SD		
BNWL	1.40	0.79	1.40	0.79	1.38	0.74	0.67 ^{ns}	0.717

Comparison of bladder control (BNBC) before, during and after RT

Like in limb weakness, bladder control also did not show any significant difference with WBRT.

Dimension	Before		During		After		Chi square value	p-value
	Mean	SD	Mean	SD	Mean	SD		
BNBC	1.03	0.18	1.03	0.18	1.05	0.22	2.00 ^{ns}	0.368

Conclusion

External beam radiotherapy with dose of 30 Gy in 10 fractions over 2 weeks achieved good palliation in terms of symptom improvement, improvement in performance status and neurological status.

In the present study, 75% of the patients achieved some improvement in the presenting symptoms. The improvement was more evident in patients with good performance status and neurological status at presentation. Whole brain radiotherapy was also generally well tolerated, with adequate supportive care.

Whole brain radiotherapy also produced an improved quality of life among the study subjects, especially in patients with good performance status and neurological function at presentation.

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