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Comparative Study of Whole Brain Radiotherapy vs Whole Brain Radiotherapy with Concurrent Temozolomide in Brain Metastases

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Abstract: *Background*: Brain metastases are secondary tumors that develop from primary malignant tumors located outside the central nervous system. It is the most common kind of intracranial tumor in adults. Brain metastases are treated with both decisive anticancer therapy and supportive care. *Objective*: To compare the efficacy of whole brain radiotherapy versus concurrent whole brain radiotherapy with Temozolomide in the treatment of brain metastases. *Method*: This quasi-experimental study was conducted in the department of Oncology in Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajganj among 68 patients from December 2018 to June 2020. Patients who attended the KYAMCH Oncology department during the study period and met the selection criteria were enrolled in the study. *Results*: In Arm A, the mean age was 56.15±10.14 years and in Arm B, the mean age was 54.06±10.24 years. Karnofsky Performance Status of most of the patients was 70 or above in both arms, which was 25 (73.50%) and 26 (76.50%) in Arm A and Arm B respectively. In Arm A, the most common primary tumor site was lung 17 (50%) and in Arm B, it was lung 18 (52.94%). In Arm A, the most common clinical feature was headache 21 (61.80%) and In Arm B, 20 (58.80%) patients too presented with headache. In Arm A, before treatment 5 (14.70%) patients had convulsion. In Arm B, before treatment 6 (17.60%) patients had convulsion. After treatment convulsion was found in 2 (5.90%) patients. The response was more in Arm B. The most common non- hematological toxicity was nausea, which developed in 17 (50%) patients in Arm A and 22 (64.70%) patients in Arm B. Though non- hematological toxicities were more in Arm B, it was not statistically significant. Thrombocytopenia was reported in 11 (32.35%) patients in Arm A and 20 (58.82%). In Arm A, CR was observed in 02 (05.90%) patients and in Arm B, CR was observed in 05 (14.70%) patients. Statistically significant radiological responses were achieved in the WBRT+TMZ arm compared to the WBRT alone arm. Adenocarcinoma overall response was achieved in 6 (17.64%) patients in Arm A and 12 (35.29%) patients in Arm B. *Conclusion*: After analyzing the result of the study it can be concluded that the efficacy of concurrent radiotherapy with Temozolomide is higher than that of radiotherapy alone in the treatment of brain metastases. The combined treatment protocol significantly improves the symptoms and signs with acceptable toxicity profile.

Keywords: Metastases, Radiotherapy, Temozolomide

1. Introduction

Brain metastases are secondary tumors that arise from original malignant tumors outside of the central nervous system. It is the most prevalent intracranial tumor form among adults [1]. The estimated incidence of newly diagnosed brain metastases in the United States is greater than 170,000 per year, and the rate of metastatic brain tumors is 10 times that of original brain tumors [2, 3].

The majority of brain metastases arise from lung (40-50%), breast (15-25%), renal (5-10%), skin (5-20%), colorectal (4-6%), and in 5-10% of cases, unknown source tumors [4, 5]. It has been observed that lung cancer is the leading source of brain metastases [6]. Less frequently do cerebral metastases manifest as early symptoms, and more than 80 percent of metastases are identified after the diagnosis of original tumors [7]. In a developing country like ours, the advanced state of disease upon presentation is mostly due to low literacy rates, poor socioeconomic status of patients, and ignorance about the disease and its complications [8].

The clinical manifestations of brain metastases are comparable to those of other intracranial space-occupying lesions, including headache (70%), convulsions (30%-60%), cognitive impairment (30%), papilledema (8%), vomiting, and focal neurological impairments [9]. The patient with severe neurological symptoms and brain metastases has a poor prognosis and a limited survival time [10].

The early detection of brain metastases is growing as a result of advances in imaging technologies. Contrast-enhanced computed tomography (CT) is frequently utilized as a first-line screening modality, while contrast-enhanced magnetic resonance imaging (MRI) is the preferred imaging modality for BM detection in clinical practice [11]. Some advanced MRI biomarkers, such as magnetic resonance spectroscopy (MRS), magnetic resonance perfusion (MRP), diffusion-weighted imaging (DWI), and diffusion tensor imaging (DTI), have the potential to improve the management of brain metastases, from early detection and diagnosis to treatment response evaluation [12].

The majority of metastases in the brain are parenchymal. Metastases may also spread to the cranium, dura, leptomeninges, and rarely to the pituitary gland, pineal gland, or choroid plexus [13]. Approximately 80% of brain metastases are found in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem [4]. In the brain, metastases are most frequently seen at the confluence of gray and white matter and at the borders of major artery and vascular areas [14]. Certain cancers, including uterine, prostate, and gastrointestinal primary tumors, can metastasis to the posterior fossa because these primary tumors obtain access to the CNS via the posterior circulation [15].

The primary objective of treatment for patients with brain metastases is to control the disease in the brain, prevent neurological impairments, and give an acceptable quality of life (QOL) [16]. Therapeutic options are restricted and dependent on various variables, including tumor histology, primary disease status, number of brain lesions, lesion size, and performance status, among others [17]. The Radiation Therapy Oncology Group (RTOG) categorized patients into three groups based on Karnofsky Performance Status (KPS), primary tumor status, the occurrence of extra-cranial metastases, and age using recursive partitioning analysis (RPA). Patients with a high KPS (70), a well-controlled main tumor, and the absence of extracranial metastases are thought to have a better prognosis [18].

The treatment of brain metastases comprises both definitive antitumor treatment and supportive care. Corticosteroids are used to alleviate neurological symptoms as part of symptomatic treatment, and anticonvulsants are provided as necessary (Soffietti et al. 2017) [19]. The optimum treatment approach for patients with a single brain metastasis is surgery and radiosurgery [20]. However, solitary metastases are uncommon, and the recommended treatment for individuals with large or multiple lesions (>4) is Whole Brain Radiotherapy (WBRT) [21]. The treatment of brain metastases with WBRT improves neurologic function in the majority of patients with a median survival of four to six months, according to RTOG phase III trials. There was no difference in survival between various dose groups, including regular fractionation (30 Gy in 10 daily fractions) and accelerated hyperfractionation (1.6 Gy twice daily to 54.4 Gy) [22]. Patients with brain metastases may experience a reduction in neurological symptoms, an improvement in quality of life, and a lengthening of their survival time, according to certain researchers [23, 24].

The relevance of systemic chemotherapy in the treatment of brain metastases remains unclear. Chemotherapeutic drugs' efficacy is primarily determined by their sensitivity to primary tumors and their ability to pass the blood-brain barrier [25]. It is considered that the restricted ability of most chemotherapeutic drugs to pass the blood-brain barrier is one of the primary reasons why they are less effective against central nervous system diseases [26]. Temozolomide (TMZ) is a novel oral alkylating drug of the imidazotetrazine series that has exhibited anticancer potential against a range of solid malignancies [27, 28]. The clinical activity of TMZ is correlated with the activity of O6-alkylguanine-DNA alkyltransferase, a DNA repair enzyme that eliminates DNA damage induced by methylation at the O6 position of guanine [28]. TMZ has an exceptional ability to cross the blood-brain barrier and reaches therapeutic concentrations in the brain [25]. TMZ's primary adverse effect is myelosuppression, however it is treatable in the majority of patients [7].

Recent phase II research suggests that TMZ is safe and dramatically increases the overall response rate (ORR) when used with WBRT [29]. [30] According to another study, the concurrent use of WBRT and TMZ dramatically improves neurological functions and quality of life. Cao et al. (2015) found non-significant improvement in local control of brain metastases in WBRT with TMZ-treated patients. Several studies [31, 32] indicated a substantial difference in adverse effects between individuals treated with WBRT plus TMZ and

those treated with WBRT alone. LV et al. (2018) discovered no significant differences between the two groups in terms of toxicity [33].

There is a great deal of heterogeneity in the treatment outcomes of BM in studies conducted by researchers from throughout the world. However, there are very few published statistics on this topic in Bangladesh. The purpose of this study is to examine the effectiveness of TMZ administered concurrently with WBRT with WBRT alone in the treatment of patients with brain metastases.

2. Objective

To compare the efficacy of whole brain radiotherapy versus concurrent whole brain radiotherapy with Temozolomide in the treatment of brain metastases.

3. Methods and Materials

This quasi-experimental studywas conducted in the department of Oncology in Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajganj from December 2018 to June 2020. Patients who attended the KYAMCH Oncology department during the study period and met the selection criteria were enrolled in the study. The research work was carried out after obtaining ethical clearance from the Institutional Review Board of KYAMCH. Purposive sampling technique was followed in this study. A total of 79 patients were selected from the KYAMCH from December 2018 to June 2020. After assessment for eligibility, 11 patients were excluded and a total of 68 patients were included in the study according to selection criteria. The first patient was selected for Arm A by lottery, then the next patient for Arm B and so on.

3.1. Inclusion Criteria

1. Age: 18 to 70 years.
2. Sex: both male and female.
3. Cytology/Histology proven primary cancer with radiological evidence of multiple brain metastases.
4. The metastatic lesion not suitable for surgery or radiosurgery.
5. Karnofsky Performance Status >50.

3.2. Exclusion Criteria

1. Chemotherapy received in previous 3 weeks.
2. Patients who had received prior radiotherapy for brain metastases.
3. Severely ill.
4. Pregnancy or lactating woman.

3.3. Data Collection and Analysis

A structured data collection form was the research instrument. After selecting the patients, written informed consent was taken from each patient before his/her participation in the study. History was documented according to the prescribed data-sheet. Findings of observation were recorded in the prescribed data collection form. The possibility of bias in the study was acknowledged and kept limited as much as possible. Data analysis was done according to the objectives of the study by using the SPSS (Statistical Package for Social Science) Software program version 24.0 for Windows, available in the institute. The analysis was done either by the Z-test or chi-square test to compare the response and the toxicities of treatment in both arms. The results were presented in tables and figures. The p-value of less than 0.05 was taken as significant.

4. Results

In Arm A, the age range was 38-70 years with mean age 56.15±10.14 years and in Arm B, the age range was 36-70 years with mean age 54.06±10.24 years. The number of patients was more in the 61-70 year age group in both arms. (Figure 1)

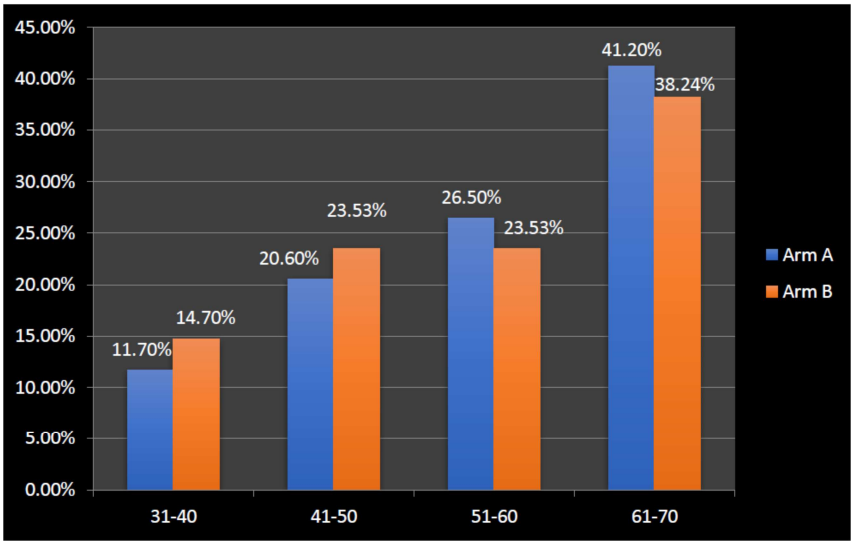

Figure 1. *Distribution of the patients according to age (N=68).*

The number of male patients was more in both arms, which is 24 (70.60%) in Arm A and 27 (79.40%) in Arm B. (Figure 2)

Karnofsky Performance Status of most of the patients was 70 or above in both arms, which was 25 (73.50%) and 26 (76.50%) in Arm A and Arm B respectively. KPS below 70 was found in 9 (26.5%) and 8 (23.5%) patients in Arm A and Arm B, respectively.

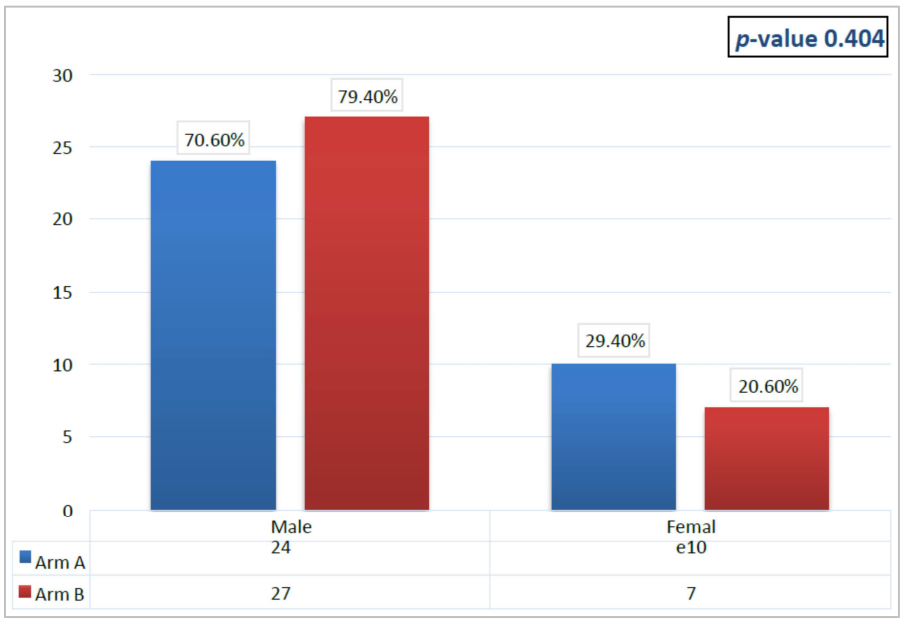

Figure 2. *Distribution of the patients according to gender (N=68).*

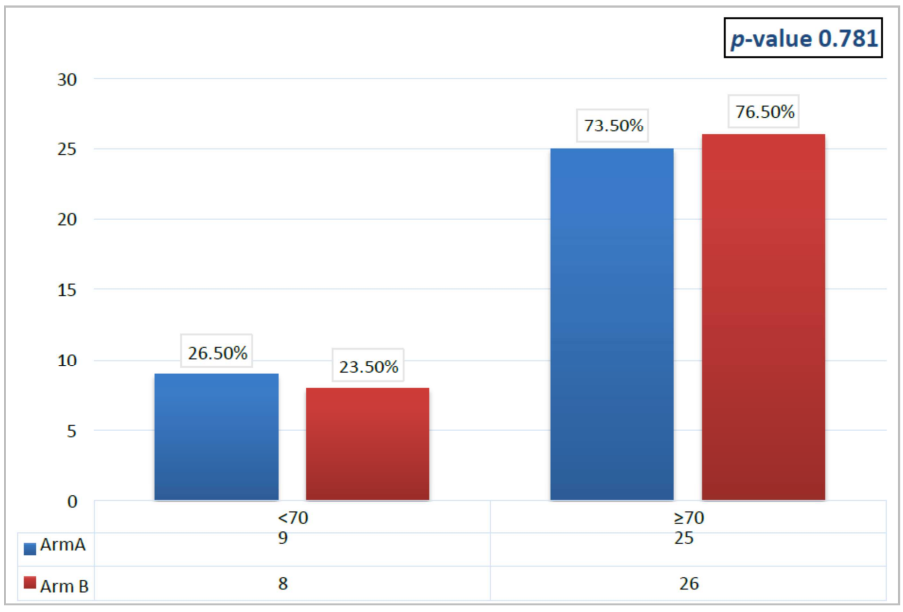

Figure 3. *Distribution of the patients according to Karn of sky Performance Status (N=68).*

In Arm A, among 34 patients most common primary tumor site was lung 17 (50%) followed by breast 7 (20.59%), colorectal 5 (14.71%), kidney 2 (5.88%), skin 1 (2.94%), thyroid 1 (2.94%), gall bladder 1 (2.94%). In Arm B, it waslung 18 (52.94%), breast 7 (20.59%), colorectal 4 (11.77%), kidney 2 (5.88%), skin 1 (2.94%), thyroid 1 (2.94%), gall bladder 1 (2.94%). (Table 1)

Table 1. *Distribution of the patients according to the primary tumor site (N=68).*

Site of Tumor	Arm A	Arm B	P- Value
Lung Breast	17 (50%) 7 (20.59%),	18 (52.94%) 7 (20.59%)	0.811

Site of Tumor	Arm A	Arm B	P- Value
Colorectal	5 (14.71%)	4 (11.77%)	
Kidney	2 (5.88%)	2 (5.88%	
Skin	1 (2.94%)	1 (2.94%)	
Thyroid	1 (2.94%)	1 (2.94%)	
Gall bladder	1 (2.94%)	1 (2.94%)	

The table shows that the patients presented with various clinical features. In Arm A, the most common clinical feature was headache 21 (61.80%), followed by cognitive impairment 15 (44.10%), focal weakness 11 (32.40%), convulsion 5 (14.70%), speech difficulty 3 (8.80%), ataxia 2 (5.90%). In Arm B, 20 (58.80%) patients presented ith headache, 15 (44.10%) with cognitive impairment, 13 (38.20%) with focal weakness, 6 (17.60%) with convulsion, 4 (11.80%) with speech difficulty, 3 (8.80%) with ataxia. (Table 2)

Table 2. *Distribution of the patients according to the clinical presentation (N=68).*

Clinical presentation	Arm A (n=34) n (%)	Arm B (n=34) n (%)	Z-test	*p*-value
Headache	21 (61.80%)	20 (58.80%)	0.121	1.000
Cognitive impairment	15 (44.10%)	15 (44.10%)	0.121	1.000
Focal weakness	11 (32.40%)	13 (38.20%)	0.243	1.000
Convulsion	05 (14.70%)	06 (17.60%)	0.121	1.000
Speech difficulty	03 (08.80%)	04 (11.80%)	0.121	1.000
Ataxia	02 (05.90%)	03 (08.80%)	0.121	1.000

In Arm A, before treatment 21 (61.80%) patients had headache. Whereas after treatment headache was found in 15 (44.10%) patients. In Arm B, before treatment 20 (58.80%) patients had headache. After treatment (9th week after completion of treatment) headache was found in 6 (17.65%) patients. The response was more in Arm B and it was statistically significant. In Arm A, before treatment 15 (44.10%) patients had cognitive impairment. Whereas after treatment cognitive impairment was found in 11 (32.45%) patients. In Arm B, before treatment 15 (44.10%) patients had cognitive impairment. After treatment (9th week after completion of treatment) cognitive impairment was found in 4 (11.76%) patients. The response was more in Arm B and it was statistically significant. In Arm A, before treatment 11 (32.40%) patients had focal weakness. Whereas after treatment focal weakness was found in 7 (20.60%) patients. In Arm B, before treatment 13 (38.20%) patients had focal weakness. After treatment (9th week after completion of treatment) focal weakness was found in 5 (14.70%) patients. The response was more in Arm B, but it was not statistically significant. In Arm A, before treatment 3 (8.80%) patients had speech difficulty. Whereas after treatment speech difficulty was found in 2 (5.90%) patients. In Arm B, before treatment 4 (11.80%) patients had speech difficulty. After treatment (9th week after completion of treatment) speech difficulty was found in 1 (2.90%) patients. The response was more in Arm B, but it was not statistically significant. In Arm A, before treatment 2 (5.90%) patients had ataxia. Whereas after treatment ataxia was found in 1 (2.90%) patients. In Arm B, before treatment 3 (8.80%) patients had ataxia. After treatment (9th week after completion of treatment) ataxia was found in 1 (2.90%) patients. The response was more in Arm B, but it was not statistically significant.

In Arm A, before treatment 5 (14.70%) patients had convulsion. Whereas after treatment convulsion was found in 3 (8.80%) patients. In Arm B, before treatment 6 (17.60%) patients had convulsion. After treatment (9th week after completion of treatment) convulsion was found in 2 (5.90%) patients. The response was more in Arm B, but was not statistically significant. (Table 3).

Table 3. *Distribution of the patients according to the clinical outcome (N=68).*

Variable	Arm A (n=34)		Arm B (n=34)		Z-test	*p*-value
	Pre treatment n (%)	Post treatment n (%)	Pre treatment n (%)	Post treatment n (%)		
Headache						
Present	21 (61.80%)	15 (44.10%)	20 (58.80%)	06 (17.65%)		
Absent	13 (38.20%)	19 (55.90%)	14 (41.20%)	28 (82.35%)	-2.129	0.033
Total	34 (100.0%)	34 (100.0%)	34 (100.0%)	34 (100.0%)		
Cognitive impairment						
Present	15 (44.10%)	11 (32.35%)	15 (44.10%)	04 (11.76%)	-2.047	0.040
Absent	19 (55.90%)	23 (67.65%)	19 (55.90%)	30 (88.24%)		
Total	34 (100.0%)	34 (100.0%)	34 (100.0%)	34 (100.0%)		
Focal weakness						
Present	11 (32.40%)	07 (20.60%)	13 (38.20%)	05 (14.70%)	-1.272	0.204
Absent	23 (67.60%)	27 (79.40%)	21 (61.80%)	29 (85.30%)		
Total	34 (100.0%)	34 (100.0%)	34 (100.0%)	34 (100.0%)		
Convulsion						
Present	05 (14.70%)	03 (08.80%)	06 (17.60%)	02 (05.90%)	-0.884	0.379
Absent	29 (85.30%)	31 (91.20%)	28 (82.40%)	32 (94.10%)		

Variable	Arm A (n=34)		Arm B (n=34)		Z-test	*p*-value
	Pre treatment n (%)	Post treatment n (%)	Pre treatment n (%)	Post treatment n (%)		
Total	34 (100.0%)	34 (100.0%)	34 (100.0%)	34 (100.0%)		
Speech difficulty						
Present	03 (08.80%)	02 (05.90%)	04 (11.80%)	01 (02.90%)	-1.102	0.271
Absent	31 (91.20%)	32 (94.10%)	30 (88.20%)	33 (97.10%)		
Total	34 (100.0%)	34 (100.0%)	34 (100.0%)	34 (100.0%)		
Ataxia						
Present	02 (05.90%)	01 (02.90%)	03 (08.80%)	01 (02.90%)	-0.373	0.711
Absent	32 (94.10%)	33 (97.10%)	31 (91.20%)	33 (97.10%)		
Total	34 (100.0%)	34 (100.0%)	34 (100.0%)	34 (100.0%)		

The below table shows non-hematological toxicities found in patients of both arms during the course of treatment and subsequent follow up. The most common non- hematological toxicity was nausea, which developed in 17 (50%) patients in Arm A and 22 (64.70%) patients in Arm B. Vomiting developed in 13 (38.20%) patients in Arm A and 18 (52.94%) patients in Arm B. Skin reaction was reported in 5 (14.70%) patients in Arm A and 7 (20.60%) patients in Arm B. 10 (29.40%) patients in Arm A and 14 (41.20%) patients in Arm B developed fatigue. Alopecia was reported in 4 (11.80%) patients in Arm A and 6 (17.60%) patients in Arm B. Though non- hematological toxicities were more in Arm B, it was not statistically significant. All toxicities were managed by conservative treatment. (Table 4)

Table 4. *Distribution of the patients according to non-hematological toxicity (N=68).*

Toxicity	Arm A (n=34) n (%)	Arm B (n=34) n (%)	χ^2test	*p*-value
Nausea				
Absent	17 (50.00%)	12 (35.30%)		
Grade-1	11 (32.40%)	13 (38.23%)		
Grade-2	05 (14.70%)	06 (17.65%)	2.120	0.548
Grade-3	01 (02.90%)	03 (08.82%)		
Total	34 (100.0%)	34 (100.0%)		
Vomiting				
Absent	21 (61.80%)	16 (47.06%)		
Grade-1	08 (23.50%)	09 (26.47%)		
Grade-2	05 (14.70%)	07 (20.59%)	1.008	0.604
Grade-3	00 (00.00%)	02 (05.88%)		
Total	34 (100.0%)	34 (100.0%)		
Skin reaction				
Absent	29 (85.30%)	27 (79.40%)		
Grade-1	04 (11.80%)	05 (14.70%)		
Grade-2	01 (02.90%)	02 (05.90%)	0.516	0.773
Total	34 (100.0%)	34 (100.0%)		
Fatigue				
Absent	24 (70.60%)	20 (58.80%)		
Grade-1	07 (20.60%)	10 (29.40%)		
Grade-2	03 (08.80%)	04 (11.80%)	1.036	0.596
Total	34 (100.0%)	34 (100.0%)		
Alopecia				
Absent	30 (88.20%)	28 (82.40%)		
Grade-1	04 (11.80%)	06 (17.60%)	0.469	0.493
Total	34 (100.0%)	34 (100.0%)		

The table shows hematological toxicities observed in patients of both arms during the course of treatment and subsequent follow up. 12 (35.29%) patients developed anemia in Arm A compared to 19 (55.88%) in Arm B. Neutropenia developed in 9 (26.47%) and 16 (52.95%) patients in Arm A and Arm B respectively. Thrombocytopenia was reported in 11 (32.35%) patients in Arm A and 20 (58.82%). patients in Arm B. Grade 2 and 3 toxicity was more in Arm B, but it was not statistically significant. (Table 5)

Table 5. *Distribution of the patients according to hematological toxicity (N=68).*

Toxicity	Arm A (n=34) n (%)	Arm B (n=34) n (%)	χ^2test	*p*-value
Anaemia				
Absent	22 (64.71%)	15 (44.12%)		
Grade-1	09 (26.47%)	12 (35.29%)		
Grade-2	03 (08.82%)	06 (17.65%)	2.739	0.254
Grade-3	00 (00.00%)	01 (02.94%)		
Total	34 (100.0%)	34 (100.0%)		
Neutropenia				

Toxicity	Arm A (n=34) n (%)	Arm B (n=34) n (%)	χ^2test	*p*-value
Absent	25 (73.53%)	18 (52.95%)		
Grade-1	08 (23.53%)	11 (32.35%)		
Grade-2	01 (02.94%)	03 (08.82%)	2.555	0.279
Grade-3	00 (00.00%)	02 (05.88%)		
Total	34 (100.0%)	34 (100.0%)		
Thrombocytopenia				
Absent	23 (67.65%)	14 (41.18%)		
Grade-1	09 (26.47%)	12 (35.29%)		
Grade-2	02 (05.88%)	05 (14.71%)	3.773	0.152
Grade-3	00 (00.00%)	03 (08.82%)		
Total	34 (100.0%)	34 (100.0%)		

The above table shows, the radiological response at the 9th week after completion of treatment according to RECIST 1. In Arm A, CR was observed in 02 (05.90%) patients, PR in 12 (35.30%) patients, SD in 15 (44.10%) patients and PD in 05 (14.70%) patients. In Arm B, CR was observed in 05 (14.70%) patients, PR in 21 (61.80%) patients, SD in 06 (17.60%) patients and PD in 02 (05.90%) patients. The overall response was also more in WBRT+TMZ arm 26 (76.50%) compared to WBRT alone arm 14 (41.20%). So statistically significant radiological responses were achieved in the WBRT+TMZ arm compared to the WBRT alone arm. (Table 6).

Table 6. *Distribution of the patients according to radiological response (N=68).*

Level of response	Arm A (n=34) n%	Arm B (n=34) n%	χ^2test	*p*-value
Complete response (CR)	02 (05.90%)	05 (14.70%)		
Partial response (PR)	12 (35.30%)	21 (61.80%)		
Overall response (CR+PR)	14 (41.20%)	26 (76.50%)	8.883	0.031
Stable disease (SD)	15 (44.10%)	06 (17.60%)		
Progressive disease (PD)	05 (14.70%)	02 (05.90%)		

Table 7 shows; in case of adenocarcinoma overall response was achieved in 6 (17.64%) patients in Arm A and 12 (35.29%) patients in Arm B. In case of ductal cell carcinoma overall response was achieved in 2 (05.88%) patients in Arm A and 6 (17.64%) patients in Arm B. In case of small cell carcinoma overall response was achieved in 1 (02.94%) patients in Arm A and 3 (08.82%) patients in Arm B. In case of clear cell carcinoma and malignant melanoma overall response was achieved in 0 (00.00%) patients in Arm A and 1 (02.94%) patients in Arm B. In case of squamous cell carcinoma, lobular carcinoma, follicular carcinoma overall response was similar in both arms.

Table 7. *Distribution of the patients according to the overall response in relation to the histopathological type of primary tumor (N=68).*

Histopathology	Arm A (n=34) n (%)	Arm B (n=34) n (%)	*p*-value
Adenocarcinoma	6 (17.64%)	12 (35.29%)	0.099
Squamous cell carcinoma	4 (11.76%)	4 (11.76%)	1.000
Ductal cell carcinoma	2 (05.88%)	6 (17.64%)	0.131
Small cell carcinoma	1 (02.94%)	3 (08.82%)	0.303
Clear cell carcinoma	0 (00.00%)	1 (02.94%)	0.312
Malignant melanoma	0 (00.00%)	1 (02.94%)	0.312
Follicular carcinoma	1 (02.94%)	0 (00.00%)	0.312
Lobular carcinoma	0 (00.00%)	0 (00.00%)	-

5. Discussion

This study compared the clinical responses, treatment-related toxicities, and efficacy of concurrent WBRT with TMZ and WBRT alone in newly diagnosed patients with brain metastases from solid tumors from December 2018 to June 2020. 68 adults with metastatic brain tumors at KYAMCH, Sirajganj, were studied. Arm A was the control group and Arm B was the observation group (each n=34). The control group got WBRT (3 Gy, 5 days a week for two weeks for a total dose of 30 Gy), while the observation group received WBRT with TMZ (75 mg/m^2/day).

In arms A and B, patients are 38-70 (mean 56.1510.14) and 36-70 (mean 54.0610.24) years old. Cao et al. (2015) included patients with ages ranging from 38-79 (mean 57.8) to 29-78 (mean 53.6) in their study [34]. In this study, 61-70-year-olds had the highest rate of metastases. Zomosa et al. (2019) discovered most patients were 50-70 [35]. Barnholtz-Sloan et al. (2004) found that brain metastases were most common in people aged 40 to 49 with primary lung cancer, 50 to 59 with primary melanoma, renal, or colorectal malignancies, and 20 to 39 with main breast cancer [36].

In this study, both male and female patients were enrolled, with more males in Arm A (70.6%) and Arm B (79.4%). Ali et al. (2014) found that males (61.7%) had more brain metastases than females (38.3%). In contrast, females made up 68.69% of Ghosh et al. (2017)'s sample [17, 5].

In this study, most patients (55.9% in Arm A and 58.8% in Arm B) were middle class. Saha et al. (2013) studied the

demographic and clinical profile of brain metastasis patients and found most were low-income [9].

In Arm A, among 34 patients, lung was the most common original tumor site, followed by breast, colorectal, kidney, skin, thyroid, and gallbladder. In Arm B, there were 18 lung, 7 breast, 4 colorectal, 2 kidney, 1 skin, 1 thyroid, and 1 gall bladder tumors. Singh et al. (2018) and Barnholtz- Sloan et al. (2004) found that lung carcinoma is the most prevalent primary for brain metastases [37, 36]. Breast cancer is the leading primary tumor generating brain metastases, according to Akhavan et al. (2014). [38, 39] Jayaraman and Rangarajan (2019) observed similar results.

KPS (>70) and no extra-cranial metastases are the best RPA survival predictors [18]. Sundstroms et al. (1998) found a link between good performance status and the absence of extracranial metastases [40]. In our study, 73.5% and 76.5% of Arm A and B patients had KPS 70. Arm A had 12 (35.3%) extracranial metastases while Arm B had 15 (44.1%). In Addeo et al. (2007) and Zhu et al. (2018), most patients had extracranial metastases [7, 31].

In Arm A, 15 (44.12%) of 34 patients had adenocarcinoma, 6 (17.65%) had squamous cell carcinoma, 6 (17.65%) had ductal cell carcinoma, 2 (5.88%) had small cell carcinoma, 2 (5.88%) had clear cell carcinoma, 1 (2.94%) had malignant melanoma, 1 (2.94%) had follicular carcinoma, and 1 (2.94%) had lobular carcinoma. Arm B had 14 (41.17%) adenocarcinomas, 5 (14.71%) squamous cell carcinomas, 6 (17.65%) ductal cell carcinomas, 2 (5.88%) small cell carcinomas, 2 (5.94%) clear cell carcinomas, 1 (2.94%) malignant melanoma, 1 (2.94%) follicular carcinoma, and 1 (2.94%) lobular carcinomas. In India, Saha et al. (2013) and Patnayak et al. (2013) revealed that adenocarcinoma (35-40%) is the most prevalent primary tumor causing brain metastases [9, 41]. Ghosh et al. (2017) observed breast infiltrative ductal carcinoma (39.13%) and lung non-small cell carcinoma (33.04%) were the most common primary histologies [5]. 16 (47.1%) and 15 (44.1%) patients in Arm A and Arm B had previous chemotherapy, while 13 (38.2%) and 8 (23.5%) had previous surgery.

In this study, headache was the most common symptom in Arm A and B, followed by cognitive impairment in 44.1% and 44.1%, focal weakness in 32.4% and 38.2%, convulsion in 14.7% and 17.6%, speech difficulty in 8.8% and 11.8%, and ataxia in 5.9% and 8.8%. Bilimagga et al. (2009) reported that headache, seizures, focal weakness, and gait instability were the most common presenting symptoms [23]. Damiens et al. (2012) found that the most common brain metastasis symptoms were neurologic impairment (64%), headache (17%), and confusion or somnolence (19%) [42].

In this study, the control and observation groups had statistically significant differences in headache and neurocognitive performance. Convulsions, focal weakness, speech problems, and ataxia were more common in the observation group, but not significantly. Liu et al. (2017) found significant improvement in WBRT plus TMZ vs. WBRT [1]. Ali et al. (2014) found that WBRT with TMZ relieved brain metastasis patients' symptoms [17]. Cao et al. (2015) showed that WBRT plus TMZ did not alleviate neurologic symptoms [34].

Patients tolerated daily TMZ during WBRT. Non-hematological effects included nausea, vomiting, skin response, exhaustion, and baldness. Both arms experienced regular nausea. TMZ+WBRT had a trend of more side effects than WBRT, although it wasn't significant ($p > 0.05$).

Anemia, neutropenia, and thrombocytopenia were the most common hematologic toxicities in this trial. Few patients suffered grade 2 and 3 toxicity, which was greater in the observation group but non-significant ($p > 0.05$). Conservative therapy addressed all toxicities. LV et al. (2018) and Chua et al. (2010) in China, Abdelgawad et al. (2017) in Egypt made similar observations [33, 43, 44]. Nausea, vomiting, alopecia, fatigue, headache, anorexia, constipation, leucopenia, anemia, and thrombocytopenia were the most common hematologic and non-hematologic toxicities in both groups.

The primary end point of the trial was radiological response to therapy at 9 weeks. CR (full response), PR (partial response), SD (stable disease), and PD (progressive disease). In Arm A, 05.90% of patients had CR, 35.30% PR, 44.10% SD, and 14.70% PD. In Arm B, CR was seen in 5 (14.7%) participants, PR in 21 (61.8%), SD in 6 (17.60%), and PD in 2 (5.59%). WBRT+TMZ had better overall response.

WBRT+TMZ achieved statistically significant radiological responses over WBRT alone. Antonadou et al. (2002) and Zhu et al. (2018) found that WBRT+TMZ considerably outperformed WBRT [29, 31]. Verger et al. (2005) showed no difference between WBRT and WBRT+TMZ in overall survival [45].

In this study, 68 patients' overall responses were examined by primary tumor histopathology. 12 (35.29%) adenocarcinoma and 6 (17.64%) ductal cell carcinoma patients in Arm B had a better overall response than Arm A patients. Addeo et al. (2007) found better response rates in NSCLC and breast cancer patients [7]. Siena et al. (2010) observed a slightly greater responder and disease control rate with WBRT with TMZ. This study [46] showed similar results. Antonadou et al. (2002)[29] studied patients with primary small cell lung cancer, non-small cell lung cancer, and breast cancer.

In patients with numerous, unresectable brain metastases, combining TMZ and WBRT improved headaches and cognitive performance. Several trials assessed the efficacy and safety of TMZ with WBRT for newly diagnosed brain metastases. Overall survival remained unaltered. Within this short survival, symptomatic alleviation is a considerable benefit for brain metastasis patients.

6. Conclusion

After analyzing the result of the study it can be concluded that the efficacy of concurrent radiotherapy with Temozolomide is higher than that of radiotherapy alone in the treatment of brain metastases. The combined treatment protocol significantly improves the symptoms and signs with acceptable toxicity profile.

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