Rep Radiother Oncol. 2015 December; 2(4):e10987. doi: 10.5812/rro.10987.

Published online 2015 December 31. **Research Article**

Toxicity, Efficacy, and Quality of Life of Addition of IMRT Boost to Whole Brain Radiation Therapy and Concurrent Temozolomide in Patients with Newly Diagnosed Brain Metastases

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Received 2015 October 11; **Revised** 2015 November 11; **Accepted** 2015 December 15.

Abstract

Background: Brain metastasis is the most common intracranial tumor in adults. Addition of boost dose to brain metastases with stereotactic radiosurgery following whole brain radiation therapy with concurrent temozolomide showed improved outcomes; hence, the current study aimed at evaluating toxicity, efficacy, and quality of life (QOL) of addition of intensity-modulated radiation therapy (IMRT) boost to whole brain radiation therapy (WBRT) and concurrent temozolomide (TMZ) in patients with newly diagnosed brain metastases.

Methods: Twenty patients with known primary histology, newly diagnosed brain metastases, underwent recursive partitioning analysis (RPA) class I/II, and fulfilling eligibility criteria were enrolled in the current study. Patients who initially received WBRT with concurrent TMZ were randomly assigned to receive IMRT boost to an additional 20 Gray (group A) or no further treatment (group B). Serial evaluations of toxicity (hematologic and non-hematologic), response (clinical, neurologic, and radiologic), and QOL were performed at 3 months and 6 months after the completion of Radiotherapy. The 2 groups were compared for toxicity, response, and QOL by appropriate statistical tests.

Results: At the median follow-up of 5 months, patients in group A demonstrated similar toxicity, superior response, and better QOL in 3 domains (physical functioning, role functioning, and global health status).

Conclusions: Addition of IMRT boost to WBRT and TMZ provided superior response and better QOL, without additional toxicity, compared with WBRT alone.

Keywords: Brain Metastases, IMRT Boost, QOL, Temozolomide, WBRT

1. Background

Brain metastasis is the most common intracranial tumor in adults. In the Caucasian population, approximately 100,000 patients have symptomatic intracranial metastases annually; a number that is 6 times more than the 17,000 patients with malignant primary brain tumors (1).

About 20% to 40% of patients with cancer develop metastatic cancer to the brain during the course of their illness and even sometimes they present with brain secondaries (2). The clinical series of brain metastasis are reported 5% to 15% and on autopsy it is in the range of 14% to 63% (2).

The primary sites of the development of brain secondaries include carcinoma of lung, breast, kidney, prostate, melanoma, and in younger patients, osteosarcoma and rhabdomyosarcoma (3).

Many patients have no or minimal symptoms of tumor, and their metastases are found during a routine medical evaluation. If there are symptoms, they depend on the site involved. Brain metastases may cause headache, dizziness, blurred vision, nausea, or other symptoms related to the nervous system. Symptoms usually evolve over a few weeks. However, hemorrhage into the metastases can cause more dramatic presentation such as propensity to bleed, which is commonly observed with tumors such as malignant melanoma, thyroid carcinoma, renal cell carcinoma, and choriocarcinoma (4).

Management consists of symptomatic care and definitive treatment. Symptomatic management with corticosteroids can result in significant improvement in quality of life (QOL) for patients with brain metastasis, alongside proper management guideline for the primary site. Definitive treatment of brain metastases is external-beam radiation therapy delivered to the whole brain; 30 Gy administered in 10 fractions is the standard of care due to its tolerability, brief treatment course, cost-effectiveness, and trend of improved survival (5).

In the study by David W. Andrews et al., patients with brain metastasis were treated with whole brain radiation therapy (WBRT) with a boost for metastasis. Results showed that prescription of higher radiation doses was not associated with a greater incidence of toxicities; instead it showed statistically significant improvement in Karnofsky performance status (KPS) and decreased steroid use at 6 months in the stereotactic radiation boost treatment group.

Recent phase II trial data suggested that temozolomide

(TMZ) was safe, and significantly improved the response rate when administered in combination with radiation therapy in patients with previously untreated brain metastases. The study by Antonadou D. suggested that concomitant treatment of solid tumors with WBRT and TMZ improves the QOL (6).

Hence, the current study aimed at evaluating the outcomes with respect to radiological response, QOL, and toxicities by giving the increased dose to metastases, using intensity-modulated radiation therapy (IMRT) technique along with WBRT and concurrent TMZ.

2. Methods

2.1. Inclusion Criteria

The study protocol and consent procedures were approved by the medical ethics review board. Inclusion criteria were patients aged 18 to 70 years with KPS $\geq$ 70, histological diagnosis of a systemic tumor and radiological evidence of brain metastases, no history of undergoing metastasectomy, radiosurgery, and chemotherapy 3 weeks prior to the study and prior to cranial radiotherapy.

After signing the informed consent, patients were randomly assigned to WBRT with IMRT boost to metastases (group A) and WBRT alone (group B) combined with chemotherapy in both of the groups.

2.2. Radiation Treatment

For the WBRT, entire brain parenchyma and meningeal reflections were treated. IMRT boost was given to the brain metastases and minimal normal brain tissue. Clinical target volume (CTV) consisted of all visualized tumor. A 2-mm margin is normally added to create a PTV, and it is reduced to 1 mm if close to any critical organs. Critical structures included bilateral eyes and optic nerves, optic chiasm, brainstem, as well as uninvolved brain. A dose of 40 Gy in 20 fractions for the WBRT and 20 Gy in 10 fractions for IMRT boost to metastatic sites were delivered 5 days a week.

2.3. Chemotherapy

Oral tablet of TMZ 75 mg/m^2 was given to patients 5 days a week in both groups half an hour before radiation therapy under fasting condition. All patients received prophylactic antiemetic oral ondansetron tablet before TMZ.

2.4. Radiological Response Assessment

All patients underwent computed tomography (CT) scan /magnetic resonance imaging (MRI) of brain 3 months and 6 months after completion of chemoradiation therapy for the radiological response assessment. Disease evaluation was done and recorded by assessing objective regression in the form of dimension of the lesions, based on RECIST (response evaluation criteria in solid tumors).

2.5. Quality of Life

EORTC QLQ (the European organization for research and treatment of cancer quality of life questionnaire) C30, translated into Kannada (local language), was used with the permission of competitive authorities. This questionnaire was filled by the patients of both groups before starting and 3 months after completion of chemoradiation therapy to compare changes in their QOL.

2.6. Toxicity

Hematological (total leucocyte count, absolute neutrophil count, platelet count, serum bilirubin, and liver enzymes) and gastrointestinal (nausea and vomiting) toxicities were recorded in accordance with the CTCAE (common terminology criteria for adverse events) version 4.3 during the treatment.

2.7. Follow-Up

Patients were on follow-up till 6 months post-chemoradiation therapy.

3. Results

3.1. Statistical Methods

Data analysis was conducted by R software, version 3.0.2. A P value < 0.05 was considered as level of significance.

Results of group A were significantly better than those of group B in 3 different domains of EORTC QOL C-30 as physical functioning, role functioning, and global health status. Hence, QOL was better in group A than group B.

4. Discussion

The WBRT is given to the patients with brain metastasis to ensure that the radiation takes care of micro metastasis, which is otherwise unaddressed, and to control presenting neurological symptoms, which can be achieved in 70% to 90% of cases without causing acute neurological side effects. The current study observed neurological improvement of 70% in both groups. There was no difference in clinical neurological responses among patients in the 2 groups.

The intention of giving boost to the visible brain metastasis was to decrease the gross tumor burden, unaddressed with 40 Gy. Hence, boost of 20 Gy was given to brain metastasis with IMRT technique. Edwards et al. (7), gave IMRT

Table 1. Characteristics of Patient and Tumors

Variable	Group A		Group B		P value
	No.	%	No.	%	
Total	10	100	10	100	
Age, y					0.478
18 - 30	1	10	1	10	
31 - 40	3	30	0	0	
41 - 50	4	40	5	50	
51 - 60	1	10	1	10	
61 - 70	1	10	3	30	
Gender					
Male	6	60	5	50	
Female	4	40	5	50	
KPS					0.154
70	5	50	6	60	
80	4	40	4	40	
90	1	10	0	0	
Neurological deficit					
Yes	2	20	3	30	
No	8	80	7	70	
Site of primary tumor					1
Lung	3	30	5	50	
Breast	6	60	5	50	
Sigmoid colon	1	10	0	0	
BSA					
< 1.4	3	30	2	20	0.776
1.4 - 1.5	7	70	4	40	
> 1.5	0	0	4	40	
No. of brain metastases					
1	5	50	1	10	
2	2	20	0	0	
3	3	30	3	30	
4	0	0	6	60	
Mean ± SD	1.8 ± 0.918		3.4 ± 0.966		

Abbreviations: BSA, Body Surface Area; KPS, Karnofsky Performance Status.

Table 2. Radiological Response Assessment

Radiological Response	Group A		Group B		P Value
	No.	%	No.	%	
Total	10	100	10	100	
After 3 months					
Progressive disease	1	10	3	30	0.49
Stable disease	2	20	1	10	
Partial Response	7	70	6	60	
After 6 months					
Partial response	6	60	5	50	0.45
Complete response	1	10	0	0	

Table 3. Survival[a]

Survival at 6 Months	Group A		Group B	
	No.	%	No.	%
Total	10	100	10	100
Alive	5	50	2	20
Dead	5	50	8	80

[a] P Value = 0.28.

Table 4. Leucopenia[a]

Leucopenia	Group A			Group B		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Week 1	10	0	0	10	0	0
Week 2	9	1	0	10	0	0
Week 3	8	2	0	7	3	0
Week 4	5	5	0	5	5	0
Week 5	3	6	1	1	8	1
Week 6	10	0	0			
Week 7	6	2	2			
Week 8	4	6	0			

[a] P Value = 0.144.

boost to brain metastasis and their results indicated no acute toxicity or morbidity associated with the boost treatment, and it was an alternate modality of treatment where single-fraction stereotactic radiosurgery (SRS) boost was not available. In the current study, toxicities were within acceptable limits.

Radiological response between the 2 groups were analyzed. The current study observed that at the end of 3 months, 70% of patients had partial response, 20% had stable disease, and 1 patient had progressive disease in group A, as evaluated by CT/MRI brain examinations.

At 6 months, 60% of the patients had partial response and 10% had complete response in both the groups. It can be concluded that the response of metastatic tumor was in

Table 5. Neutropenia[a]

Neutropenia	Group A			Group B		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Week 1	10	0	0	9	1	0
Week 2	9	1	0	9	1	0
Week 3	8	2	0	9	1	0
Week 4	5	5	0	4	6	0
Week 5	2	8	0	1	7	2
Week 6	10	0	0			
Week 7	6	4	0			
Week 8	4	6	0			

[a] P Value = 0.144.

Table 6. Thrombocytopenia[a]

Thrombocytopenia	Group A			Group B		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Week 1	10	0	0	10	0	0
Week 2	9	1	0	8	2	0
Week 3	8	2	0	9	1	0
Week 4	5	5	0	4	6	0
Week 5	3	5	2	1	7	2
Week 6	10	0	0			
Week 7	6	2	2			
Week 8	4	6	0			

[a] P Value = 0.41.

Table 7. Elevated Bilirubin Level[a]

Bilirubin	Group A			Group B		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Week 1	9	1	0	10	0	0
Week 2	8	2	0	10	0	0
Week 3	8	2	0	4	5	0
Week 4	7	3	0	5	4	0
Week 5	7	3	0	4	4	2
Week 6	10	0	0			
Week 7	6	2	2			
Week 8	4	6	0			

[a] P Value = 0.3.

both groups, but favoring group A statistically.

Footnote

Conflict of Interests: Authors declared no conflict of interest.

Table 8. Elevated Aspartate Transaminase[a]

AST	Group A			Group B		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Week 1	9	1	0	10	0	0
Week 2	8	2	0	10	0	0
Week 3	8	2	0	4	5	1
Week 4	7	3	0	5	4	1
Week 5	7	3	0	4	4	2
Week 6	10	0	0			
Week 7	8	2	0			
Week 8	8	2	0			

Abbreviation: AST, Aspartate Transaminase.
[a] P Value = 0.35.

Table 9. Nausea[a]

Nausea	Group A			Group B		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Week 1	7	3	0	10	0	0
Week 2	10	0	0	10	0	0
Week 3	9	1	0	7	2	1
Week 4	5	4	1	8	2	0
Week 5	7	2	1	5	5	0
Week 6	9	1	0			
Week 7	3	5	2			
Week 8	2	6	2			

[a] P Value = 0.18.

Table 10. Vomiting[a]

Vomiting	Group A			Group B		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Week 1	9	1	0	10	0	0
Week 2	5	5	0	10	0	0
Week 3	5	5	0	7	2	1
Week 4	2	6	2	8	2	0
Week 5	4	6	0	5	5	0
Week 6	10	0	0			
Week 7	3	7	0			
Week 8	2	6	2			

[a] P Value = 1.

Table 11. Analysis of EORTC QLQ-C30 in Group A (Pre-RT v/s Post-RT)

Question No.	P Value	Comment
1.	0.006	Patients could better perform strenuous activities after RT.
2.	0.006	Patients could better walk long distances after RT.
3.	0.004	Patients could better walk short distances after RT.
4.	0.003	Patients could better stay awake after RT.
5.	0.004	Patients could better eat, dress, and wash themselves after RT.
6.	0.004	Patients could better perform daily activities after RT.
7.	0.003	Patients could better perform hobbies after RT.
8.	0.23	Shortness of breath among patients showed no statistical improvement, compared with pre-RT.
9.	0.007	Patients' pain improved after RT.
10.	0.004	Patients needed less rest after RT.
11.	0.004	Patients could better sleep better RT.
12.	0.004	Patients felt less weak after RT.
13.	0.016	Patients appetite improved after RT.
14.	0.030	Patient felt less nauseated after RT.
15.	0.026	Patients had no complaint about vomiting after RT.
16.	0.007	Patients had no complaint about constipation after RT.
17.	0.059	No statistical significant difference was observed in diarrhea episodes of the patients before and after RT.
18.	0.007	Patients felt less tired after RT.
19.	0.004	There was no interference of pain in work after RT.
20.	0.006	Patients' concentration improved after RT.
21.	0.008	Patients' tension was less after RT.
22.	0.025	Patient was less worried after RT.
23.	0.009	Patient was less irritable after RT.
24.	0.020	Patient had no depression after RT.
25.	0.149	There was no statistical significant difference in remembering things, compared with before RT.
26.	0.301	There was no statistical significance in family life.
27.	0.059	Patient felt better about social activities after RT.
28.	0.007	Financial status was exacerbated after RT.
29.	0.004	General health status was improved after RT.
30.	0.004	Quality of life was improved after RT.

Table 12. Analysis of EORTC QLQ-C30 of Group B (Pre-RT v/s Post- RT)

Question No.	P Value	Comment
1.	0.014	Patients could better perform strenuous activities after RT.
2.	0.008	Patients could better walk long distances after RT.
3.	0.034	Patients could better walk short distances after RT.
4.	0.008	Patients could better stay awake after RT.
5.	0.010	Patients could better eat, dress, and wash themselves after RT.
6.	0.038	Patients could better perform daily activities after RT.
7.	0.020	Patients could better perform hobbies after RT.
8.	0.038	Shortness of breath improved after RT.
9.	0.026	Patients' pain improved after RT.
10.	0.004	Patients needed less rest after RT.
11.	0.010	Patients could better sleep after RT.
12.	0.023	Patients felt less weak after RT.
13.	0.008	Patients appetite improved after RT.
14.	0.011	Patient felt less nauseated after RT.
15.	0.010	Patients had no complaint about vomiting after RT.
16	0.023	Patients had no complaint about constipation after RT.
17.	0.157	No statistical significant difference was observed regarding diarrhea episodes in patients before and after RT.
18.	0.010	Patients felt less tired after RT.
19.	0.004	There was no interference of pain in work after RT.
20.	0.008	Patients' concentration improved after RT.
21.	0.026	Patients' tension was less after RT.
22.	0.004	Patient less worried after RT.
23.	0.011	Patient were less irritable after RT.
24.	0.004	Patient had no depression after RT.
25.	0.030	There was no statistical significant difference in remembering things, compared with before RT.
26.	0.026	There was no statistical significance in family life.
27.	0.023	Patient had better feelings in social activities after RT.
28.	0.492	Financial status did not change after RT.
29.	0.058	General health did not change and no statistical significant difference was noted.
30.	0.006	Quality of life was slightly exacerbated, compared with before RT.

Table 13. Analysis of EORTC QLQ-C30 of Group A v/s Group B

Question No.	P Value	Result
1.	0.080	No statistical difference between the groups.
2.	0.051	No statistical difference between the groups.
3.	0.004	Group A > group B
4.	0.005	Group A > group B
5.	0.077	No statistical difference between the groups.
6.	0.004	Group A > group B
7.	0.000	Group A > group B
8.	0.785	No statistical difference between the groups.
9.	0.258	No statistical difference between the groups.
10.	0.749	No statistical difference between the groups.
11.	0.132	No statistical difference between the groups.
12.	0.094	No statistical difference between the groups.
13.	0.487	No statistical difference between the groups.
14.	0.295	No statistical difference between the groups.
15.	0.512	No statistical difference between the groups.
16.	0.749	No statistical difference between the groups.
17.	0.268	No statistical difference between the groups.
18.	0.216	No statistical difference between the groups.
19.	1	No statistical difference between the groups.
20.	0.207	No statistical difference between the groups.
21.	0.251	No statistical difference between the groups.
22.	0.512	No statistical difference between the groups.
23.	0.346	No statistical difference between the groups.
24.	0.160	No statistical difference between the groups.
25.	0.719	No statistical difference between the groups.
26.	0.386	No statistical difference between the groups.
27.	0.673	No statistical difference between the groups.
28.	0.001	Group A > group B
29.	0.009	Group A > group B
30.	0.001	Group A > group B

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