ORIGINAL ARTICLE

Quality of Life and Symptoms Control in Brain Metastasis After Palliative Whole Brain Radiotherapy Using Two Different Protocols

Muhammad Sohail Akhtar[1], Farzana Kousar[3], Shahab Fatmi[2], Kaukab Jabeen[1] and Kalsoom Akhtar[2]

ABSTRACT

Objective: To compare the quality of life and symptomatic improvement after palliative radiotherapy to brain metastasis using two different treatment protocols.

Study Design: Comparative study.

Place and Duration of Study: Bahawalpur Institute of Nuclear Medicine and Oncology, Bahawalpur, from January 2009 to November 2010.

Methodology: Patients presenting with brain metastasis referred to Bahawalpur Institute of Nuclear Medicine and Oncology, Bahawalpur for whole brain radiotherapy (WBRT) were included. Patients were divided in two groups. In group A WBRT 30 Gys in 10 fractions were given. While in group B 30 Gys in 15 fractions to whole brain followed by 20 Gys in 10 fractions boost to primary metastatic site with 2 cm margins were given. Follow-up was done at 1 and 3 months.

Results: A total of 46 patients with brain metastasis were enrolled with median Karnofsky performance score 50. Median age was 64 years. Most common presenting symptoms were headache, weakness, balance problem and early fatigability. Fifty percent of patients had improvement in their presenting symptoms after completion of palliative radiotherapy at one month and three months follow-up. There was a statistically significant improvement in headache, nausea or vomiting, focal weakness, dizziness, balance problem and problems with smell, hearing and tingling sensation in group B patients as compared to group A.

Conclusion: More controlled and better quality of life was observed in patient given 30 Gys in 15 fractions followed by a boost of 20 fractions to primary metastatic site versus WBRT with 30 Gys in 10 fractions and in patients with metastatic sites are less than three and having difference not more than 2 cm apart between two metastatic sites.

Key words: *Whole brain radiotherapy. Brain metastasis. Fractions. Palliative. Balance problem. Fatigability. Quality of life.*

INTRODUCTION

The incidence of brain metastasis often occurs as a paradoxical result of the effectiveness of anti-cancer agents that do not cross the blood-brain barrier, but acts effectively on the primary tumour or extracranial metastasis.[1,2] Brain metastasis occur in upto 40% of all adult cancer patients and occur 10 times more often than primary brain tumours.[3,4] The prognosis of the majority of patients with brain metastasis is poor, with most patients surviving only 3 - 6 months.[5,6] The prognosis of patients with 1 or 2 brain metastasis appears to be better than that of patients with more brain metastasis.[7,8]

Depending on the location of the brain metastasis, neurological symptoms may include headache, focal weakness, mental disturbance, behaviour changes, seizures, speech difficulty and ataxia.[9] Patients with good performance status and limited extracranial disease are often considered for surgical excision or radiosurgery or both. The objective of the radiotherapy treatment is to provide symptomatic relief and possibility to improve survival. Nowadays whole-brain radiotherapy (WBRT) alone is the most common treatment for patients with multiple brain metastasis. However, an increased dose administered to the entire brain could increase risk of late toxicity.[10] This risk of relevant late toxicity would be less if the increased dose was administered to the metastatic site only (WBRT boost) rather than to the whole brain.

Use of corticosteroids to decrease the cerebral oedema has been associated with rapid improvement in symptoms. However, high dose and prolonged use of corticosteroid can have adverse side effects and following radiotherapy corticosteroid are gradually tapered and discontinued.[11]

Mostly clinical trials have defined the efficacy of WBRT treatment with following end points. Survival response, radiological or imaging response, observer-relate neurological symptoms, time to recurrence of intracranial disease and cause of death. However, few studies have focused on quality of life and improvement in patients related symptoms as primary outcome.

The objective of this study was to determine prospectively patient related symptoms and quality of life in both arms.

[1] *Department of Radiotherapy / Nuclear Medicine[2], BINO Hospital, Bahawalpur.*

[3] *Department of Nuclear Medicine, CENUM, Lahore.*

Correspondence: *Dr. Muhammad Sohail Akhtar, 545 Neelam Block, Allama Iqbal Town, Lahore.*
E-mail: dr_sakhtar@hotmail.com

Received March 15, 2011; accepted March 12, 2012.

METHODOLOGY

This study was conducted at Bahawalpur Institute of Nuclear Medicine and Oncology from January 2009 - November 2010. All patients with brain metastasis having one to three metastatic lesions were considered for this study. Approval for the study was obtained from research and ethical board of the hospital. A well-informed consent was obtained from all study subjects. A pre-designed proforma was used to collect geographic and clinical information. Patients with good performance status and isolated intracranial disease were referred to the neurosurgical clinic for consideration of surgical resection. The patients who were reluctant for surgery or referred by neurosurgeons as being irresectable were included in the study.

Patient demographic information, disease characteristic, cancer history, treatment details and outcome of the initial consultation were collected. Patients were divided in two groups. Group A patient received whole brain radiotherapy 30 Gys in 10 fractions. Group B included patients who received 30 Gys in 15 fractions to whole brain followed by 20 Gys to metastatic site in 10 fractions.

The choice of whether the patients received either WBRT alone or WBRT boost was based on the location of the metastatic site and maximizing benefit versus risk of radiation to the specific site. This decision was made by the treating WBRT oncologist, as well as according to institutional policy. Location and extent of metastasis were defined by either computed tomography (CT) or magnetic resonance imaging (MRI). The patients received dexamethasone at doses of 12 - 32 mg/day during WBRT and were given tapering schedule after radiotherapy. WBRT was performed with Cobalt 60 and 1.5 megavolt photon beams. WBRT was delivered using parallel opposed fields (90° and 270°). Both orbitae were spared using individual blocks or multi-leaf collimators. The WBRT boost volume encompassed the initial extent of the metastasis according to pre-radiation imaging plus a safety margin of 1 cm.

Quality of life was measured in both groups and follow-up was done at 1 and 3 months after treatment. The patients who died or lost for this follow-up period were excluded. Spitzer Quality of Life Index was used at inclusion and at each follow-up Components of 5 domains were general activity, daily living, health, support and outlook. Each domain is rated 0-2 and each score is accompanied by verbal description. For example in health domain the patient could report either feeling well or “great” most of the time (score 2), lacking in energy or being not entirely “up-to-par” occasionally (score 1), or feeling very ill or “lousy,” weak and washed out for most of the week (score 0).

The symptoms checklist was used to capture changes in symptoms associated with two groups. Each symptom severity in the previous week was rated as mild, moderate or severe symptoms.

The primary end point of this study was to assess post-WBRT quality of life in patients with brain metastasis dividing in two groups. The statistical analyses were done using the Statistical Program of Microsoft Excel 2003 for windows. Chi-square test was applied for categorical variables. P-value less than 0.05 was considered significant.

RESULTS

Forty-six patients with brain metastasis were referred to BINO for palliative radiotherapy. Fifty-six percent of the patients were female and 44% of the patients were male. Patients with Spitzer QOL score ≤ 3 were included in this study. Number of brain metastasis was 1 in 37% patients and 2-3 metastatic lesions were present in 63% of population. Most common primary site for brain metastasis was lung (52%) and breast (24%). The characteristics of the patient at the time of inclusion are detailed in Table I.

Table I: Baseline characteristics of the patients.

Variables	No. (%)
Age at radiation:	
< 50 years	18 (39)
> 50 years	28 (61)
Range	35-88 years
Gender	
Male	20 (43.5)
Female	26 (56.5)
Primary site	
Lungs	24 (52)
Breast	11 (23.9)
Genito-urinary	06 (13)
Intestines	01 (2)
Others	04 (8.7)
No. of brain metastasis:	
Single	17 (37)
2-3	29 (63)
Karnofsky performance score:	
Median	50
Range	30-100
Extra-cranial disease under control	
Yes	09 (19)
No	23 (50)
Unknown	14 (30)
Whole brain radiotherapy	
Group A: 30 Gys/10 F	25 (54)
Group B:30 Gys 15 F	21 (46)
followed by 20 Gys to metastatic site	

Spitzer's quality of life scoring was done in total population before radiotherapy. Patients with 2% or < 2% were considered in each domain. Changes in QOL scoring were noted in both groups at 1 month and 3 months follow-up.

All patients who are Spitzer QOL at baseline were included in the evaluation; we found a statistically significant improvement in group B patient in daily living domain after 1 month. But no statistically significant difference was observed in rest of QOL domains. Statistically significant difference was seen in activity, daily living and need of support domain after 3 months follow-up. We found that the differences in the QOL scores between the two study arms were significant only in one domain at 1 month and in three domains i.e. activity, daily living and support at 3 months follow-up.

The presenting symptoms include headache (61%), focal weakness (46%), confusion (22%), dizziness (39%), balance problem (54%), seizures (13%), speech difficulties (17%), visual disturbance (29%), numbness (35%), excessive fatigue (72%) and nausea (54%). Severity of symptoms were graded as mild, moderate and severe and any change in severity of symptoms was noted in follow-up period as shown in Table III after 1 month and in Table IV after 3 months of follow-up.

Patients in group A have more severity in symptoms after 1 month as compared to group B patients. Statistically significant changes were noted in focal weakness, memory loss, early fatigue and nausea or vomiting.

Fifty percent of patients had improvement in their presenting symptoms after completion of palliative radiotherapy at 3 months follow-up. There was a statistically significant improvement in headache, focal weakness, dizziness, balance problem, fatigue, trouble in concentration, problems with smell, hearing and tingling sensation in group B patients as compared to group A patient. Patients experienced more severity in post-radiation effects in group A as compared to group B. Statistically significant difference was also observed in nausea or vomiting complaint of the patient in group B patients as compared to group A which is more significant after 3 months follow-up. These findings were more remarkable in the patients with single brain metastasis lesion along with controlled extracranial disease. Patients presenting with brain metastatic lesions not very apart form each other also showed a better response.

Twenty percent patients had further impairment in their neurologic functions because of progression of brain metastasis, uncontrolled primary tumour or recurrence.

Table II: Change of QOL after WBRT in both groups after 1 and 3 months of follow-up.

	Decreased		No change		Increased		p-value
	A	B	A	B	A	B	
QOL after 1month							
Activity	40% (10)	14% (3)	48% (12)	53% (11)	12% (3)	33% (7)	0.08
Daily living	44% (11)	9.5% (2)	32% (8)	52% (11)	24% (6)	48% (10)	0.02*
Health	40% (10)	19% (4)	44% (11)	33% (7)	16% (4)	48% (10)	0.05
Support	8% (2)	14% (3)	72% (18)	72% (15)	20% (5)	14% (3)	0.73
Outlook	36% (9)	24% (5)	40% (10)	38% (8)	24% (6)	38% (8)	0.48
QOL after 3 months							
Activity	40% (10)	9.5% (2)	40% (10)	47% (10)	20% (5)	43% (9)	0.01*
Daily living	36% (9)	9.5% (2)	32% (8)	24% (5)	32% (8)	66% (14)	0.03*
Health	52% (13)	28% (6)	32% (8)	24% (5)	16% (4)	48% (10)	0.06
Support	24% (6)	52% (11)	40% (10)	28% (6)	36% (9)	19% (4)	0.02*
Outlook	32% (8)	28% (6)	40% (10)	43% (9)	28% (7)	28% (6)	0.96

**Significant at p-value < 0.05*

Table III: Symptoms severity postradiation assessment in both groups after 1 month.

Symptoms	Decreased		No change		Increased		p-value
	A (n = 25)	B (n = 21)	A (n = 25)	B (n = 21)	A (n = 25)	B (n = 21)	
Headache	32% (8)	52% (11)	36% (9)	24% (5)	32% (8)	24% (5)	0.37
Weakness	16% (4)	43% (9)	24% (6)	33% (7)	60% (15)	24% (5)	0.001*
Memory loss	24% (6)	57% (12)	40% (10)	19% (4)	36% (9)	24% (5)	0.06
Dizziness	24% (6)	33% (7)	40% (10)	33% (7)	36% (9)	33% (7)	0.77
Balance problem	16% (4)	33% (7)	28% (7)	43% (9)	56% (14)	24% (5)	0.07
Seizures	12% (3)	43% (9)	36% (9)	28% (6)	52% (13)	28% (6)	0.05
Speech difficulty	20% (5)	38% (8)	60% (15)	38% (8)	20% (5)	24% (5)	0.28
Vision problem	16% (4)	43% (9)	48% (12)	24% (5)	36% (9)	33% (7)	0.09
Problem with smell, hearing and tingling	16% (4)	24% (5)	52% (13)	52% (11)	32% (8)	24% (5)	0.78
Fatigue	20% (5)	19% (4)	8% (2)	38% (8)	72% (18)	43% (9)	0.04*
Difficulty in concentration	20% (5)	23% (5)	24% (6)	33% (7)	56% (14)	43% (9)	0.66
Nausea / vomiting	20% (5)	43% (9)	16% (4)	38% (8)	64% (16)	19% (4)	0.009*

**Significant at p-value < 0.05*

Table IV: Changes of symptoms after WBRT in both groups after 3 months.

Symptoms	Decreased		No change		Increased		p-value
	A (n = 25)	B (n = 21)	A (n = 25)	B (n = 21)	A (n = 25)	B (n = 21)	
Headache	20% (5)	52% (11)	20% (5)	28% (6)	60% (15)	19% (4)	0.01*
Weakness	24% (6)	43% (9)	36% (9)	24% (5)	40% (10)	24% (5)	0.25
Memory loss	24% (6)	40% (10)	40% (10)	28% (6)	36% (9)	24% (5)	0.24
Dizziness	20% (5)	57% (12)	40% (10)	19% (4)	40% (10)	24% (5)	0.03*
Balance problem	20% (5)	43% (9)	16% (4)	33% (7)	64% (16)	24% (5)	0.02*
Seizures	16% (4)	28% (5)	32% (8)	33% (7)	52% (13)	42% (9)	0.82
Speech difficulty	12% (3)	28.6% (6)	60% (15)	52% (11)	28% (7)	19% (4)	0.34
Vision problem	16% (4)	19% (4)	44% (11)	52% (11)	40% (10)	28% (6)	0.72
Problem with smell, hearing and tingling	16% (4)	28% (5)	24% (6)	52% (11)	60% (15)	24% (5)	0.04*
Fatigue	12% (3)	43% (9)	24% (6)	38% (8)	64% (16)	19% (4)	0.004*
Difficulty in concentration	20% (5)	42% (9)	20% (5)	38% (8)	72% (15)	19% (4)	0.01*
Nausea / vomiting	16% (4)	52% (11)	20% (5)	24% (5)	64% (16)	24% (5)	0.01*

**Significant at p-value < 0.05*

A recurrence anywhere in the brain (local or distant intracerebral failure) during the follow-up period occurred in 10 patients (21%). The rates of grade 3 acute toxicity according to the National Cancer Institute Common Toxicity Criteria (version 2.0) were 6% in Group A and 4% in Group B patients.

DISCUSSION

QOL has become an increasingly important end point in addition to conventional measurements of survival in cancer trials. Quality of life can be seen as a balance between minimizing treatment risks and maximizing benefits, including physical and psychological effects. As patients with brain metastasis have limited survival, so we need treatment options that are less morbid and maximizing quality of life. Various treatment options are available for example, steroids, palliative radiotherapy, debulking surgery, stereotactic radiosurgery, palliative chemotherapy and supportive management. It was observed in patients with brain metastasis median survival is one month without treatment, 2 months with steroids, and 3 - 6 months with cranial irradiation.[11] Various radiosensitizers, chemotherapy options and different radiotherapy dose fractionation schedules have also been explored to improve the outcome of brain metastasis.

Certain types of primary cancers have a prediction for spread to central nervous system. Lung and breast make-up about 60% of all brain metastasis and metastasis from unknown primary contribution is 1-18%.[12] Depending on the location of the brain metastasis, patients may suffer from neurologic symptoms that include headaches, focal weakness, mental disturbances, behavioural changes, seizures, speech difficulty, and ataxia. WBRT and steroids have been considered as a standard treatment of choice for brain metastasis. The benefit of WBRT on quality of life and neurological symptoms are not clear yet in majority of patients with poor performance status and active extracranial disease.

This study was focused on quality of life as the primary objective. The findings from this study indicate that 43% of patients had stable disease or improved symptoms. Certain quality of life domains i.e. daily living and activity as well as support are significantly improved overtime in 54% of patients respectively. Rest of the domains and symptoms did not change significantly following WBRT. Although, amendable improvement in the quality of life and symptoms severity was not evident, WBRT may have contributed to the stabilization of the symptoms progression and quality of life deterioration. However, we have observed that patient with three or less than three metastasis deposits in brain treated with 30 Gys to whole brain followed by 20 Gys in 10 fractions to metastatic site showed better response and improved quality of life.

An interesting finding was that patients who demonstrated good radiologic response to WBRT had improvement in their neurological function and fine motor co-ordination, but not in short as well as longterm memory. This suggests that WBRT, although improving certain aspects of cognition by reducing intracranial tumour burden, may not improve memory to the same extent, and one possible explanation for this is that WBRT might specifically impair hippocampus related functions such as memory and learning. Dementia with WBRT in long-term survivors is frequently quoted as justification for the avoidance of WBRT.[13]

Whole-brain radiation therapy (WBRT) is still considered a major treatment modality for non-resectable brain metastasis especially in patients with multiple metastasis in whom surgery or radiosurgery has a limited role. Similarly, a randomized study of WBRT or control group postsurgery or post-radiosurgery by Roos *et al*. was also terminated prematurely because of its slow accrual. As a result of the small sample size

(n = 19), the investigators did not conduct a detailed QOL analysis. They found that the differences in the global health scores and global QOL scores between the two study arms were non-significant at 2 months (p = 0.94) and at 5 months (p = 0.50). The investigators concluded that their study did not indicate that WBRT caused deterioration in overall health or overall QOL.[14]

Patients whose baseline neurocognitive functions (NCF) were already impaired are concerned about possible worsening of their NCF after WBRT. Progression of brain metastasis and uncontrolled extracranial disease explains some of the NCF impairment after WBRT. A prospective Radiation Therapy Oncology Group trial demonstrated that the average reduction in mini-mental status examination (MMSE) scores for patients whose BMs were radiographically controlled, was less than for those with uncontrolled metastasis, suggesting that progression of brain metastasis explains some of the NCF impairment after WBRT.[15]

For patients with a better prognosis, the results of Addeo *et al.* Yaneva *et al.* and Scott *et al.* showed that certain parameters of QOL significantly improved after WBRT.[16-18]

This study has a few limitations. The main difficulty was in collecting data in a population of patients whose life expectancy was short. Patients with short survival and deterioration of health may contribute to high attrition rates. A marked number of patients had either progressed in their illness or had died at 1 month follow-up. Consequently, the drop-out bias affected the research study so we have to exclude these patients. Only those were included who were able to complete follow-up assessments and are thus likely have a better prognosis than are the patients lost to follow-up or died in follow-up period.

Other thing should be considered when interpreting the findings to determine the benefit of WBRT/ 30 Gys with 20 Gys boost. Its effect needs to be distinguished from those of WBRT or appearance of new brain metastatic site or uncontrolled extracranial disease.

Another problem is the choice of QOL methodology. Although a number of validated QOL questionnaires specific to the concerns of metastatic brain cancer patients have been developed, no standard questionnaire has currently been established for this patient population, making comparisons of QOL across difficult trials. Spitzer Q-L index was used in this study as a measurement of QOL in this study which most of the time fulfill the requirement but it has limitation in neurocognitive and executive functions.

CONCLUSION

The findings in this study are similar to the literature in that majority with brain metastasis may not have improved regarding quality of life and symptoms in both arms. However, offering 30 Gys to whole brain and 20 Gys in boost to metastasis site is a reasonable option for patients with limited metastatic sites, having difference not more than 02 cm apart between two metastatic sites and controlled primary disease as compared to whole brain radiotherapy.

REFERENCES

1. Gercovich FG, Luna MA, Gottlieb JA. Increased incidence of cerebral metastases in sarcoma patients with prolonged survival from chemotherapy. Report of cases of leiomysarcoma and chondrosarcoma. *Cancer* 1975; **36**:1843-51.
2. Tsao MN, Lloyd NS, Wong RK, Rakovitch E, Chow E, Laperriere N. Radio therapeutic management of brain metastasis: a systemic review and meta-analysis. *Cancer Treat Rev* 2005; **31**: 256-73.
3. Arnold SM, Patchell RA. Diagnosis and management of brain metastasis. *Hematol Oncol Clin North Am* 2001; **15**:1085-107.
4. Wen PY, Black PM, Loeffler JS. Metastatic brain cancer. In: De Vita V, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 6th ed. Philadelphia: *Lippincott Williams & Wilkins;* 2001.p. 2655-670.
5. Zimm S, Wampler GL, Stablein D, Hazra T, Young HF. Intracerebral metastasis in solid tumour patients: natural history and results of treatment. *Cancer* 1981; **48**:384-94.
6. Sundstrom JT, Minn H, Lertola KK, Nordmann E. Prognosis of patients treated for intracranial metastases with whole-brain irradiation. *Ann Med* 1998; **30**:296-9.
7. Nieder C, Nestle U, Motaref B, Walter K, Niewald M, Schable K. Prognostic factors in brain metastasis: should patients be selected for aggressive treatment according to recursive partitioning analysis (RPA) classes? *Int J Radiat Oncol Biol Phys* 2000; **46**:297-302.
8. Weltman E, Salvajoli JV, Brandt RA, de Morais Hanriot R, Prisco FE, Cruz JC, *et al.* Radiosurgery for brain metastasis: a score index for predicting prognosis. *Int J Radiat Oncol Biol Phys* 2000; **46**:1155-61.
9. Spitzer WO, Dohson AJ, Hall J, Chesterman A, Levi J, Shepherd R, *et al.* Measuring the quality of life of cancer patients: a concise quality of life index for use by physicians. *J Chronic Diseases* 1981; **34**:585-97.
10. Patchell RA. The management of brain metastasis. *Cancer Treat Rev* 2003; **29**:533-40.
11. Posner JB. Management of central nervous system metastasis. *Sem Oncol* 1977; **4**:81-91.
12. Nguyen T, DeAngelis LM. Treatment of brain metastasis. *J Support Oncol* 2004; **2**:405-10.
13. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastasis correlates with survival and improved neurocognitive function. *J Clin Oncol* 2007; **25**:1260-6.
14. Roos DE, Wirth A, Burmeister BH, Spry NA, Drummond KJ, Beresford JA, *et al.* Whole brain irradiation following surgery or radiosurgery for solitary brain metastasis: mature results of a pre-maturely closed randomized trans-Tasman Radiation Oncology Group trial (TROG 98.05). *Radiother Oncol* 2006; **80**: 318-22.

15. Regine WF, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastasis patients treated with accelerated-fractionation vs. accelerated hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91-04. *Int J Radiat Oncol Biol Phys* 2001; **51**:711-7.

16. Addeo R, Caraglia M, Faiola V, Capasso E, Vincenzi B, Montella L, *et al*. Concomitant treatment of brain metastasis with whole brain radiotherapy and temozolomide (TMZ) is active and improves quality of life. *BMC Cancer* 2007; **7**:18.

17. Yaneva MP, Semerdjieva MA. Assessment of the effect of palliative radiotherapy for cancer patients with intracranial metastasis using EORTC-QOL-C30 questionnaire. *Folia Med (Plovdiv)* 2006; **48**:23-9.

18. Scott C, Suh J, Stea B, Nabid A, Hackman J. Improved survival, quality of life, and quality-adjusted survival in breast cancer patients treated with efaproxiral (Efaproxyn) plus wholebrain radiation therapy for brain metastasis. *Am J Clin Oncol* 2007; **30**: 580-7.

.....☆.....