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A Comparative Study of two Fractionations Schedule of Palliative Radiation Therapy in Metastatic Brain Tumour

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Abstract

Background: *Management of Brain Metastases is a significant health care problem and is most common intracranial malignancy in adults. Whole brain radiotherapy (WBRT) is a mainstay of treatment. However, there is need to develop fractionation schedules, but total dose still remains dilemma. This prospective study aims to determine treatment outcome and prognostic factors by making comparison of long-course and short-course WBRT schedules.*

Materials and Methods: *Sixty patients presented with symptomatic brain metastases previously untreated with WBRT were randomized in two arms containing 30 patients. Arm A treated with 30 Gy, 3 Gy/fraction (fr.), 10 fr. and arm B 20 Gy, 4 Gy /fr. (5fr.). All patients were assessed during WBRT and after completion of WBRT.*

Results: *At 6 month of completion of WBRT objective response rate complete and partial (CR+PR) was 36.6% in arm A and 40% in arm B (p=0.72). WBRT regimen was not associated with survival (p=0.79). On multivariate analysis, age ≤ 65 years (p < 0.05), Karnofsky performance score (KPS) ≥ 70 (vs <70, p < 0.01), no extra-cranial metastases (p < 0.01) were significantly associated with improved survival.*

Conclusions: *This study suggests that two fractionation schedules showed comparable results. Therefore, short-course WBRT may be used as an effective option in favor of small treatment time and convenient for patients.*

Keywords: *Brain metastases, Whole Brain Radiotherapy, Fractionation schedules.*

Introduction

Metastatic brain tumors are the most common intra-cranial malignancy in adults.[1]Metastatic brain tumor out number primary brain tumors by a factor of 10 to 1, with autopsy series demonstrating a 10-30% incidence rate for all patients with a diagnosis of cancer [2]. Brain metastases can be diagnosed at the same time or within one month of primary diagnosis, which occurs in about one-third of cases [3] (synchronous) or after the primary has been diagnosed (metachronous). Although every solid tumor may spread to brain. The most common primary site is lung followed by breast. The majority of patients presents with neurologic sign and symptoms.[4] Although Computed tomography (CT) scan may be useful in diagnosis, the modality of choice is Magnetic resonance imaging (MRI) as it is more sensitive to determine the number, distribution and size of lesions.[5] Typically, brain metastases are solid or ring enhancing lesion(s), pseudospherical in shape, multiple in number, occur in the grey-white matter junction[6] and occurs most frequently in the cerebral hemisphere (80%) followed by cerebellum (15%) and brain stem (<5%). In addition, lepto-meninges can also be involved. Key elements driving decision making for brain metastases care are patient factors and tumor factors. Patient factors includes patient's overall age, condition, performance status and systemic disease burden. Tumor factors include histological type, number, location of lesions, size of lesions, and more recently the biology of tumor based on molecular and genetic testing. Current treatment paradigms employ several treatment modalities including whole brain radiotherapy (WBRT), open surgical resection, Gamma knife and Cyberknife, traditional chemotherapy and newer targeted biological agents. Corticosteroids are frequently used to control brain edema. At present supportive care along with WBRT remains the standard of care [7] for all patients with multiple symptomatic brain metastases and lesions that are not amenable for surgical resection

As the overall survival for patients with brain metastases remains poor, the use of prognostic scales help to guide therapies. One of the useful prognostic scales was based on 1200 patients from three consecutive Radiation Therapy Oncology Group (RTOG) phase 3 brain metastases trials [8] from 1979 to 1993. Using recursive partitioning analysis (RPA) three well defined prognostic groups (RPA class I, II and III) were identified based on age (< 65 or = 65 and older), KPS of >70, = 70 or < 70, absence or presence of extra-cranial metastases and primary tumor status. In this study comparison was done in two palliative WBRT schedules in terms of evaluation disease outcome and prognostic factors.

Materials and Methods

Total 60 patients of brain metastases with a known primary were enrolled .All patients had already registered at regional cancer institute, Bikaner with a histo-pathologically proven malignancy. Patients were randomized in two arms, A and B, 30 patients in each arm, by using the web site Randomization.com prior to start WBRT. Patients characteristics were described in table 1,

Arm A treated with WBRT dose 30 Gy, 3 Gy/fraction (10 fr.) and arm B 20 Gy, 4 Gy/fr. (5fr.) on Telecobalt units Therateron 780 C and 780 E. WBRT was given by bilateral portals. Supportive care (specially mannitol, dexamethasone) was started at the beginning of treatment and also continued during radiotherapy. All statistical analyses were performed by using SPSS for windows, version 20.0

Results

A total of 60 patients of two arms were analyzed during WBRT and on follow-up at 1, 3 and 6 months after completion of radiotherapy. The treatment response in both arms was assessed by Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1). At completion of study objective response, complete response + partial response (CR+PR) was 36.6% (11 patients) in arm

A and 40% (12 patients) in arm B (p= 0.72). The median survival was 147days and 159 days in arm A and arm B respectively (p= 0.59). At 6 month overall survival was 43.3% in arm A and 40% in arm B; p= 0.79. The WBRT schedule had no significant impact on survival (Fig. 1). On multivariate analysis, (Table 3) improved survival was significantly associated with age ≤ 65 years, 95% confidence interval (CI) =1.65-5.87, p < 0.05, KPS ≥70, 95% CI= 1.57-6.39, p < 0.01, lack of extra-cranial metastases 95% CI=1.55-10.59 and p < 0.01. Multivariate analysis was showing prognostic factors for survival these were age, KPS score, lack of extra-cranial metastases.

Quality of life (QOL) score was assessed on basis of **EORTC QLQ-C30** questionnaire . QOL improved on follow-up studies in both arms similarly and on 3rd follow-up; p= 0.86.

Table 1: Baseline characteristics of patients

Characteristics of patients		**Number of patients**	
Age	≤ 65 years	**Arm A**	**Arm B**
		25	**24**
	>65 years	5	6
Sex	Male	17	19
	Female	13	11
KPS score	≥70	19	16
	<70	11	14
Socio-economic status	Urban	6	9
	Rural	24	21
Number of lesions	Single	3	1
	Multiple	27	29
Extra-cranial metastases	Yes	19	21
	No	11	9
Primary site of disease	Lung	15	19
	breast	9	6
	others	6	5

Table 2: Univariate analysis of different prognostic factors with survival after 1st, 2nd and 3rd follow up

Characteristics	**At 1st follow up**	**At 2nd follow up**	**At 3rd follow up**	**P value**
Sex				
Male	32 (88.9)	21 (58.3)	13 (36.1)	0.27
Female	22 (91.7)	18 (75.0)	12 (50.0)	
Age				
≤65 Years	45 (91.8)	36 (73.5)	23 (46.9)	0.01
>65 years	9 (81.8)	3 (27.3)	2 (18.2)	
KPS				
<70	21 (84.0)	11 (44.0)	4 (16.0)	<0.001
≥70	33 (94.3)	28 (80.0)	21 (60.0)	
Primary lesion				
Single	4 (100.0)	4 (100.0)	4 (100.0)	0.20
Multiple	50 (89.3)	35 (62.5)	21 (37.5)	
Extracranial metastasis				
Yes	34 (85.0)	22 (55.0)	10 (25.0)	0.002
No	20 (100.0)	17 (85.0)	15 (75.0)	

Table 3 : Multivariate analysis showing prognostic factors for survival

Prognostic factor	**Risk ratio**	**95% CI**	**P value**
Age ≤ 65	2.89	1.65-5.87	<0.05
KPS ≥70	3.17	1.57-6.39	<0.01
Extracranial metastasis	4.05	1.55-10.59	<0.01

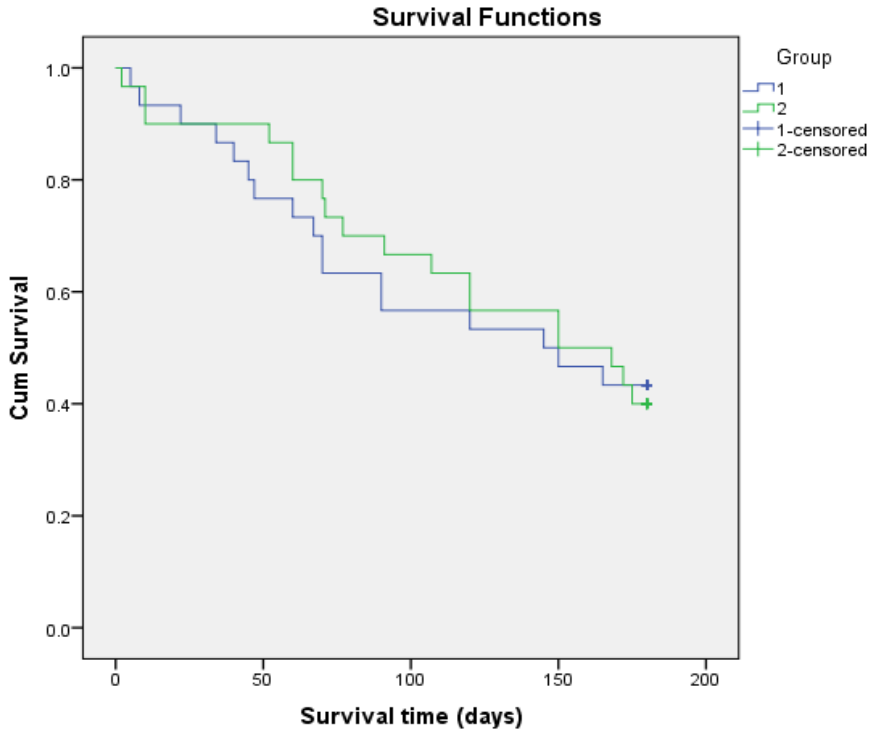

Figure 1: Comparison of short-course WBRT with 20 Gy in five fractions versus long-course WBRT with higher total doses (30 Gy in ten fractions) regarding survival following WBRT. (p=0.91)

Discussion

With gradual improvements in the care of cancer patients, longer survival is expected even in patients having multiple metastatic lesions in brain. WBRT is the most frequently administered treatment for patients with brain metastases. The shortest possible WBRT regimen that is as effective as longer programs would be the best option.

The present study compared short-course WBRT with 20 Gy in 5 fractions (4Gy/fr.) to long-course schedule with 30 Gy in 10 fr. (3 Gy/fr.) in 60 patients with known primary. As higher dose was prescribed in long-course than short-course, so long-course would be expected with better treatment response. The biological effectiveness of radiation schedules can be estimated with equivalent dose in 2 Gy fr. (EQD2). The EQD2 takes into account both total dose and dose/fr.[9]. The EQD2 for long-course is 32.5 Gy and for short-course was 23.3 Gy. Therefore, on basis of EQD2, one would still expect a better outcome after long-course WBRT than short-course. In contrast to these expectations, the median survival was 159 days in short-course and 147 days in long-course arm; p = 0.59.

Findings from the present study showed agreement with other studies that compared short-course and long-course WBRT programs with regard to survival in the treatment of brain metastases. Harwood et al compared 10 fractions of 3 Gy each with single-fraction of 10 Gy in 101 patients with brain metastases, and found median survival 4.0 months vs.4.0 months [10] similar results. Priestman et al observed a marginal advantage in median survival of one week (84 days vs. 77 days ; p = .04)) when 10 fractions of 3Gy each compared with 2 fractions of 6 Gy each in 533 patients.[11] Chatani et al[12] compared 5 fr. of 4 Gy each with 10 fr. of 3 Gy each in 70 patients of lung cancer with elevated dehydrogenase level. The 6 month median survival was 3.4 months and 2.4 months respectively (p= .94). According to the findings of present study, short-course WBRT may be considered preferable than longer schedule, as patients with brain metastases are often debilitated and would benefit by spending less time in receiving WBRT. In current study

objective treatment response on basis of RECIST Criteria (complete + partial) at 6 month post radiotherapy follow-up was 36.6% (11 patient) in arm A and in arm B 40% (12 patients) p =0.72. Overall survival was virtually the same in both treatment regimens.

The treatment of brain metastases also depends on the number of lesions. Patients with multiple lesions were reported not so much benefited from aggressive treatment such as surgical resection or radiosurgrey as single lesion or very limited number of brain metastases having patients [13,14]. In our study single lesion in brain having patients were very less so it was not reported as a prognostic factor. In the present study, improved survival was significantly associated with younger age [(≤65 years), p=<0.05], KPS value ≥70, p=<0.01, lack of extra-cranial metastases (p=<0.01) These findings were according with the RPA reported by Gasper et al [8].In this analysis age, KPS, lack of extra-cranial metastases were identified as the strongest predictors of survival in patients with brain metastases.

Lagerwaard and Levendag reported that lower systemic tumor activity showed better median survival ranging from 6.6 months for "none" (controlled primary with no systemic metastases) to 3.4 months and 2.4 months in "limited" (controlled primary) and "extensive"(uncontrolled primary with systemic metastases) group of patients respectively[15]. In our study there is only one patient, a female patient from short-course from "none" group having better survival > 1 year. We observed treatment response was not showing significance among two arms. One patient from long-course showed progressive disease (PD) in the form of new lesions at 3rd follow-up, so further treatment line should be changed. Quality of life (EORTC-QLQ-C-30) improved in both arms on follow-up was non-significant (p=0.86).

Conclusions

This prospective randomized study was undertaken to evaluate treatment response, overall response and quality of life in two different fractionation schedules of WBRT in patients with brain metastases. Study of prognostic factors was also a important concern of this study. Both arms were showing comparable results. Short-course regimen appears preferable for the patients having multiple lesions, absence of extra-cranial metastases, older age and lesser KPS values. As short-course WBRT is less time consuming and more convenient, so in future it may be recommended.

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