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RESEARCH ARTICLE

# Comparison of Long-Course and Short-Course Whole-Brain Radiotherapy for Brain Metastases: A Prospective Randomized Study

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## Abstract

**Background:** Brain metastases represent the most common intracranial malignancy in adults and remain a major therapeutic challenge. Whole-brain radiation therapy (WBRT) continues to be an important palliative treatment modality for patients with symptomatic brain metastases. However, the optimal fractionation schedule remains a subject of clinical consideration, particularly regarding symptom control, survival outcomes, and healthcare resource utilization. This prospective randomized study aimed to compare overall survival outcomes between two WBRT fractionation schedules and to identify prognostic factors associated with survival. **Materials and Methods:** A total of 60 previously untreated patients with symptomatic brain metastases were prospectively randomized to receive WBRT using either a long-course regimen (30 Gy delivered in 10 fractions; Arm A) or a short-course regimen (20 Gy delivered in 5 fractions; Arm B). Patients were evaluated during treatment and at 1, 3, 6, 9, and 12 months after completion of WBRT. Overall survival, treatment response, prognostic factors, and quality of life outcomes were assessed. **Results:** At 12 months after WBRT, the objective response rate (complete and partial responses) was 8.0% in Arm A and 16.66% in Arm B. No significant difference in overall survival was observed between the two treatment groups ($p = 0.42$). Multivariate Cox regression analysis demonstrated that the absence of extracranial metastases was significantly associated with improved survival at 12 months after WBRT, while age and the number of brain lesions showed trends toward better survival outcomes. Quality of life assessment using the EORTC QLQ-C30 questionnaire demonstrated comparable improvements in both groups. **Conclusions:** Both WBRT fractionation schedules demonstrated comparable survival and quality-of-life outcomes in patients with symptomatic brain metastases. Short-course WBRT may represent a reasonable alternative for selected patients by reducing treatment duration and healthcare resource burden without compromising clinical outcomes.

**Keywords:** Brain metastases, Whole-brain radiotherapy, WBRT fractionation, Long-course WBRT, Short-course WBRT

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## Introduction

Brain metastases represent the most common intracranial malignancy in adults, occurring in approximately 20–40% of patients with cancer. Autopsy studies have reported brain involvement in 10–30% of patients with systemic malignancies, highlighting brain metastases as a frequent neurological complication associated with substantial morbidity and mortality [1,2].

The reported incidence of brain metastases has increased over recent decades, likely due to improvements in neuroimaging techniques, earlier detection, and advances in systemic cancer therapies that have prolonged patient survival. Brain metastases may occur synchronously with the diagnosis of the primary malignancy or develop later as metachronous lesions [3]. Lung cancer represents the most common primary source, followed by breast cancer; however, almost any solid tumor has the potential to

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metastasize to the brain. Magnetic resonance imaging (MRI) remains the preferred diagnostic modality because of its superior sensitivity in detecting the number, location, and size of metastatic lesions [4].

Approximately 80% of brain metastases occur within the cerebral hemispheres, followed by the cerebellum and brainstem. Lesions are frequently located at the gray-white matter junction and may present as multiple solid or ring-enhancing masses. Leptomeningeal involvement may also occur in a subset of patients [5].

Treatment decisions for patients with brain metastases depend on multiple patient- and tumor-related factors. Patient-related factors include age, performance status, neurological condition, and the extent of extracranial disease, whereas tumor-related factors include histological subtype, number, size, and location of lesions, as well as molecular characteristics. Current therapeutic approaches include corticosteroids, radiotherapy, surgery, stereotactic radiosurgery, systemic therapy, and supportive care. Without treatment, median survival is approximately one month, whereas corticosteroid therapy and cranial irradiation may extend survival to approximately two and three to six months, respectively [6].

Whole-brain radiotherapy (WBRT) remains an important palliative treatment option for patients with multiple symptomatic brain metastases or lesions that are unsuitable for surgical resection or stereotactic approaches [7]. However, because overall survival remains limited, treatment selection should consider both expected clinical benefit and the patient's overall condition. Prognostic scoring systems have therefore been developed to assist clinical decision-making. One widely used model was derived from 1200 patients enrolled in three consecutive Radiation Therapy Oncology Group (RTOG) phase III trials conducted between 1979 and 1993. Using recursive partitioning analysis (RPA), three prognostic classes were identified based on age, Karnofsky Performance Status (KPS), extracranial metastases, and primary tumor status [8].

Although WBRT is widely used for palliation, the optimal fractionation schedule remains controversial, particularly in terms of balancing survival outcomes, symptom control, quality of life, and healthcare resource utilization. Therefore, this prospective randomized study aimed to compare two commonly used WBRT fractionation schedules (30 Gy in 10 fractions versus 20 Gy in 5 fractions) and to evaluate their effects on overall survival, treatment response, quality of life, and prognostic factors associated with patient outcomes.

## Material and Methods

*Study Design and Setting*

This prospective randomized study was conducted at the State Cancer Institute and Research Institute, S.M.S. Medical College, Jaipur, India, and its associated hospitals. The study was conducted between February 2023 and July 2025. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants before enrollment.

*Study Population*

A total of 59 patients with brain metastases from histopathologically confirmed primary malignancies were enrolled in the study and randomly allocated into two treatment groups (Arm A and Arm B) before initiation of whole-brain radiotherapy (WBRT). Baseline demographic and clinical characteristics of the patients are summarized in Table 1.

*Eligibility Criteria*

Patients aged ≤80 years were eligible for inclusion if they had a histopathologically confirmed primary malignancy with radiologically confirmed brain metastases and measurable intracranial lesions assessable by magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CECT). Patients were excluded if they had previously received prophylactic cranial irradiation, had undergone prior treatment for primary or metastatic tumors, had any contraindication to radiotherapy, presented with uncontrolled comorbid conditions such as severe hypertension or diabetes mellitus, or refused to provide written informed consent.

*Treatment Protocol and Follow-up*

Patients in Arm A received WBRT at a total dose of 30 Gy delivered in 10 fractions of 3 Gy each over two weeks, whereas patients in Arm B received 20 Gy delivered in 5

Table 1. Baseline Demographic and Clinical Characteristics of Patients According to WBRT Fractionation Group.

| Patient characteristics | Arm A (n=29) (%) | Arm B (n=30) (%) | p-value |
|---|---|---|---|
| Age, years | | | |
| ≤65 | 25 (86.2) | 24 (80.0) | |
| >65 | 4 (13.8) | 6 (20.0) | |
| Sex | | | |
| Male | 18 (62.1) | 20 (66.7) | |
| Female | 11 (37.9) | 10 (33.3) | |
| Karnofsky Performance Status (KPS) | | | |
| ≥70 | 19 (65.5) | 16 (53.3) | |
| <70 | 10 (34.5) | 14 (46.7) | |
| Site of residence | | | |
| Urban | 6 (20.7) | 10 (33.3) | |
| Rural | 23 (79.3) | 20 (66.7 | |
| Number of brain lesions | | | |
| Single lesion | 2 (6.9) | 2 (6.7) | |
| Multiple lesions | 27 (93.1) | 28 (93.3) | |
| Extracranial metastases | | | |
| Present | 18 (62.1) | 21 (70.0) | |
| Absent | 11 (37.9) | 9 (30.0) | |
| Primary tumor site | | | |
| Lung | 15 (51.7) | 18 (60.0) | |
| Breast | 8 (27.6) | 7 (23.3) | |
| Others | 6 (20.7) | 5 (16.7) | |

fractions of 4 Gy each over one week. Radiotherapy was delivered using a telecobalt unit with bilateral opposed portals.

Supportive management, including corticosteroids (dexamethasone) and measures for intracranial pressure control (such as mannitol when clinically indicated), was initiated at the start of treatment and continued throughout the radiotherapy course.

Patients were evaluated at 1, 3, 6, 9, and 12 months following completion of WBRT. Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and overall survival outcomes were recorded.

*Statistical Analysis*

Statistical analyses were performed using SPSS software for Windows, version 23.0. Continuous variables were summarized using appropriate descriptive statistics, and categorical variables were expressed as frequencies and percentages. Overall survival was estimated using the Kaplan–Meier method, and survival differences between treatment groups were assessed using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify independent prognostic factors associated with overall survival. A p-value <0.05 was considered statistically significant.

## Results

A total of 59 patients from both treatment arms were analyzed before initiation of WBRT and were followed at 1, 3, 6, 9, and 12 months after completion of radiotherapy. Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. At the end of the 12-month follow-up period, the objective response rate (complete response plus partial response; CR + PR) was 8.0% (n = 2) in Arm A and 16.66% (n = 4) in Arm B.

The median overall survival was 7.96 months in Arm A and 11.22 months in Arm B. Kaplan–Meier survival analysis demonstrated no statistically significant difference in overall survival between the two WBRT fractionation schedules (p = 0.42) (Table 2).

Among the evaluated prognostic variables, the presence of extracranial metastases was significantly associated with overall survival based on Fisher's exact test and chi-square analysis (p = 0.038). Other factors, including gender, age, Karnofsky Performance Status (KPS), and number of brain lesions, were not significantly associated with survival outcomes.

Quality of life was assessed using the EORTC QLQ-C30 questionnaire. Both treatment groups demonstrated comparable improvements in quality-of-life scores during follow-up, with no statistically significant difference between the groups (p = 0.86).

## Discussion

Advances in cancer diagnosis and treatment have resulted in prolonged survival among patients with metastatic disease; consequently, the incidence of brain metastases has increased. Although brain metastases are often considered an advanced stage of systemic malignancy, appropriate local treatment can provide meaningful symptom relief and may contribute to improved quality of life and survival outcomes. In many patients, mortality is primarily related to progression of extracranial disease rather than intracranial recurrence.

Whole-brain radiotherapy (WBRT) remains one of the most commonly used treatment approaches for patients with multiple symptomatic brain metastases who are not suitable candidates for surgery or stereotactic radiosurgery. However, the optimal WBRT fractionation schedule remains a matter of clinical debate. A shorter treatment course may be advantageous for patients with limited life expectancy by reducing treatment duration, hospital visits, and healthcare burden, provided that clinical outcomes are not compromised.

The present study compared two commonly used WBRT regimens: 30 Gy delivered in 10 fractions and 20 Gy delivered in 5 fractions. Although the long-course regimen provides a higher total radiation dose and a higher biologically effective dose, our findings demonstrated no significant difference in overall survival between the two fractionation schedules. The equivalent dose in 2 Gy fractions (EQD2), which considers both total radiation dose and dose per fraction, was higher in the long-course regimen; however, this dosimetric advantage did not translate into a measurable survival benefit in our cohort [9].

Our findings are consistent with previous studies evaluating different WBRT fractionation schedules. Harwood et al. compared a 30 Gy in 10 fractions regimen with a single 10 Gy fraction in patients with brain metastases and reported comparable median survival outcomes between treatment groups [10]. Similarly,

Table 2. Univariate Analysis of Prognostic Factors Associated with Overall Survival.

| Prognostic factor | Category | Median OS (months) | p-value |
|---|---|---|---|
| Gender | Male | 5.11 | 0.691 |
| | Female | 7.02 | |
| Age | ≤65 years | 6.53 | 0.065 |
| | >65 years | 3.20 | |
| KPS score | <70 | 2.71 | 0.223 |
| | ≥70 | 7.26 | |
| Number of brain lesions | Single | 10.50 | 0.065 |
| | Multiple | 5.60 | |
| Extracranial metastases | Present | 4.83 | 0.038 |
| | Absent | 6.90 | |

Priestman et al. observed only a modest survival difference when comparing different fractionation approaches, suggesting limited clinical benefit from prolonged treatment schedules in patients with advanced disease [11]. Chatani et al. also reported no significant survival difference between 20 Gy in 5 fractions and 30 Gy in 10 fractions among patients with brain metastases from lung cancer [12].

In the context of limited survival expectancy among many patients with brain metastases, the selection of WBRT schedules should consider not only tumor control but also patient convenience, quality of life, and healthcare resource utilization. Therefore, short-course WBRT may represent a reasonable alternative for selected patients, particularly those with poor prognosis or extensive systemic disease, when equivalent clinical outcomes can be achieved.

Prognostic factors play an important role in treatment selection and outcome prediction in patients with brain metastases. The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification identified age, Karnofsky Performance Status (KPS), extracranial metastases, and primary tumor status as important determinants of survival [8]. In the present study, younger age, higher KPS score, and absence of extracranial metastases were associated with improved survival outcomes, which is consistent with previous prognostic models.

Lagerwaard and Levendag also demonstrated that the extent of systemic disease significantly influences survival among patients with brain metastases, with better outcomes observed in patients with controlled primary tumors and absence of extracranial metastatic disease [13]. These findings highlight the importance of considering systemic disease status when selecting treatment intensity and predicting prognosis.

Quality of life is a critical outcome in patients undergoing palliative radiotherapy. In our study, both WBRT regimens resulted in comparable improvements in quality-of-life scores assessed using the EORTC QLQ-C30 questionnaire, suggesting that the shorter treatment schedule did not negatively affect patient-reported outcomes.

Overall, the findings of this prospective randomized study indicate that short-course WBRT provides survival and quality-of-life outcomes comparable to those of long-course WBRT. Considering the reduced treatment duration and lower burden on patients and healthcare facilities, short-course WBRT may be considered an appropriate option for selected patients with symptomatic brain metastases.

In conclusion, This prospective randomized study demonstrated comparable treatment response, overall survival, and quality-of-life outcomes between long-course and short-course WBRT regimens in patients with brain metastases. Prognostic factors, particularly patient and disease-related characteristics, remain important considerations in predicting survival outcomes. Given the similar clinical outcomes observed, short-course WBRT may represent a reasonable treatment option for selected patients by reducing treatment duration and minimizing the burden of prolonged radiotherapy schedules on patients and healthcare facilities.

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*Statement of Transparency and Principles*

- The authors declare no conflict of interest.
- The study was approved by the Research Ethics Committee of the authors' affiliated institution.
- The study data are available upon reasonable request.
- All authors contributed to the implementation of this research.

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