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Original Research Article

Long-course versus short-course palliative cranial irradiation in brain metastases: a comparative study

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ABSTRACT

Background: Brain metastases are the most common intracranial malignancy in adults and their management poses a significant healthcare problem. Of the various options available, whole brain radiotherapy (WBRT) remains the mainstay of treatment. Nonetheless, there is a need to develop fractionation schedules for best symptom palliation and prolonged survival. This prospective study aims to compare treatment outcome in terms of overall survival in two different WBRT schedules and determine the prognostic factors affecting this outcome.
Methods: Sixty previously untreated patients with symptomatic brain metastases were randomized in two arms of 30 patients each to receive WBRT. Arm A patients received 30Gy in 10 fractions (long-course) and arm B received 20Gy in 5 fractions (short-course). All patients were assessed during and after completion of WBRT at 1, 3, 6, 9 and 12 months.
Results: At 12 months post WBRT, the objective response rate i.e. complete and partial response (CR+PR) was 6.67% in arm A and 13.34% in arm B (p=0.96). Both WBRT regimens showed similar survival (p=0.65). On multivariate linear regression analysis, age ≤65 years, Karnofsky performance score (KPS) ≥70 and lack of extra-cranial metastases were significantly associated with improved survival at the end of 12 months post WBRT. EORTC QLQ-C30 showed similar improvement in quality of life in both the arms (p=0.86).
Conclusions: This study suggests comparable results in the two fractionation schedules. Therefore, short-course WBRT may be used as a more convenient option in favour of shorter hospital stay and lesser burden on RT machines.

Keywords: Brain metastases, Fractionation schedules, Long course, Short course, Whole Brain Radiotherapy

INTRODUCTION

Brain metastases are the most common intracranial malignancy in adults affecting 20-40% of all cancer patients. They represent one of the most frequent neurological complications of systemic cancer as a major cause of morbidity and mortality out numbering 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.[1,2] The incidence has increased with time probably as a result of advances in neuroimaging which has led to early detection of brain metastases as well as advances in treatment of primary tumor and systemic disease which has led to improved

survival. These can be diagnosed at the same time or within one month of primary diagnosis (synchronous) which occurs in about one-third of cases or after the primary has been diagnosed (metachronous).[3]

Although every solid tumor may spread to the brain, the most common primary site is lung followed by breast. Magnetic resonance imaging (MRI) is the diagnostic modality of choice as it is more sensitive in determining the number, distribution and size of lesions.[4] Typically, brain metastases are multiple, solid or ring enhancing lesions, pseudo-spherical in shape, found in the grey-white matter junction and occur most frequently in the cerebral hemisphere (80%) followed by cerebellum (15%) and brain stem (<5%). In addition, lepto-meninges can also be involved.[5]

Key elements driving decision making for brain metastases care are patient factors and tumor factors. Patient factors include their age, general 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 steroids, radiotherapy, surgery, stereotactic radiosurgery, chemotherapy and supportive management. Median survival is around one month without treatment, two months with steroids, and three to six months with cranial irradiation.[6] At present, supportive care along with WBRT remains the standard of care for all patients with multiple symptomatic brain metastases and lesions that are not amenable for surgical resection.[7]

As the overall survival for patients with brain metastases remains poor, the use of prognostic scales helps 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 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 years and older), KPS (≥70 and <70), absence or presence of extracranial metastases and primary tumor status. [8] In this study comparison was done between two palliative WBRT schedules in terms of evaluation of disease outcome, prognostic factors and overall survival.

METHODS

Study area: Acharya Tulsi Regional Cancer Treatment & Research Institute, Sardar Patel Medical College & associated group of hospitals, Bikaner, India.

Study population & period: A total of 60 patients of brain metastasis with a known, histopathologically proven primary were enrolled from February 2016 to July 2017 and randomised into two arms, A and B, prior to start of Whole Brain Radiation Therapy (WBRT). Patient characteristics were as described in (Table 1).

Inclusion criteria

- Age ≤80 years
- Histopathologically proven primary malignancy with brain metastasis
- Measurable brain metastasis assessable by MRI/CECT

Exclusion criteria

- Patients who had received prophylactic RT for brain metastasis
- History of any previous treatment for primary or secondary tumours
- Any contraindications for RT
- Uncontrolled co-morbidities like hypertension, diabetes mellitus, etc
- Refusal to give written informed consent

Study design

Patients in arm A were treated with a total dose of 30Gy (3Gy per fraction in 10 fractions over 2 weeks); and those in arm B were treated with a total dose of 20Gy (4Gy per fraction in 5 fractions over 1 week) on telecobalt units - Theratron 780C and 780E. Patients were treated with bilateral portals and supportive care (mannitol, dexamethasone, etc.) was started at the beginning of treatment and continued throughout the WBRT. They were followed up at 1,3,6,9 and 12 months after treatment completion for response assessment (RECIST, version 1.1) and overall survival.

Statistical analyses

The median survival was compared using the Kaplan-Meier survival curve. Univariate and multivariate linear regression analyses were done to establish the prognostic factors for overall survival. All the statistical analyses were performed by using SPSS for windows, version 23.0

RESULTS

All 60 patients of the two arms were analyzed prior to WBRT and followed up at 1, 3, 6, 9 and 12 months after completion of RT. The treatment response in both arms was assessed by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

At completion of study, the objective response i.e. complete response + partial response (CR+PR) was 6.67% (2 patients) in arm A and 13.34% (4 patients) in arm B (p= 0.96). The median survival was 132.5 days and 159 days in arm A and arm B respectively (p=0.65). On Kaplan-Meier survival analysis curve, the WBRT schedules had no significant impact on survival (p=0.65) (Figure 1).

Table 1: Baseline characteristics of patients.

Patient characteristics		Number of patients	
		Arm A	Arm B
Age	</=65 years	25	24
	>65 years	5	6
Gender	Male	17	19
	Female	13	11
KPS*	>/=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

*The Karnofsky Performance Score (KPS) ranking runs from 100 to 0, where 100 is "perfect" health and 0 is “death”

On univariate analysis of different prognostic factors (Table 2), age <65 years (p=0.0040), KPS >70 (p=0.0007), single primary lesion (p=0.0168) and absence of extra-cranial metastasis (p=0.0039) were statistically significant in improving overall survival up to 1-year post WBRT. On multivariate linear regression analysis of prognostic factors on overall survival at 12months post WBRT, (Table 3) improved survival was significantly associated with age ≤65 years (p=0.036), KPS ≥70 (p=0.002) and lack of extra-cranial metastases (p=0.001). Single primary lesion was not statistically significant (p=0.199) in improving survival 1 year post WBRT on multivariate analysis. Quality of life (QOL) score was assessed on basis of EORTC QLQ-C30 questionnaire. QOL improved on follow-up studies in both arms similarly (p=0.86).

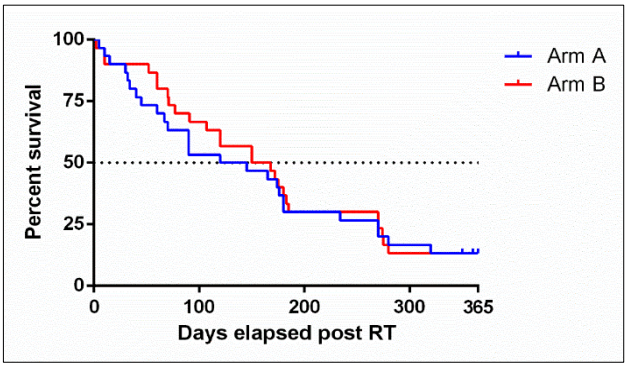

Figure 1: Comparison of long-course WBRT with 30Gy in ten fractions versus short-course WBRT with 20Gy in five fractions in terms of survival following RT (p=0.65).

Table 2: Univariate analysis of different prognostic factors with survival after 1st, 2nd, 3rd, 4th and 5th follow up.

Characteristics	Pre WBRT	1st F/U	2nd F/U	3rd F/U	4th F/U	5th F/U	Mean O.S.±S.E.M*	p-value
Gender								
Male	36(100)	32(88.9)	21(58.3)	13(36.1)	9(25.0)	4(11.0)	147.7±19.42	0.2765
Female	24(100)	22(91.7)	18(75.0)	12(50.0)	9(38.0)	3(13.0)	181.0±23.00	
Age								
</=65 years	49(100)	45(91.8)	36(73.5)	23(46.9)	18(37.0)	7(14.0)	180.8±16.53	0.004
>65 years	11(100)	9(81.8)	3(27.3)	2(18.2)	0(0)	0(0)	72.82±18.05	
KPS Score								
<70	25(100)	21(84.0)	11(44.0)	4(16.0)	3(12.0)	1(4.0)	103.6±18.08	0.0007
>/=70	35(100)	33(94.3)	28(80.0)	21(60.0)	15(43.0)	6(17.0)	202.0±19.35	
Primary lesion								
Single	4(100)	4(100.0)	4(100.0)	4(100.0)	3(75.0)	2(50.0)	292.5±43.08	0.0168
Multiple	56(100)	50(89.3)	35(62.5)	21(37.5)	15(27.0)	5(9.0)	151.6±14.93	
Extra-cranial metastases								
Yes	40(100)	34(85.0)	22(55.0)	10(25.0)	10(25.0)	2(5.0)	137.8±15.47	0.0039
No	20(100)	20(100.0)	17(85.0)	15(75.0)	8(40.0)	5(25.0)	237.0±31.62	

*Mean Overall Survival (O.S.) + Standard Error of Measurement (S.E.M)

DISCUSSION

Gradual improvements in the care of cancer patients have led to a longer survival in patients with metastatic lesions in the brain. The development of brain metastases is often viewed as the end stage of the disease course. Aggressive management of brain metastases is effective in both symptom palliation and the prolongation of life. The majority of patients with controlled intracranial metastases will expire from systemic disease rather than

from recurrence of these metastases. Out of the various options available, WBRT is the most frequently administered treatment for patients with multiple brain metastases. The best option would be the shortest possible WBRT regimen that is as effective as longer programs in terms of symptom control and overall survival. The present study compared long-course WBRT with 30Gy in 10 fractions (3Gy/fraction) to a short-course schedule with 20Gy in 5 fractions (4Gy/fraction) in 60 patients with known primary. Prescription of a higher dose in the long-course arm leads to the expectation of a better treatment response. The biological effectiveness of radiation schedules can be estimated with equivalent dose in 2 Gy/fraction (EQD2). The EQD2 takes into account both total dose and dose/fraction.[9] The EQD2 for long-course was 32.5Gy and for short-course was 23.3Gy. Therefore, on the 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 arm and 132.5 days in long-course arm (p=0.65).

Findings from the present study showed similarity 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 3Gy each with single-fraction of 10Gy in 101 patients with brain metastases and found similar median survival of 4.0 months vs. 4.0 months.[10] Priestman et. al. observed a marginal advantage in median survival of one week (84 days vs. 77 days; p=0.04)) when 10 fractions of 3Gy each were compared with 2 fractions of 6Gy each in 533 patients.[11] Chatani et. al. compared 5 fractions of 4Gy each with 10 fractions of 3Gy each in 70 patients of brain metastases with primary lung cancer and an elevated lactate dehydrogenase level. The 6-month median survival was 3.4 months and 2.4 months respectively (p=0.94).[12] In concordance with the findings of the present study, short-course WBRT may be considered preferable than the longer schedule, as patients with brain metastases are often debilitated and would benefit by spending less time in receiving WBRT. In the current study, objective treatment response on the basis of RECIST Criteria (complete+partial) at 12 months post radiotherapy follow-up was 6.67% (2 patients) in arm A and 13.34% (4 patients) in arm B (p=0.96).

Overall survival was virtually similar in both treatment regimens (p=0.65). The treatment of brain metastases also depends on the number of lesions. Patients with multiple lesions were not reported to benefit much from aggressive treatments like surgical resection or radiosurgery as patients with single or very limited number of brain metastases.[13,14] In our study, patients with a single lesion were very few; hence it was not reported as a prognostic factor. Improved survival was significantly associated with younger age [(≤65 years), p=0.036], KPS value ≥70 (p=0.002) and lack of extra-cranial metastases (p=0.001). These findings were in accordance with the RPA reported by Gasper et. al.[8] In this analysis, age, KPS and 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 for "limited" (controlled primary) and 2.4 months for "extensive" (uncontrolled primary with systemic metastases) group of patients.[15] In our study there was only one female patient from the short-course who belonged to the "none" group having better survival of more than one year. We observed no significant differences in treatment response among the two arms. One patient from long-course showed progressive disease (PD) in the form of new lesions at 4th follow-up, so the further treatment line was changed. Quality of life (EORTC-QLQ-C-30) improved similarly in both arms (p=0.86).[7]

CONCLUSION

This prospective randomized study was undertaken to evaluate treatment response, overall survival and quality of life in two different fractionation schedules of WBRT in patients with brain metastases. Study of prognostic factors was also of important concern in this study. Both arms showed comparable results. As short-course WBRT is less time consuming and more convenient for the patient as well as the institute, it may be recommended in the future.

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