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Trifiletti, Daniel
Ballman, Karla
Brown, Paul
et al.

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Optimizing Whole Brain Radiation Therapy Dose and Fractionation: Results From a Prospective Phase 3 Trial (NCCTG N107C [Alliance]/CEC.3)

Daniel M. Trifiletti, MD[*], **Karla V. Ballman, PhD**[†,‡], **Paul D. Brown, MD**[§], **S. Keith Anderson, MS**[†,§], **Xiomara W. Carrero, BS**[†,§], **Jane H. Cerhan, PhD**[§], **Anthony C. Whitton, MD**[‖], **Jeffrey Greenspoon, MD**[‖], **Ian F. Parney, MD**[§], **Nadia N. Laack, MD**[§], **Jonathan B. Ashman, MD**[¶], **Jean-Paul Bahary, MD**[#], **Costas G. Hadjipanayis, MD**[**], **James J. Urbanic, MD**[††], **Fred G. Barker II, MD**[‡‡], **Elana Farace, PhD**[§§], **Deepak Khuntia, MD**[‖‖], **Caterina Giannini, MD**[§], **Jan C. Buckner, MD**[§], **Evanthia Galanis, MD**[§], **David Roberge, MD**[#]

[*]Mayo Clinic, Jacksonville, Florida

[†]Alliance Statistics and Data Center, Mayo Clinic, Rochester, Minnesota

[‡]Weill Medical College of Cornell University, New York, New York

[§]Mayo Clinic, Rochester, Minnesota

[‖]Juravinski Cancer Centre, Hamilton, Ontario, Canada

[¶]Mayo Clinic, Phoenix/Scottsdale, Arizona

[#]CHUM, Montreal, QC, Canada

[**]Mount Sinai Beth Israel, New York, New York

[††]University of California San Diego, Moores Cancer Center, La Jolla, California

[‡‡]Massachusetts General Hospital Cancer Center, Boston, Massachusetts

[§§]Penn State University College of Medicine, Hershey, Pennsylvania

[‖‖]Precision Cancer Specialists and Varian Medical Systems, Palo Alto, California

Abstract

Purpose: Whole brain radiation therapy (WBRT) remains a commonly used cancer treatment, although controversy exists regarding the optimal dose/fractionation to optimize intracranial tumor control and minimize resultant cognitive deficits.

Methods and Materials: NCCTG N107C [Alliance]/CEC.3 randomized 194 patients with brain metastases to either stereotactic radiosurgery alone or WBRT after surgical resection. Among the 92 patients receiving WBRT, sites predetermined the dose/fractionation that would be used for all patients treated at that site (either 30 Gy in 10 fractions or 37.5 Gy in 15 fractions). Analyses were performed using Kaplan-Meier estimates, log rank tests, and Fisher's exact tests.

Corresponding author: Daniel M. Trifiletti, MD; trifiletti.daniel@mayo.edu.

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Results: Among 92 patients treated with surgical resection and adjuvant WBRT, 49 were treated with 30 Gy in 10 fractions (53%), and 43 were treated with 37.5 Gy in 15 fractions (47%). Baseline characteristics, including cognitive testing, were well balanced between groups with the exception of primary tumor type (lung cancer histology was more frequent with protracted WBRT: 72% vs 45%, $P = .01$), and 93% of patients completed the full course of WBRT. A more protracted WBRT dose regimen (37.5 Gy in 15 fractions) did not significantly affect time to cognitive failure (hazard ratio [HR], 0.9; 95% confidence interval [CI], 0.6-1.39; $P = .66$), surgical bed control (HR, 0.52 [95% CI, 0.22-1.25], $P = .14$), intracranial tumor control (HR, 0.56 [95% CI, 0.28-1.12], $P = .09$), or overall survival (HR, 0.72 [95% CI, 0.45-1.16], $P = .18$). Although there was no reported radionecrosis, there is a statistically significant increase in the risk of at least 1 grade ≥3 adverse event with 37.5 Gy in 15 fractions versus 30 Gy in 10 fractions (54% vs 31%, respectively, $P = .03$).

Conclusions: This post hoc analysis does not demonstrate that protracted WBRT courses reduce the risk of cognitive deficit, improve tumor control in the hypoxic surgical cavity, or otherwise improve the therapeutic ratio. Adverse events were significantly higher with the lengthened course of WBRT. For patients with brain metastases where WBRT is recommended, shorter course hypofractionated regimens remain the current standard of care.

Summary

This post hoc analysis of N107C does not demonstrate that protracted WBRT courses reduce the risk of cognitive deficit, improve tumor control, or otherwise improve the therapeutic ratio. Adverse events were significantly higher with the lengthened course of WBRT.

Introduction

Whole brain radiation therapy (WBRT) for patients with brain metastases remains a commonly used cancer treatment today, although it has been associated with cognitive decline after therapy.[1,2] In recent years, several efforts have been explored to reduce the risk of cognitive decline after WBRT, including concurrent memantine and hippocampal avoidance,[3,4] as well as the omission of WBRT altogether.[5]

Despite these advances, controversy has existed for decades regarding the optimal dose and fractionation to optimize intracranial tumor control and minimize resultant cognitive deficits. Several prior prospective trials demonstrated similar overall survival (OS) regardless of WBRT dose.[6–9] There has since been a trend toward improved OS of patients with brain metastases, likely owing to a combination of more effective systemic therapies and more aggressive treatment.[10] As a result of this improved patient survival and the fear of the cognitive toxicity of WBRT, the controversy as to the optimum dose and fractionation of WBRT remains relevant today.

There does exist radiobiologic rationale that a more prolonged WBRT course, with lower dose per treatment, could result in decreased neuronal injury and improved tumor control, particularly in a hypoxic tumor environment such as that of a surgical cavity.[11] Presumably, this widening of the therapeutic ratio is the impetus for the continued utilization of prolonged WBRT courses in this patient population.

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Our primary aim was to use the recent results of N107C/CEC.3, a prospective clinical trial for patients with brain metastases,[1] to evaluate the impact of WBRT dose and fractionation on postoperative bed tumor control, total intracranial tumor control, OS, cognitive outcomes, and other adverse events.

Methods and Materials

In brief, North Central Cancer Treatment Group N107C/CEC.3 was a prospective randomized trial that enrolled 194 patients across 48 institutions in the United States and Canada (XXXXX is now part of Alliance for Clinical Trials in Oncology). These patients were randomized to have their tumor bed managed with either stereotactic radiosurgery alone or WBRT.[1] Before patient enrollment, each participating institution provided approval from institutional review boards, and each patient provided written informed consent (ClinicalTrials.gov identifier). Patients with up to 3 unresected brain metastases (any nonbrain primary tumor histology aside from germ cell tumors, small cell lung cancer, and lymphoma) and a tumor cavity of less than 5.0 cm maximum dimension were permitted enrollment. The Consolidated Standards of Reporting Trials diagram for this study has been previously reported.[1] Among the 92 patients receiving WBRT, sites predetermined the fractionation schedule that would be used for all patients treated at that site to be either 30 Gy in 10 fractions or a more protracted course of 37.5 Gy in 15 fractions (protracted WBRT). Cytotoxic chemotherapy was not allowed concurrently with WBRT.

Cognitive failure after enrollment was defined as a decline of more than 1 standard deviation from baseline in 1 of the 6 cognitive tests performed during the follow-up period.[1] All treatment-related toxicities and adverse events were recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. OS was defined as the time from randomization to death. Surgical bed control was defined as time from randomization to recurrence in the local surgical bed. Intracranial tumor control was defined as time from randomization to recurrence in the local surgical bed, progression of unresected metastases, distant brain recurrence, or development of leptomeningeal disease. Analyses were performed using univariate analyses including Kaplan-Meier estimates,[12] log rank tests,[13] χ^2 tests,[14] and Fisher's exact tests,[15–17] as well as multivariate Cox regression analysis where appropriate to investigate the primary aim of this analysis. $P < .05$ was considered statistically significant. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. All analyses were based on the study database frozen on February 18, 2017.

Results

Patient cohort

The original reporting of XXXXX did not find significant differences when comparing stereotactic radiosurgery to the different WBRT fractionation schedules.[1] Among 92 patients treated with surgical resection and adjuvant WBRT, 49 were treated with 30 Gy in 10 fractions (53%), and 43 were treated with 37.5 Gy in 15 fractions (47%). Of these, 94% and 93% of patients in each arm, respectively, completed their planned course of WBRT.

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Baseline characteristics, including cognitive testing, were well balanced between groups with the exception of primary tumor type, perhaps owing to referral patterns at the institution level (Table 1). The median follow-up period for cognitive failure from enrollment was 10.2 and 12.6 months in the 30 Gy and 37.5 Gy WBRT groups, respectively, ($P = .18$).

Impact on clinical outcomes and adverse events

As demonstrated in Figure 1, protracted WBRT dose/fractions did not significantly affect time to cognitive failure (hazard ratio [HR], 0.91 [95% confidence interval {CI}, 0.6-1.39], $P = .66$), surgical bed control (HR, 0.52 [95% CI, 0.22-1.25], $P = .14$), intracranial tumor control (HR, 0.56 [95% CI, 0.28-1.12], $P = .09$), or OS (HR, 0.72 [95% CI, 0.45-1.16], $P = .18$). On multivariate analysis, after controlling for age, systemic disease control duration, number of brain metastases, primary tumor histology, and surgical cavity size, WBRT fractionation did not affect OS (HR, 0.74 [95% CI, 0.43-1.27], $P = .28$ favoring 37.5 Gy). Although there were no reports of radionecrosis, there is a statistically significant increase in the risk of at least 1 grade 3 or higher adverse event with 37.5 Gy in 15 fractions versus 30 Gy in 10 fractions (54% vs 31%, respectively, $P = .03$). Table 2 provides the reported results of adverse events during the follow-up period (Table E1 (available online at https://doi.org/10.1016/j.ijrobp.2019.10.024) contains adverse events occurring with incidence of less than 3%).

Discussion

These results provide modern evidence that protracted WBRT courses, beyond 30 Gy in 10 fractions, are not associated with improved cognition, tumor control, or survival. Adverse events were significantly higher in patients treated to 37.5 Gy in 10 fractions. These results serve to support 30 Gy in 10 fractions as the preferred WBRT dose and fractionation among patients with brain metastases. In addition, these data provide further support for the fractionation schedule (30 Gy in 10 fractions) typically used in hippocampal avoidance.[3]

Using the linear quadratic formula, the biologically effective dose (BED), assuming an α/β of 10 for malignant cells, is 46.9 Gy and 39 Gy, a 20% increase, when using 37.5 Gy in 10 fractions and 30 Gy in 10 fractions, respectively. This increase in BED could increase intracranial tumor control rates with relatively less cognitive injury (BED of 100 Gy and 90 Gy, respectively, an 11% increase, assuming an α/β of 1.5 for normal brain). In contrast, these results suggest that further attempts to improve the therapeutic ratio of WBRT could have more impact through the development of novel radiosensitizers,[18] novel radioprotectants,[4] or other advances in WBRT delivery including hippocampal avoidance,[3] as opposed to changes in dose and fractionation schedules.

These data are limited in several ways, not the least of which is that this study was not designed or powered to evaluate the impact of WBRT dose and fractionation on these outcomes. It is possible that a study designed and powered to test this hypothesis could yield different results. Researchers at each institution chose their preferred WBRT schedule, and it is possible that baseline confounding across institutions could limit the applicability of these results. Moreover, although XXXXX was not powered to test WBRT fractionation, there is a

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possible trend of improvement in intracranial control with the use of protracted WBRT courses. However, we urge caution in this interpretation, particularly in light of the demonstrated increase of grade 3+ adverse events in this cohort.

Additionally, this study did not compare alternative WBRT schedules, including further protracted courses (up to 50.4 Gy), further hypofractionated courses (ie, 20 Gy in 5 fractions), the details of systemic therapies delivered over the study period, or even the omission of WBRT.[5] Further research is needed to better define the optimum dose and technique for WBRT in patients with brain metastases.

Conclusions

This post hoc analysis does not demonstrate that protracted WBRT courses significantly reduce the risk of cognitive deficit, improve tumor control in the hypoxic surgical cavity, or otherwise improve the therapeutic ratio. Adverse events were significantly higher with the lengthened course of WBRT. For patients with brain metastases for whom WBRT is recommended, a shorter course of hypofractionated regimen remains the current standard of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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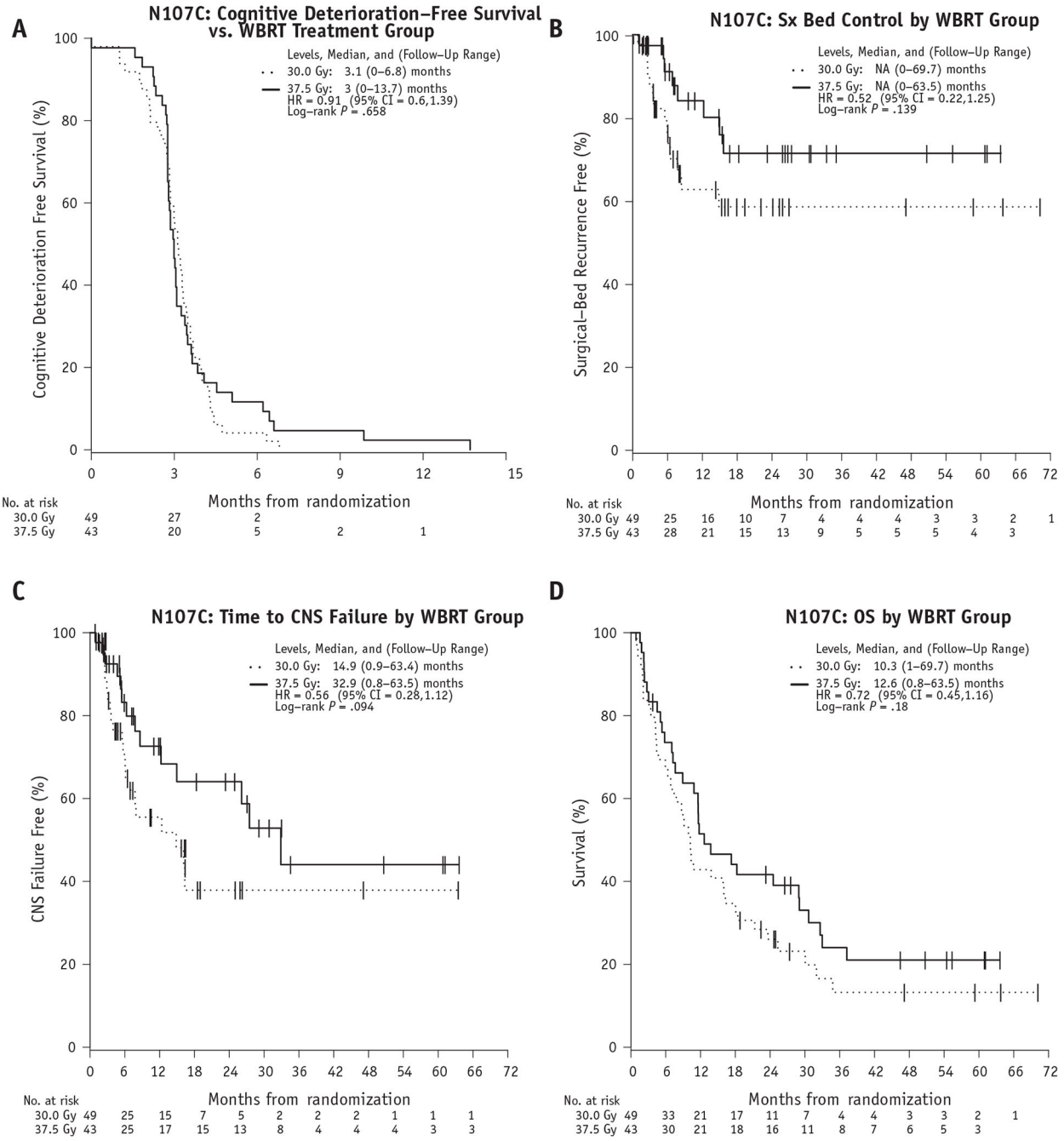

Fig. 1.

The impact of whole brain radiation therapy dose and fractionation on subsequent time to cognitive failure (A), surgical bed control (B), intracranial tumor control (C), and overall survival (D).

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Table 1

Baseline patient characteristics of the 92 patients enrolled in N107C that were subsequently randomized to WBRT after surgical resection, stratified by WBRT dose and fractionation

Baseline characteristics by WBRT dose				
	37.5 Gy (N = 43)	**30 Gy (N = 49)**	**Total (N = 92)**	***P* value**
Median age (range)	62 (48-81)	63 (41-81)	62 (41-81)	.4176 *
Sex				.2148 †
Female	19 (44.2%)	28 (57.1%)	47 (51.1%)	
Male	24 (55.8%)	21 (42.9%)	45 (48.9%)	
Systemic disease controlled				.1193 †
≤3 mo	28 (65.1%)	24 (49.0%)	52 (56.5%)	
>3 mo	15 (34.9%)	25 (51.0%)	40 (43.5%)	
No. brain metastases				.5298 †
1	34 (79.1%)	36 (73.5%)	70 (76.1%)	
2-4	9 (20.9%)	13 (26.5%)	22 (23.9%)	
Primary malignant disease				**.0144** †, ‡
Breast	1 (2.3%)	4 (8.2%)	5 (5.4%)	
Colorectal	1 (2.3%)	9 (18.4%)	10 (10.9%)	
Lung	31 (72.1%)	22 (44.9%)	53 (57.6%)	
Skin/melanoma	6 (14.0%)	2 (4.1%)	8 (8.7%)	
Bladder	1 (2.3%)	0 (0.0%)	1 (1.1%)	
Kidney	1 (2.3%)	1 (2.0%)	2 (2.2%)	
Gynecologic	0 (0.0%)	3 (6.1%)	3 (3.3%)	
Unknown primary	1 (2.3%)	5 (10.2%)	6 (6.5%)	
Other	1 (2.3%)	3 (6.1%)	4 (4.3%)	
Resection cavity diameter (cm)				.3284 †
≤3	28 (65.1%)	27 (55.1%)	55 (59.8%)	
>3	15 (34.9%)	22 (44.9%)	37 (40.2%)	
Performance score				.0810 †

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Baseline characteristics by WBRT dose				
	37.5 Gy (N = 43)	**30 Gy (N = 49)**	**Total (N = 92)**	***P* value**
0	9 (20.9%)	21 (42.9%)	30 (32.6%)	
1	30 (69.8%)	25 (51.0%)	55 (59.8%)	
2	4 (9.3%)	3 (6.1%)	7 (7.6%)	
Extent resection				.2130[†]
Subtotal	4 (9.3%)	9 (18.4%)	13 (14.1%)	
Total (gross)	39 (90.7%)	40 (81.6%)	79 (85.9%)	
Education level				.7396[†]
Missing	3	1	4	
K - 12	24 (60.0%)	31 (64.6%)	55 (62.5%)	
College/vocational 1 y	3 (7.5%)	4 (8.3%)	7 (8.0%)	
College/vocational 2 y	5 (12.5%)	3 (6.3%)	8 (9.1%)	
College/vocational 3 y	0 (0.0%)	1 (2.1%)	1 (1.1%)	
College/vocational ≥4 y	3 (7.5%)	5 (10.4%)	8 (9.1%)	
Post graduate (MA, MS)	3 (7.5%)	1 (2.1%)	4 (4.5%)	
Professional degree (MD, PhD)	0 (0.0%)	1 (2.1%)	1 (1.1%)	
Other	2 (5.0%)	2 (4.2%)	4 (4.5%)	

Abbreviation: WBRT = whole brain radiation therapy.

[*] Kruskal-Wallis.

[†] χ^2.

[‡] $P < .05$.

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Table 2

Physician reported severe adverse events (grade ≥3 or any grade 1-2 experienced by more than 10% of patients) after WBRT, stratified by WBRT dose and fractionation*

	37.5 Gy in 15 fx (n = 43)				30 Gy in 10 fx (n = 49)			
Adverse event term	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Alopecia	22 (51.2%)				27 (55.1%)			
Fatigue	15 (34.9%)	1 (2.3%)			6 (12.2%)			
Nausea	14 (32.6%)	2 (4.7%)			21 (42.9%)	2 (4.1%)		
Cognitive disturbance	13 (30.2%)	5 (11.6%)			8 (16.3%)	1 (2.0%)		
Vomiting	8 (18.6%)	1 (2.3%)			13 (26.5%)	1 (2.0%)		
Dermatitis radiation	8 (18.6%)				6 (12.2%)			
Hearing impaired	7 (16.3%)	7 (16.3%)			6 (12.2%)	1 (2.0%)		
External ear inflammation	6 (14.0%)							
Anorexia		3 (7.0%)				1 (2.0%)		
Dehydration		3 (7.0%)				3 (6.1%)		
Hyperglycemia		2 (4.7%)				2 (4.1%)		
Seizure		2 (4.7%)					1 (2.0%)	
Weight loss		2 (4.7%)						
Generalized muscle weakness		2 (4.7%)						
Peripheral motor neuropathy		1 (2.3%)			8 (16.3%)			
Death NOS				1 (2.3%)				2 (4.1%)
Hypoalbuminemia						2 (4.1%)		
Hypophosphatemia						2 (4.1%)		
Thromboembolic event						2 (4.1%)		1 (2.0%)
Sepsis							2 (4.1%)	
Neoplasms benign, mal, unspec—Oth								2 (4.1%)

Abbreviations: fx = fraction; NOS = not otherwise specified; WBRT = whole brain radiation therapy.

*Adverse events with <3% frequency reported in supplemental table (available online at https://doi.org/10.1016/j.ijrobp.2019.10.024).