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Treatment for Brain Metastases With Stereotactic Radiation vs Hippocampal-Avoidance Whole Brain Radiation

A Randomized Clinical Trial

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IMPORTANCE Brain metastases are common in patients with cancer, and radiation is often used for management. Among patients with more than 4 brain metastases, the effects of stereotactic radiation targeting only individual tumors, compared with whole brain radiation with hippocampal avoidance, which radiates both tumors and normal brain, remain unknown.

OBJECTIVE To determine whether stereotactic radiation improves symptom severity and interference with daily functioning, compared with whole brain radiation with hippocampal avoidance.

DESIGN, SETTING, AND PARTICIPANTS Phase 3, open-label, randomized clinical trial conducted at 4 United States–based centers. Eligible patients had 5 to 20 brain metastases and no prior brain-directed radiation. Enrollment occurred between April 11, 2017, and May 17, 2024 (final follow-up, March 18, 2025).

INTERVENTION Stereotactic radiation, compared with whole brain radiation with hippocampal avoidance.

MAIN OUTCOMES AND MEASURES Mean weighted patient-reported symptom severity and interference score change over 6 months postbaseline relative to baseline using the MD Anderson Symptom Inventory–Brain Tumor instrument (scale, 0-10; score change range, -10 to 10; -10 = best). A clinically meaningful Δ was defined as 0.98.

RESULTS Of 196 randomized patients (mean age, 61 years; 129 [66%] female; 176 [90%] White; median number of brain metastases, 14 [IQR, 11-18]; 49 [25%] with prior neurosurgical resection), 83 (42%) completed the 6-month assessment. For the primary outcome, between baseline and postbaseline assessments through the 6-month follow-up, stereotactic radiation changed the weighted composite MD Anderson Symptom Inventory–Brain Tumor score from 2.69 to 2.37 (mean change, -0.32) and hippocampal-avoidance whole brain radiation changed the score from 2.29 to 3.03 (mean change, 0.74) (mean difference, -1.06 [95% CI, -1.54 to -0.58]; $P < .001$). Related grade 3-5 adverse events occurred in 12 patients (12%) in the stereotactic radiation group and 13 patients (13%) in the hippocampal-avoidance whole brain radiation group; grade 1-3 fatigue was most frequent (27 [28%] vs 43 [44%], respectively).

CONCLUSIONS AND RELEVANCE In patients with 5 to 20 brain metastases, these findings support stereotactic radiation over hippocampal-avoidance whole brain radiation to improve symptoms and interference with daily functioning, key components of quality of life.

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Brain metastases occur when cancer originating elsewhere spreads to the brain. Approximately 200 000 to 250 000 patients develop brain metastases annually in the United States, comparable to the incidence of primary breast, prostate, lung, and colorectal cancer.^{1,2} Unlike lung, liver, or bone metastases, brain metastases are generally less responsive to systemic therapy such as chemotherapy because the blood-brain barrier impedes drug penetration.³ Consequently, radiation therapy is commonly used.⁴

Two radiation modalities are used to treat brain metastases: whole brain radiation, which delivers a moderate dose of radiation to the entire brain, including tumors and normal tissue, and stereotactic radiation, which focuses only on visible tumors with higher biologic doses. Randomized clinical trials have demonstrated that stereotactic radiation preserves neurocognitive function and patient-reported outcomes compared with whole brain radiation in patients with 4 or fewer brain metastases; consequently, stereotactic radiation represents the standard of care for these patients.⁵⁻⁹ To our knowledge, for patients with more than 4 brain metastases, published, randomized comparisons of stereotactic radiation vs whole brain radiation are lacking.¹⁰ Hippocampal-avoidance whole brain radiation, a newer technique that spares hippocampal regions important for memory, reduced neurocognitive toxicity as measured by a comprehensive neurocognitive battery compared with traditional whole brain radiation in a randomized trial¹¹; this technique is now preferred for patients receiving whole brain radiation who lack hippocampal/perihippocampal metastases and have an expected survival of 4 months or more.^{12,13} However, no randomized clinical trials have compared stereotactic radiation and hippocampal-avoidance whole brain radiation. Therefore, this clinical trial was designed to determine whether stereotactic radiation reduced symptom severity and symptom-based interference with daily functioning, measured by the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) instrument, compared with hippocampal-avoidance whole brain radiation, in patients with 5 to 20 brain metastases.

Methods

Study Design and Population

The study was coordinated by Brigham and Women's Hospital/Dana-Farber Cancer Institute (Boston, Massachusetts) and conducted at 3 additional centers, including academic (Rhode Island Hospital/Brown University Health, Providence, Rhode Island) and community (Milford Regional Medical Center, Milford, Massachusetts; South Shore Health, Weymouth, Massachusetts) sites. The Dana-Farber Cancer Institute institutional review board approved this study. Reporting followed CONSORT guidelines. Participants provided written informed consent. Race and ethnicity were self-reported using fixed-choice categories and collected to describe the population/assess group comparability. Patient discussions informed study design, without formal public involvement. The original study protocol is available in Supplement 1, the protocol amendment history in Supplement

Key Points

Question Among patients with 5 to 20 brain metastases, does stereotactic radiation targeting individual tumors reduce symptom burden and interference with daily function compared with hippocampal-avoidance whole brain radiation?

Findings In this randomized clinical trial of 196 patients, mean composite MD Anderson Symptom Inventory-Brain Tumor score (average of symptom severity and interference after baseline minus baseline; score range, -10 to 10; -10 = best) was -0.32 for stereotactic radiation and 0.74 for hippocampal-avoidance whole brain radiation (mean difference, -1.06).

Meaning Stereotactic radiation improved symptoms and interference, key components of quality of life, compared with hippocampal-avoidance whole brain radiation in patients with 5 to 20 brain metastases.

ment 2, the final protocol in Supplement 3, and the statistical analysis plan in Supplement 4.

Inclusion Criteria

At the start of the clinical trial in April 2017, only patients with 5 to 15 brain metastases from biopsy-proven solid malignancies were eligible. In October 2018, eligibility was changed to people with 5 to 20 metastases to increase generalizability of the results rather than in response to enrollment difficulty. Additional eligibility criteria included age 18 to 80 years and Karnofsky Performance Status Scale 70 to 100 (self-care capable).

Exclusion Criteria

Exclusion criteria were prior brain-directed radiation; widespread/definitive leptomeningeal disease; underlying small cell lung cancer, lymphoma, or myeloma; stage 5 chronic kidney disease/end-stage kidney disease; inability to undergo contrast-enhanced magnetic resonance imaging of the brain; and unresected brain metastases larger than 5.0 cm. Prior neurosurgical resection and systemic therapy for intracranial disease were permitted.

Randomization

Participants were randomized in a nonblinded, parallel-group design (1:1) to stereotactic radiation or hippocampal-avoidance whole brain radiation using computer-generated permuted blocks (size = 4) overseen by the study statistician, stratified by primary tumor (non-small cell lung, breast, melanoma, other) and prior neurosurgical resection vs not. Randomization was centrally implemented by the Dana-Farber/Harvard Cancer Center Office of Data Quality through a secured/centralized electronic database. Allocation was concealed from study personnel, including those enrolling patients, until assignment.

Interventions

Treating radiation oncologists underwent credentialing for contouring (outlining brain metastases on medical imaging) and radiation planning via central review of an enrolled patient's contours and treatment plan before treatment by the study principal investigator/physics chair; approval permitted subsequent treatments without review, whereas edits precluded

credentialing and required resubmission for a subsequent patient. Hippocampal-avoidance whole brain radiation was dosed to 30 Gy, delivered in 10 daily fractions (treatments), with memantine.^{11,14} Stereotactic radiation was delivered on a Varian linear accelerator, either in 1 day (stereotactic radiosurgery; standard dose = 20 Gy) or 5 daily fractions (stereotactic radiotherapy; standard dose = 30 Gy, except for tumors entirely removed neurosurgically, for which 25 Gy targeting the surgical cavity was used). Dose reductions were permitted if indicated, per protocol.¹⁵ Follow-up brain magnetic resonance imaging occurred every 2 months for 1 year, then every 2 to 4 months or as clinically indicated. Systemic therapy (eg, chemotherapy), additional radiation, and salvage neurosurgical resection were permitted in both groups poststudy intervention as indicated clinically.

Primary Outcome

The primary outcome was the change in composite MDASI-BT score, between (1) baseline and (2) postbaseline assessments through 6 months, including assessments at 3 weeks and 2, 4, and 6 months. The composite MDASI-BT score was calculated as the equally weighted mean of (1) symptom severity (22 items: 13 core cancer-related, 9 brain tumor-specific) and (2) interference with daily functioning (6 items).¹⁶ The MDASI-BT, validated in brain metastases, rates each domain from 0 to 10, with higher scores indicating greater severity or interference.¹⁷ The range of the MDASI-BT composite score change between postbaseline and baseline is -10 (greatest reduction in symptom severity and interference) to 10 (greatest worsening of symptom severity and interference). The minimal clinically important difference for the MDASI-BT in this population is unknown; a clinically meaningful composite score difference was defined as 0.98, the average of severity (0.70) and interference (1.25) thresholds, representing half the difference observed between patients with good vs poor performance status (Karnofsky Performance Status Scale 90-100 vs ≤80, respectively).¹⁷

Secondary Outcomes

Secondary outcomes included overall survival, neurologic death, new brain metastases, local recurrence, progressive intracranial disease, radiation necrosis, leptomeningeal disease, steroid use, seizures, salvage therapies (including salvage stereotactic radiation, whole brain radiation therapy, and neurosurgical resection), functional independence, Karnofsky Performance Status, neurocognitive function, and per-metastasis end points including local recurrence, salvage therapy for local recurrence, salvage neurosurgical resection, radiographic radiation necrosis, and symptomatic radiation necrosis. Unless stated otherwise, the minimal clinically important difference for these end points is not definitively known.

Overall survival was measured from registration to death from any cause using medical record review. Neurologic death was defined as death due to marked, progressive radiographic intracranial progression accompanied by corresponding neurologic symptomatology in the absence of systemic disease progression or systemic symptoms of a life-threatening nature as assessed via medical record and imaging review.¹⁸ New brain metastases were newly visualized enhancing tu-

mors distinct from treated targets, and local recurrence was tumor progression within a treated metastasis, both assessed on brain imaging.¹⁹ Progressive intracranial disease was defined as the composite of new brain metastases, local recurrence, or leptomeningeal disease, as assessed via imaging or cerebrospinal fluid cytology. Radiation necrosis (ie, injury to radiated brain) was defined radiographically (ie, imaging based) and considered symptomatic if associated with neurologic symptoms or treated with corticosteroids, bevacizumab, or resection. Leptomeningeal disease was defined as diffuse leptomeningeal enhancement on imaging (contrast uptake in the pia/arachnoid/subarachnoid spaces) or malignant cells in cerebrospinal fluid.²⁰ Steroid use was defined as initiation of dexamethasone in patients not receiving steroids at enrollment based on medical record review. Seizures were defined as new seizure-related events after enrollment, identified via medical records. Salvage therapies, including salvage stereotactic radiation, whole brain radiation therapy, and neurosurgical resection, were assessed using review of medical records.

Functional independence was measured using the Barthel Index (range, 0-100; higher scores indicate greater independence) at baseline, 4 months, and 12 months.²¹ Karnofsky Performance Status Scale (range, 0-100, higher values indicate better function), was clinician-assessed at baseline, 3 weeks, 2 months, and every 2 months thereafter for 1 year. The minimal clinically important difference was 10 points.^{22,23}

Neurocognitive function was evaluated at baseline, 4 months, and 12 months using a standardized battery consisting of the Hopkins Verbal Learning Test-Revised Total Recall (rote verbal learning across 3 trials), Delayed Recall (delayed memory), and Recognition (memory storage/recognition); Trail Making Test Parts A and B (visuomotor processing speed and divided attention/set shifting, respectively); Controlled Oral Word Association Test (verbal fluency); and Mini-Mental State Examination (global cognition; range, 0-30; higher scores indicate better function). Patient-reported cognitive functioning was assessed concurrently with the Medical Outcomes Study Cognitive Functioning Scale-Revised and converted to a normative score (range, 7.51-58.61; higher scores reflect better cognitive function). Motor dexterity was assessed with the Grooved Pegboard Test. All assessments except the Mini-Mental State Examination and Medical Outcomes Study Cognitive Functioning Scale-Revised were converted to z scores, with higher values indicating better performance.

In addition to per-patient assessment, the following outcomes were tabulated on a per-metastasis level via magnetic resonance imaging of the brain or, in the case of salvage therapy and symptomatic radiation necrosis, medical record review: local recurrence, salvage therapy for local recurrence, salvage neurosurgical resection, radiographic radiation necrosis, and symptomatic radiation necrosis. Post hoc per-patient and per-metastasis analyses are not presented.

Adverse Effects

Adverse events were assessed at each visit via medical record review and direct patient questioning about new or worsening neurologic symptoms or treatment-related toxicities.

Statistical Analysis

For the primary outcome, within-patient mean changes in MDASI-BT composite scores were calculated as the mean of postbaseline assessments at 3 weeks, 2 months, 4 months, and 6 months, minus baseline. Scores were weighted by the square root of the number of postbaseline assessments. Group comparisons used weighted *t* tests. MDASI-BT score normality was confirmed using the Shapiro-Wilk test and Q-Q plots.

For secondary outcomes, overall survival was evaluated using Kaplan-Meier curves and a stratified log-rank test; all other per-patient, time-to-event outcomes were assessed using cumulative incidence curves and a stratified Gray test. Permetastasis outcomes were assessed via Fine-Gray competing-risks models incorporating sandwich estimators for intrapatient correlations. For time-to-event analyses (except overall survival), the competing event of death was considered an absorbing event rather than a censoring event. Changes in performance status, functional independence, neurocognitive function, and motor dexterity were assessed using treatment × time interactions derived from generalized estimating equations incorporating exchangeable correlation structures and robust variance estimators.

Secondary outcomes should be considered exploratory/hypothesis-generating given the large number of comparisons without adjustment for multiple testing. Following protocol finalization, the statistical analysis plan updated secondary outcome definitions to ensure that each end point could be ascertained from neurocognitive, functional, clinical, and imaging data and applied consistently across clinicians and study personnel; assessment of the primary outcome remained unchanged. All outcome-based analyses were conducted based on the group that patients were randomized to, regardless of treatment received or protocol adherence. Data were analyzed using R version 4.4.1 (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute Inc). $P < .05$ was considered statistically significant.

Statistical Power Calculation

MDASI-BT symptom severity was used to power the study; a clinically meaningful change was deemed as 0.70 points, representing half the difference in scores observed between patients with a good vs poor performance status (Karnofsky Performance Status Scale 90-100 vs ≤ 80 , respectively).¹⁷

Assuming an individual standard deviation of 2 points, a within-patient standard deviation of 1.38 for postbaseline assessments, correlation between baseline and postbaseline assessments of 0.60, 80% power, a 2-sided α of .05, and an effect size of 0.44, the study required 83 patients per group with postbaseline data to power the superiority design. MDASI-BT compliance was projected at 45% by 6 months, mainly limited by death. To minimize missing data, dedicated research coordinators prioritized obtaining MDASI-BT assessments. Anticipating 18% dropout before postbaseline assessment, largely death-related and random, the sample size was increased to 98 per group (196 total). For the primary end point, all available postbaseline data were analyzed using weighted methods under a missing-at-random assumption without imputation. No efficacy-based early stopping rules were applied.

Results

Study Population, Randomization, and Adherence

Between April 2017 and May 2024, 196 patients enrolled, 98 per group, completing planned accrual. The last follow-up was March 18, 2025. Median follow-up in surviving patients was 24 months. Baseline characteristics are reported in **Table 1**. Mean age was 61 years; 129 (66%) were female, 176 (90%) White, and 7 (4%) Hispanic. The median number of brain metastases was 14; 25% underwent prior neurosurgical resection. The **Figure** summarizes recruitment, randomization, and follow-up. Of 98 patients randomized to stereotactic radiation, 96 initiated treatment. One could not tolerate the mask required for radiation and deteriorated; 1 died before treatment. In the hippocampal-avoidance whole brain radiation group, 89 of 98 patients initiated treatment; 5 refused assigned randomization and received stereotactic radiation after institutional review board approval, 2 died before treatment, 1 withdrew, and 1 required urgent systemic therapy. Radiation-related parameters are presented in eTables 1 and 2 in **Supplement 5**.

Primary Outcome

Of 196 randomized patients, 83 (42%) completed the 6-month assessment. For the primary outcome, between baseline and postbaseline assessments through the 6-month follow-up, stereotactic radiation changed the weighted composite MDASI-BT score from 2.69 to 2.37 (mean change, -0.32) and hippocampal-avoidance whole brain radiation changed the score from 2.29 to 3.03 (mean change, 0.74) (mean difference, -1.06 [95% CI, -1.54 to -0.58]; $P < .001$).

Secondary Outcomes

Median survival in the stereotactic radiation and hippocampal-avoidance whole brain radiation groups was 8.3 vs 8.5 months, respectively ($P = .30$) (**Table 2**; eFigure 1 in **Supplement 5**), with 80 vs 85 (total = 165) deaths. Neurologic mortality was not significantly different (1-year cumulative incidence, 9.4% vs 8.5%; $P = .35$), with 19 vs 18 neurologic deaths, respectively.

New brain metastases were more common in the stereotactic radiation vs hippocampal-avoidance whole brain radiation group (1-year cumulative incidence, 45.4% vs 24.2%; $P = .003$); local recurrence occurred in 3.2% vs 39.5% at 1 year ($P < .001$), respectively. Respective 1-year cumulative incidence of progressive intracranial disease was 46.4% in the stereotactic radiation group vs 39.4% in the hippocampal-avoidance whole brain radiation group ($P = .15$), while rates of radiographic radiation necrosis at 1 year were 14.8% vs 1.1% ($P = .001$). Leptomeningeal disease developed in 8.3% vs 3.2% at 1 year ($P = .12$), respectively. Dexamethasone initiation in patients not taking steroids at enrollment was less common in the stereotactic radiation group (1-year cumulative incidence, 52.2% vs 72.2%; $P = .03$). The 1-year cumulative incidence of seizures was 11.4% in the stereotactic radiation group vs 15.8% in the hippocampal-avoidance whole brain radiation group ($P = .44$).

Among salvage interventions, the 1-year cumulative incidence of posttreatment salvage stereotactic radiation was 15.5% vs 22.7% in the stereotactic radiation vs hippocampal-avoidance whole brain radiation groups, respectively ($P = .20$). In total, 9 patients (9.2%) vs 1 (1.0%) required posttreatment salvage whole brain radiation (1-year cumulative incidence, 5.1% vs 1.0%; $P = .02$), respectively. Salvage craniotomy occurred in 9.4% vs 6.3% at 1 year ($P = .41$), respectively.

Functional independence via the Barthel Index was better in the stereotactic radiation group at both postbaseline time points assessed (Table 3; eFigure 2 in Supplement 5): 4 months (between-group difference, 6.79 [95% CI, 1.19-12.38]; $P = .02$) and 12 months (between-group difference, 7.92 [95% CI, 1.34-14.49]; $P = .02$). Karnofsky Performance Status scores were better in the stereotactic radiation group at every time point between 2 and 12 months posttreatment, with between-group differences ranging from 6.53 points at 2 months (95% CI, 2.77-10.28; $P = .001$) to 11.80 points at 8 months (95% CI, 7.29-16.32; $P < .001$).

Several objective neurocognitive tests showed better function, reflected by z -score differences, in the stereotactic radiation group including 12-month Hopkins Verbal Learning Test-Revised Total Recall (mean difference, 0.83 [95% CI, 0.07-1.59]; $P = .03$), Delayed Recall (mean difference, 1.25 [95% CI, 0.35-2.16]; $P = .006$), and Recognition (mean difference, 1.62 [95% CI, 0.52-2.72]; $P = .004$); 4-month Trail Making Test A (mean difference, 0.86 [95% CI, 0.11-1.60]; $P = .02$); 12-month Trail Making Test B (mean difference, 4.11 [95% CI, 0.37-7.86]; $P = .03$); and the 4-month Controlled Oral Word Association Test (mean difference, 0.53 [95% CI, 0.14-0.91]; $P = .007$). No neurocognitive test favored hippocampal-avoidance whole brain radiation. There were no significant between-group, postbaseline differences in the general neurocognitive screening measure (Mini-Mental State Examination), self-reported cognitive symptoms (Medical Outcomes Study Cognitive Functioning Scale-Revised), or motor dexterity (Grooved Pegboard) (Table 4; eFigure 3 and eTable 3 in Supplement 5) at any point.

At the brain metastasis level, of 2683 evaluable metastases in patients randomized to stereotactic radiation ($n = 1419$) vs hippocampal-avoidance whole brain radiation ($n = 1264$), 12 (0.8%) and 155 (12.3%) displayed a local recurrence (hazard ratio [HR], 0.07 [95% CI, 0.03-0.16]; $P < .001$), 11 (0.8%) and 95 (7.5%) required salvage therapy (HR, 0.10 [95% CI, 0.04-0.24]; $P < .001$), and 13 (0.9%) and 8 (0.6%) underwent salvage craniotomy for any underlying reason (HR, 1.53 [95% CI, 0.52-4.48]; $P = .44$). Radiographic radiation necrosis occurred in 57 (4.0%) vs 9 (0.7%) brain metastases, respectively (HR, 6.17 [95% CI, 1.34-28.33]; $P = .02$), while symptomatic radiation necrosis occurred in 22 (1.6%) vs 3 (0.2%) lesions (HR, 7.36 [95% CI, 0.88-61.47]; $P = .07$) (eTable 4 in Supplement 5).

Adverse Events

Postbaseline adverse effects by group are outlined in eTable 5 in Supplement 5; those possibly, probably, or definitely related to radiation are reported in eTable 6 in Supplement 5. The most common related adverse effects were grade 1-3 fatigue

Table 1. Baseline Patient Characteristics by Group at Enrollment

	Stereotactic radiation ^a (n = 98)	Hippocampal-avoidance whole brain radiation ^a (n = 98)
Age, mean (SD) [No.], y	61 (11) [98]	60 (13) [98]
Sex, No. (%)		
Female	65 (66)	64 (65)
Male	33 (34)	34 (35)
Race, No. (%) ^b		
Asian	6 (6)	2 (2)
Black or African American	4 (4)	2 (2)
White	86 (88)	90 (92)
More than 1 race	0	3 (3)
Other ^c	2 (2)	1 (1)
Hispanic or Latino ethnicity, No./total (%) ^b	1/94 (1)	6/93 (6)
Charlson Comorbidity Index, median (IQR) [No.] ^d	0 (0-1) [98]	0 (0-1) [97]
Karnofsky Performance Status score 90-100, No./total (%) ^e	47/97 (48)	45/92 (49)
Primary cancer, No. (%)		
Non-small cell lung cancer	44 (45)	43 (44)
Breast	21 (21)	23 (23)
Melanoma	9 (9)	9 (9)
Other	24 (24)	23 (23)
Neurologic symptoms, No./total (%)	60/98 (61)	60/97 (62)
Seizures, No./total (%)	14/98 (14)	12/97 (12)
Extracranial metastases, No./total (%)	82/98 (84)	78/97 (80)
Progressive extracranial metastases, No./total (%) ^f	71/82 (87)	61/78 (78)
No. of prior systemic therapy regimens for metastatic disease, median (IQR) [No.]	1 (0-2) [98]	1 (0-3) [96]
Dexamethasone, No./total (%)	52/98 (53)	53/98 (54)
Prior neurosurgical resection, No./total (%)	24/98 (24)	25/98 (26)
No. of brain metastases, median (IQR) [No.]	15 (11-19) [98]	13 (9-17) [98]
Maximal unidimensional size of largest metastasis, median (IQR) [No.], mm	20 (12-27) [98]	20 (12-29) [98]

^a Percentages may not add up to 100 due to rounding.

^b Race and ethnicity were self-reported using fixed-choice categories and collected to describe the population and assess group comparability.

^c Other race was a prespecified choice which participants selected directly.

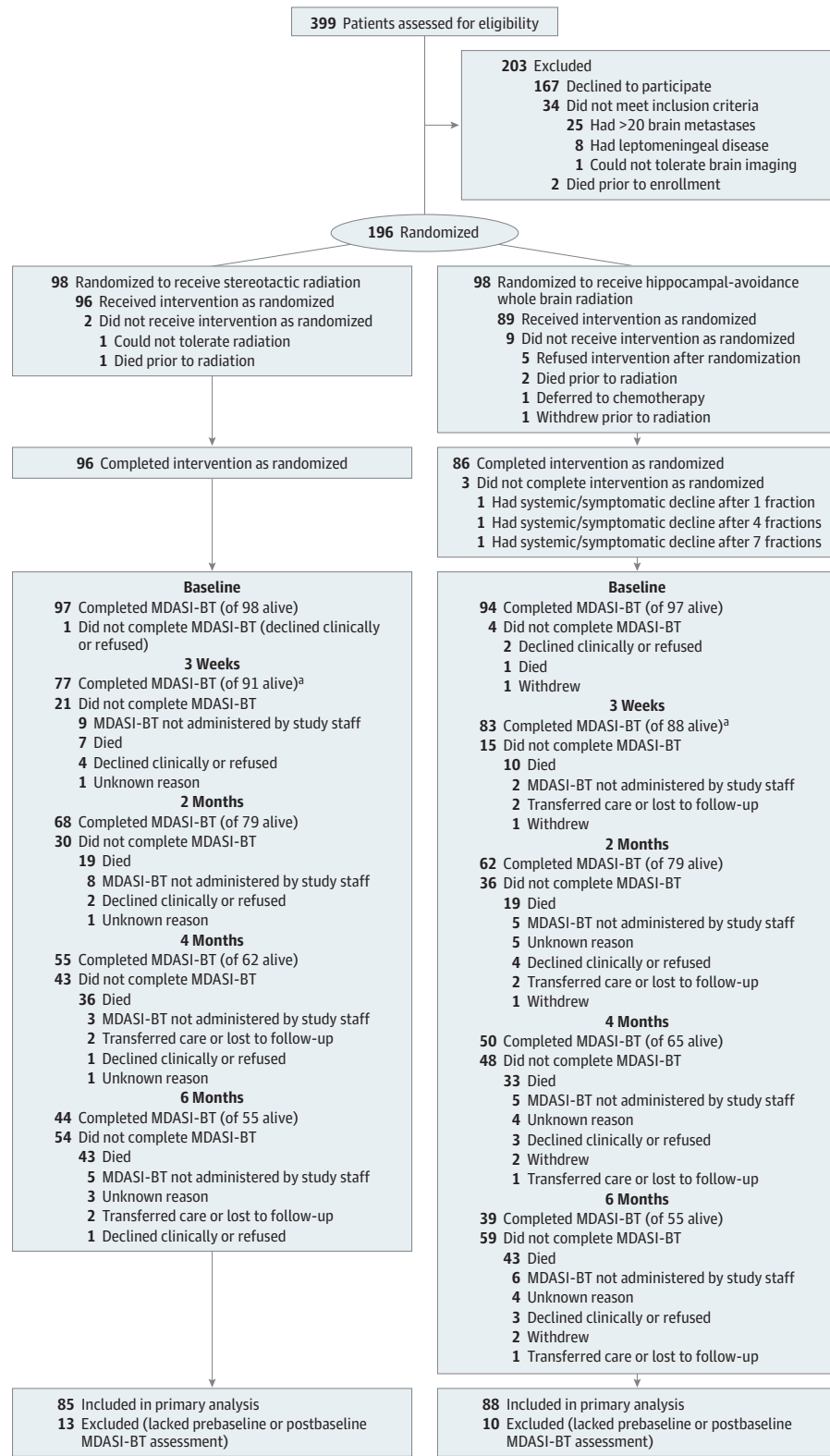
^d Excludes cancer leading to diagnosis of brain metastases to not inflate all scores by 6.

^e As opposed to Karnofsky Performance Status Scale score 70 to 80. Karnofsky Performance Status Scale scores range from 0 to 100, with higher scores indicating better function. Scores near the study means (approximately 80-90) reflect patients who are able to carry out normal activity normally or with some effort and who harbor minor or some signs or symptoms of disease.

^f Among patients with extracranial metastases.

($n = 27$ [28%]), headache ($n = 15$ [15%]), and nausea ($n = 13$ [13%]) with stereotactic radiation and fatigue ($n = 43$ [44%]), anorexia ($n = 22$ [22%]), and headache ($n = 13$ [13%]) with hippocampal-avoidance whole brain radiation. No differences in related grade 3 or greater events were noted (12% vs 13%).

Figure. Flow Diagram Depicting Recruitment, Randomization, and Follow-Up of Trial Participants



Patients without a single postbaseline MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT) assessment were excluded from the primary outcome analysis. Deaths and withdrawals only increase with time; other categories for missing MDASI-BT assessments vary by time point.

^aTwelve patients had their first postbaseline MDASI-BT assessment after 3 weeks (8 stereotactic radiation; 4 hippocampal-avoidance whole brain radiation). Of these, 6 were first assessed at 2 months (5 and 1, respectively), 4 at 4 months (3 and 1, respectively), and 2 at 6 months (0 and 2, respectively). The remaining 161 patients (77 and 84, respectively) were first assessed at 3 weeks.

Table 2. Cancer-Related Time-to-Event Outcomes in Patients Randomized to Stereotactic Radiation vs Hippocampal-Avoidance Whole Brain Radiation

Outcome ^a	Stereotactic radiation		Hippocampal-avoidance whole brain radiation		P value
	No. of events/No. of participants (%)	12-mo Cumulative incidence (95% CI), %	No. of events/No. of participants (%)	12-mo Cumulative incidence (95% CI), %	
Overall survival ^b	80/98 (82)	41.1 (31.3-50.7)	85/98 (87)	42.8 (32.7-52.6)	.30
Neurologic death	19/98 (19)	9.4 (4.6-16.3)	18/98 (18)	8.5 (3.9-15.3)	.35
New brain metastases	51/97 (53)	45.4 (35.2-55.0)	31/95 (33)	24.2 (16.1-33.3)	.003
Local recurrence	6/97 (6)	3.2 (0.8-8.3)	43/95 (45)	39.5 (29.5-49.3)	<.001
Progressive intracranial disease	53/97 (55)	46.4 (36.2-56.0)	43/95 (45)	39.4 (29.4-49.2)	.15
Radiographic radiation necrosis	19/97 (20)	14.8 (8.5-22.8)	3/95 (3)	1.1 (0.1-5.3)	.001
Leptomeningeal disease	12/97 (12)	8.3 (3.8-14.9)	4/95 (4)	3.2 (0.8-8.3)	.12
Dexamethasone initiation in patients not taking steroids at enrollment	27/46 (59)	52.2 (36.7-65.6)	34/45 (76)	72.2 (55.7-83.4)	.03
Seizure	16/98 (16)	11.4 (6.0-18.6)	17/98 (17)	15.8 (9.3-24.0)	.44
Salvage stereotactic radiation	20/98 (20)	15.5 (9.1-23.5)	26/98 (27)	22.7 (14.7-31.7)	.20
Salvage whole brain radiation ^c	9/98 (9)	5.1 (1.9-10.8)	1/98 (1)	1.0 (0.1-5.1)	.02
Salvage neurosurgical resection	15/98 (15)	9.4 (4.6-16.3)	7/98 (7)	6.3 (2.6-12.5)	.41

^a Measured from enrollment until event, death, or censoring due to loss to follow up, withdrawal, or last assessment.

^b For overall survival, No. of events = total number of deaths.

^c With or without hippocampal avoidance.

Table 3. Functional Outcomes in Patients Randomized to Stereotactic Radiation vs Hippocampal-Avoidance Whole Brain Radiation

Time point	No. (%)		Mean difference (95% CI) ^a	P value
	Stereotactic radiation (n = 98)	Hippocampal-avoidance whole brain radiation (n = 98)		
Barthel Index^b				
Baseline	92 (94)	82 (84)	1.53 (-1.95 to 5.01)	
4 mo	46 (47)	37 (38)	6.79 (1.19 to 12.38)	.02
12 mo	22 (22)	18 (18)	7.92 (1.34 to 14.49)	.02
Karnofsky Performance Status^c				
Baseline	97 (99)	92 (94)	-0.87 (-2.91 to 1.18)	
3 wk	79 (81)	76 (78)	2.89 (-0.09 to 5.87)	.06
2 mo	70 (71)	65 (66)	6.53 (2.77 to 10.28)	.001
4 mo	55 (56)	50 (51)	9.51 (5.12 to 13.90)	<.001
6 mo	45 (46)	47 (48)	7.51 (2.87 to 12.14)	.002
8 mo	37 (38)	35 (36)	11.80 (7.29 to 16.32)	<.001
10 mo	35 (36)	30 (31)	7.76 (3.55 to 11.98)	<.001
12 mo	31 (32)	29 (30)	8.64 (4.62 to 12.66)	<.001

^a Mean differences should be interpreted as the stereotactic radiation group minus the hippocampal-avoidance whole brain radiation group; positive differences reflect higher functional independence (Barthel Index) or performance status (Karnofsky Performance Status) of the stereotactic radiation group.

^b The Barthel Index ranges from 0 to 100, with higher scores indicating greater functional independence. Larger differences indicate increasingly better functional independence in the Stereotactic Radiation group.

^c Karnofsky Performance Status Scale ranges from 0 to 100, with higher scores indicating better function. Scores near the study means (approximately 80-90) reflect patients who are able to carry out normal activity normally or with some effort and who harbor minor or some signs or symptoms of disease. Differences between groups are reported as absolute mean differences, where larger positive values indicate superior performance status in the Stereotactic Radiation group.

Discussion

In this trial, patients with 5 to 20 brain metastases randomized to stereotactic radiation reported fewer symptoms and less functional interference than those receiving

hippocampal-avoidance whole brain radiation. The magnitude of benefit (difference in score change, -1.06) approximated half the difference between patients with good vs poor Karnofsky Performance Status.¹⁷ These results support stereotactic radiation for patients with 5 to 20 brain metastases.

Table 4. Neurocognitive Function in Patients Randomized to Stereotactic Radiation vs Hippocampal-Avoidance Whole Brain Radiation

Measure, time point	No. (%)		Mean difference (95% CI) ^a	P value
	Stereotactic radiation (n = 98)	Hippocampal-avoidance whole brain radiation (n = 98)		
Hopkins Verbal Learning Test-Revised^b				
Total Recall				
Baseline	85 (87)	75 (77)	0.02 (-0.39 to 0.44)	
4 mo	47 (48)	30 (31)	0.37 (-0.19 to 0.93)	.20
12 mo	20 (20)	16 (16)	0.83 (0.07 to 1.59)	.03
Delayed Recall				
Baseline	81 (83)	75 (77)	-0.06 (-0.54 to 0.42)	
4 mo	45 (46)	29 (30)	0.43 (-0.21 to 1.07)	.19
12 mo	19 (19)	16 (16)	1.25 (0.35 to 2.16)	.006
Recognition				
Baseline	81 (83)	74 (76)	-0.03 (-0.49 to 0.43)	
4 mo	43 (44)	29 (30)	0.24 (-0.35 to 0.82)	.43
12 mo	19 (19)	15 (15)	1.62 (0.52 to 2.72)	.004
Trail Making Test^b				
Part A				
Baseline	83 (85)	75 (77)	0.55 (-0.63 to 1.73)	
4 mo	45 (46)	32 (33)	0.86 (0.11 to 1.60)	.02
12 mo	18 (18)	15 (15)	2.95 (-0.10 to 5.99)	.06
Part B				
Baseline	80 (82)	73 (74)	-0.13 (-3.26 to 3.01)	
4 mo	43 (44)	30 (31)	0.78 (-0.84 to 2.40)	.35
12 mo	18 (18)	15 (15)	4.11 (0.37 to 7.86)	.03
Controlled Oral Word Association Test^b				
Baseline	82 (84)	73 (74)	-0.07 (-0.43 to 0.28)	
4 mo	46 (47)	30 (31)	0.53 (0.14 to 0.91)	.007
12 mo	19 (19)	16 (16)	0.47 (-0.05 to 0.98)	.08
Mini-Mental State Examination^c				
Baseline	80 (82)	74 (76)	0 (-0.79 to 0.79)	
4 mo	44 (45)	28 (29)	0.53 (-0.53 to 1.59)	.33
12 mo	18 (18)	15 (15)	0.86 (-0.49 to 2.21)	.21
Medical Outcomes Study Cognitive Functioning Scale-Revised^d				
Baseline	92 (94)	84 (86)	-1.50 (-4.49 to 1.49)	
4 mo	46 (47)	39 (40)	1.39 (-1.58 to 4.36)	.36
12 mo	23 (23)	19 (19)	0.76 (-4.18 to 5.70)	.76

^a Mean differences should be interpreted as the stereotactic radiation group minus the hippocampal-avoidance whole brain radiation group; positive differences reflect higher performance of the stereotactic radiation group.

^b Tests of neurocognitive function, except the Mini-Mental State Examination and the Medical Outcomes Study Cognitive Functioning Scale-Revised, were transformed into z scores. z Scores were interpreted as follows: score greater than 2.0, exceptionally high; 1.36 to 2.0, above average; 0.68 to 1.35, high average; -0.67 to 0.67, average; -0.68 to -1.35, low average; -1.36 to -2.0, below average; and less than -2.0, exceptionally low. Larger positive differences indicate superior performance in the stereotactic radiation group.

^c The Mini-Mental State Examination is scored on a 0 to 30 scale; higher differences indicate better function in the stereotactic radiation group.

^d The Medical Outcomes Study Cognitive Functioning Scale-Revised range is 0 to 100, with higher scores indicating better cognitive functioning; with conversion to a normative score, range is 7.51 to 58.61. Larger differences favor better performance in the stereotactic radiation group.

This study extends prior work by demonstrating that the advantages of stereotactic radiation apply to patients with more than 4 brain metastases.⁵⁻⁹ In addition, although hippocampal-avoidance whole brain radiation improves outcomes over traditional whole brain radiation,¹¹ stereotactic radiation offers greater benefit relating to symptom severity and interference with daily functioning. The results underscore a paradigm shift toward precision techniques that prioritize patient well-being.

Patients randomized to stereotactic radiation developed new brain metastases in previously uninvolved areas more than those randomized to hippocampal-avoidance whole brain radiation but infrequently required salvage whole brain radiation (5.1% at 1 year). These results suggest that stereotactic radiation often avoids, rather than merely delays, whole brain radiation when paired with frequent magnetic resonance imaging-based surveillance, although confirmatory studies are needed.

Radiation therapy has historically been important for brain metastases because many systemic therapies lack blood-brain barrier penetration.³ Recently, brain-penetrant-targeted or immune-based drugs have fostered deferral of up-front radiation in select patients.²⁴⁻³⁰ However, even in such patients, the brain is often the first site of progression. To enhance generalizability, this trial included patients initially treated for brain metastases with systemic therapy. As systemic therapy improves and survival lengthens, the value of stereotactic radiation over hippocampal-avoidance whole brain radiation may increase, because neurocognitive benefits increased with longer follow-up.

Limitations

This study has several limitations. First, it was not blinded and the primary outcome was subjective. Second, differences

in outcomes were often modest in magnitude. Third, high mortality limited long-term data collection, reducing precision and biasing outcomes toward survivors. Fourth, randomization was not stratified by treating center, allowing possible unmeasured imbalances. Fifth, the minimal clinically important difference had not been defined for many study outcome measures.

Conclusions

In patients with 5 to 20 brain metastases, these findings support stereotactic radiation over hippocampal-avoidance whole brain radiation to improve symptom burden and interference with daily functioning, key components of quality of life.

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Data Sharing Statement: See Supplement 6.

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