Original Study

Stereotactic Radiosurgery Versus Whole Brain Radiation Therapy: A Propensity Score Analysis and Predictors of Care for Patients With Brain Metastases From Breast Cancer

Walker Mainwaring,[1] John Bowers,[1] Ngoc Pham,[1] Todd Pezzi,[2] Mihir Shukla,[1] Mark Bonnen,[1] Michelle Ludwig[1]

Abstract

Brain metastases from breast cancer have historically been treated with whole-brain therapy, but the use of stereotactic radiosurgery is increasing. The National Cancer Database was used to compare patients who had received either modality of radiation therapy. Higher income, private insurance, treatment at academic centers, and longer overall survival were all associated with stereotactic radiosurgery use.

Background: Metastases to the brain occur in 10%-16% of patients with breast cancer, with incidence reportedly increasing. Historically, brain metastases (BM) have been treated with whole-brain radiation therapy (WBRT), but stereotactic radiosurgery (SRS) is an increasingly favored treatment option. In this study we used a population-level database to compare patterns of care and survival between WBRT and SRS for BM from breast cancer. **Materials and Methods:** The National Cancer Database was used to select patients treated with radiation for BM from primary breast cancer. Groups were classified on the basis of the modality of radiation delivered to the brain and compared across several demographic factors. A Kaplan−Meier survival curve and Cox multivariate analysis were used to compare overall survival. A matched analysis using propensity scores was used to further reduce confounders and compare survival. **Results:** The treatment groups were significantly different across several socioeconomic variables including income, insurance status, and treatment setting. The percentage of patients who received SRS increased dramatically in the second half of the analyzed time period ($P < .001$). Unadjusted median survival was significantly longer for patients who received SRS versus those who received WBRT ($P < .001$). This finding persisted after propensity score-matching. **Conclusion:** Receipt of SRS was associated with different socioeconomic variables and longer overall survival compared with WBRT, highlighting the need for less toxic treatment for patients who are now living longer. The results revealed important socioeconomic differences between patients selected for SRS versus WBRT and emphasizes disparities in access to modern radiation techniques across the United States.

[1]Department of Radiation Oncology, Baylor College of Medicine, Houston, TX
[2]Division of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX

Address for correspondence: Michelle Ludwig, MD, MPH, PhD, Department of Radiation Oncology, Baylor College of Medicine, One Baylor Plaza, Mail Stop: BCM711, Houston, TX 77030
E-mail contact: michelle.ludwig@bcm.edu

Introduction

Metastases to the brain occur in 25%-35% of patients with systemic cancer, and the incidence is increasing.[1] This phenomenon is thought to be the result of therapies that allow patients to live longer, and the poor ability of systemic therapy to cross the blood−brain barrier, making the brain a sanctuary site for disease. Brain metastases (BM) are approximately 10 times more common than primary intracranial tumors.[2] Traditionally, BM have been treated with whole-brain radiation therapy (WBRT),[3] which historically uses approximately 10 fractions of low-dose radiation. This was preferred because it provided control of neurologic symptoms,

treated visible and occult metastases, and was widely available.[4] However, evidence has emerged that indicates WBRT might cause neurocognitive decline among some patients.[5,6] Furthermore, recent trials comparing outcomes in patients after stereotactic radiosurgery (SRS) with or without WBRT have indicated that, although there is increased rates of local recurrence, requiring further salvage therapy, there is no decrease in overall survival with the omission of WBRT.[5,7] Thus the use of SRS is becoming increasing popular. SRS, including fractionated SRS, uses 1-5 fractions to deliver high-dose radiation to the tumor with a high degree of precision that minimizes the dose to healthy tissues. It is routinely used to treat 1-3 small (<4 cm) BM, and recent studies have even examined its use in patients with ≥10 metastases.[8,9] Because of the evidence showing that patients are more likely to die from systemic disease than from their BM,[8] physicians are increasingly choosing SRS to minimize treatment toxicities and improve patients' quality of life.[10]

Few studies have examined predictors that ultimately lead to treatment with SRS or WBRT. This study aimed to use the National Cancer Database (NCDB), a population-based data set, to examine treatment patterns influencing treatment modalities and outcomes for breast cancer patients with BM. Breast cancer was chosen because it is the most common cancer globally, the most common cause of cancer in women, and a frequent source of central nervous system metastases.[11] Herein, we examine the factors influencing SRS or WBRT and survival analysis for patients with BM from breast cancer.

Materials and Methods

Institutional review board approval was obtained from Baylor College of Medicine to complete this study. The NCDB currently captures information on 70% of all malignancies diagnosed annually in the United States. The American College of Surgeons' Commission on Cancer and the American Cancer Society acquire and maintain the database, which contains detailed data on disease parameters, treatments, patient characteristics, and outcomes. The level of detail captured by the NCDB is unique and provides specific data regarding treatment site, treatment source, radiation dose, and treatment technique. We were granted access to the NCDB Breast Cancer Database, containing data of 2,246,280 patients who were diagnosed between 2004 and 2014.

The primary objective of this study was to use a large population to determine patterns of radiation treatment for BM treated with WBRT or SRS; specifically, differences in age, race, sex, Charlson/Deyo score, median income quartile, facility academic status, insurance type, year of diagnosis, hormone receptor (HR, referring to either estrogen or progesterone receptor positivity)/HER2 receptor status, and rate of distant site surgeries between the two. Furthermore, in this study we sought to compare the overall survival between the patients who received the 2 different treatments.

Statistical analysis was performed using SPSS version 24 (IBM Corp, Armonk, NY). The χ^2 test and multivariable logistic regression test were used to compare the groups across health care system and demographic factors, and a Kaplan−Meier survival curve was used to compare survival outcomes between the 2 treatments. Cox univariate and multivariate survival regressions were used to compare survival across several factors.

To further reduce the effects of confounding variables, a matched analysis using propensity scores was performed. Propensity scores were generated using the matching plug-in in R version 3.2.0 (The R-project for statistical computing; Vienna, Austria), and groups were matched 1:1 with replacement using a caliper of 0.2. Matching analysis was performed using age, facility setting, insurance, year of diagnosis, race, Charlson/Deyo Score, and median income quartile as covariates. Matching variables were chosen on the basis of variables used in previous studies[12,13] in combination with factors that were significant in multivariate survival analysis. However, distant-site surgery and HR/HER2 receptor status were not included in the matching process. The information available on distant-site surgeries in the NCDB is nonspecific, and does not define if the surgery was intracranial, spinal, or to another distant site, which is why it was not chosen as a covariate during propensity score-matching. Similarly, HR/HER2 receptor status was included in the χ^2 and survival analyses but was not used in the matching process because of missing information for a large percentage (57.5%) of subjects. A standardized mean difference between groups was generated for each variable. A χ^2 test was performed to further support efficacy of the matching process, with P values <.05 indicating significant difference. Survival differences between groups were again analyzed using Kaplan−Meier survival curve and Cox survival regressions.

We included only patients who received radiation to the brain and were age eighteen years or older in the final analysis. Treatment groups (SRS or WBRT) were distinguished on the basis of the modality of radiation delivered to the brain, and further verified with fractionating and dosing criteria. We only included patients in the SRS group who had received 1-6 fractions of radiation for a total of 12-30 Gy and only those who had received 10-15 fractions for a total of 25-40 Gy in the WBRT group to eliminate subjects who were erroneously labeled with a wrong radiation modality (although 1-5 fractions is the standard for SRS, a significant number of patients received 6 fractions and thus were included in the stereotactic sample). Group assignments were determined according to the first intracranial radiation course of SRS or WBRT. An attempt was made to further categorize individuals who underwent additional courses of intracranial radiation; however, because of the limitations of the database, this could not be reliably determined. Finally, only subjects diagnosed through 2013 were included to allow for at least 1 year of follow-up, and male patients were excluded (Figure 1).

Results

A total of 2213 patients were included in the final analysis, and the details of group characteristics are shown in Table 1. Among the final cohort, 1997 (90.2%) received WBRT and 216 (9.8%) received SRS. Groups were similar in percentage of patient age, race, and Charlson/Deyo score. Patients who received SRS therapy were associated with a higher median quartile group compared with patients who received WBRT ($P = .01$). Those who received treatment at academic centers were more likely to receive SRS ($P = .001$), as were those with private insurance compared with other types of insurance ($P < .001$). The percentage of patients who received SRS increased dramatically in the second half of the analyzed time period (2009-2013 compared with 2004-2008; $P < .001$). Patients who received SRS were more likely to have HR-negative (HR$^-$)/HER2$^-$ (triple-negative), HR$^-$/HER2$^+$, or

| Figure 1 | Criteria for Subject Selection |
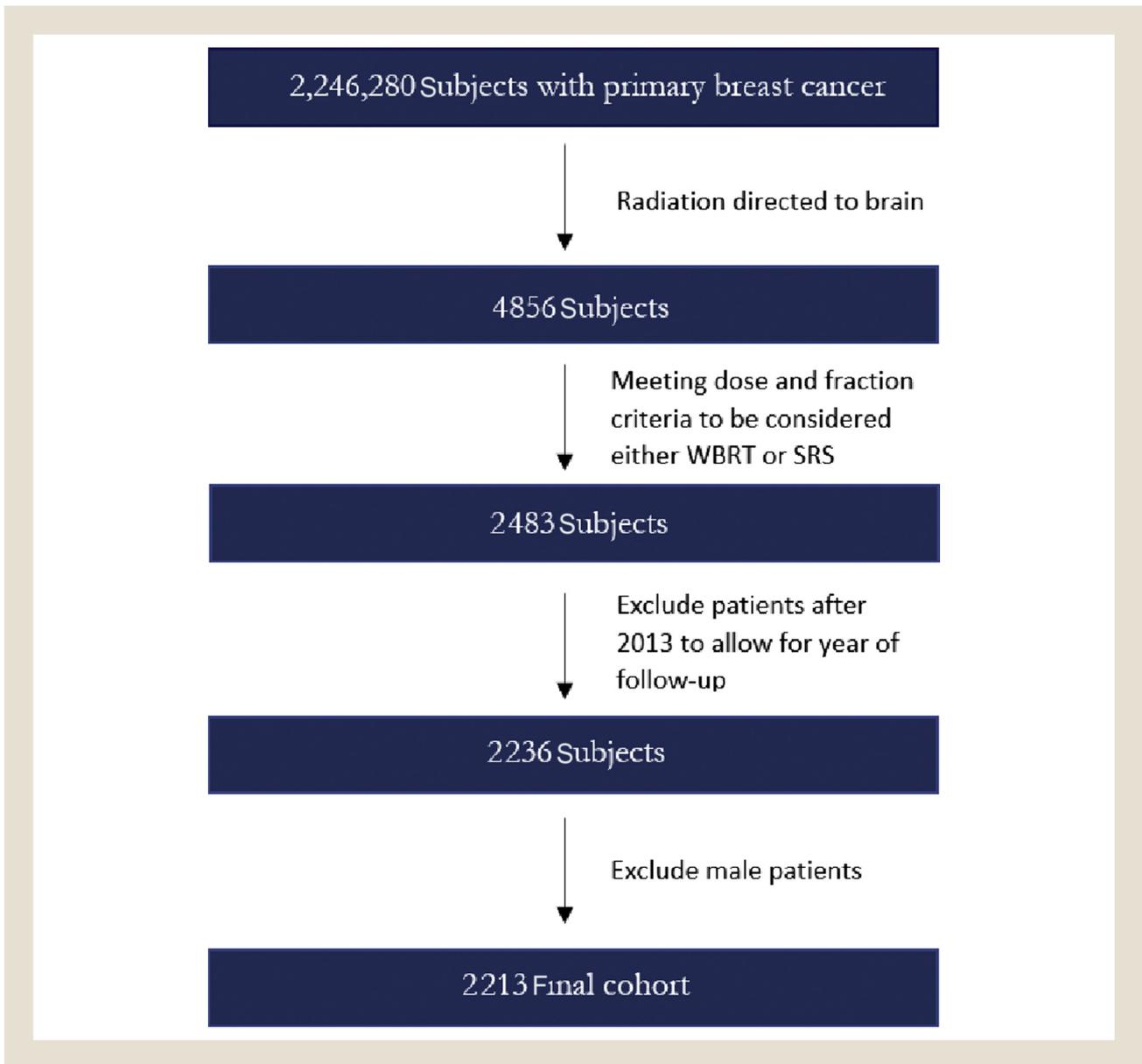
Abbreviations: SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

HR$^+$/HER2$^+$ cancers compared with WBRT ($P < .001$). Finally, SRS was associated with a higher rate of distant site surgeries compared with WBRT ($P < .001$).

Univariate survival analysis (Table 2) indicated longer survival in the SRS group compared with the WBRT group (hazard ratio, 0.575; 95% confidence interval [CI], 0.487-0.679; $P < .001$). Hispanic race was significantly associated with better survival compared with Caucasian race (hazard ratio, 0.763; 95% CI, 0.622-0.936; $P = .009$), as were median income quartile of $36,000-45,999 (hazard ratio, 0.820; 95% CI, 0.720-0.933; $P = .003$) and $46,000 or greater (hazard ratio, 0.683; 95% CI, 0.597-0.781; $P < .001$) compared with lower incomes and diagnosis in the second half of years recorded (2009-2013 compared with 2004-2008; hazard ratio, 0.867 95% CI, 0.791-0.951; $P = .002$). Older age was

associated with worse survival (hazard ratio, 1.02; 95% CI, 1.015-1.023; $P < .001$), as were Medicare (hazard ratio, 1.629; 95% CI, 1.461-1.816; $P < .001$) and uninsured (hazard ratio, 1.229; 95% CI, 1.037-1.456; $P = .018$) insurance status compared with private insurance. Black race (hazard ratio, 1.160; 95% CI, 1.036-1.298; $P = .01$) compared with Caucasian race, and those in comprehensive community cancer centers (hazard ratio, 1.256; 95% CI, 1.128-1.398; $P < .001$) or other centers (hazard ratio, 1.142; 95% CI, 1.014-1.287; $P = .029$) compared with academic centers also showed a survival difference. Triple-negative cancers were associated with worse survival compared with HR$^+$/HER2$^-$ (hazard ratio, 0.0562; 95% CI, 0.472-0.668), HR$^-$/HER2$^+$ (hazard ratio, 0.559; 95% CI, 0.440-0.710), HR$^+$/HER2$^+$ (hazard ratio, 0.377; 95% CI, 0.296-0.480), and cancers without receptor status data (hazard

Table 1 Group Differences in Matched and Unmatched Subject Samples

Covariate	Unmatched Sample				Matched Sample			
	WBRT (n = 1997)	SRS (n = 216)	P	SMD	WBRT (n = 216)	SRS (n = 216)	P	SMD
Age, y			.284				.870	
<55	771 (38.6)	95 (44.0)		0.111	89 (41.2)	95 (44.0)		0.056
55-64	639 (32.0)	60 (27.8)		−0.090	62 (28.7)	60 (27.8)		−0.021
65-74	397 (19.9)	37 (17.1)		−0.077	36 (16.7)	37 (17.1)		0.012
75 or older	190 (9.5)	24 (11.1)		0.046	29 (13.4)	24 (11.1)		−0.073
Race			.258				.920	
White (Non-Hispanic)	1379 (69.1)	157 (72.7)		0.077	155 (71.8)	157 (72.7)		0.021
Black (Non-Hispanic)	419 (21.0)	34 (15.7)		−0.138	30 (13.9)	34 (15.7)		0.051
Asian	37 (1.9)	6 (2.8)		0.057	8 (3.7)	6 (2.8)		−0.056
Hispanic	129 (6.5)	13 (6.0)		−0.017	16 (7.4)	13 (6.0)		−0.058
Other	33 (1.7)	6 (2.8)		0.066	7 (3.2)	6 (2.8)		−0.028
Median Income Quartile, $			.010				.902	
<30,000	338 (17.6)	27 (12.9)		−0.145	35 (16.2)	37 (17.1)		0.025
30,000-35,999	357 (18.6)	27 (12.9)		−0.085	39 (18.0)	44 (20.4)		0.057
36,000-45,999	547 (28.5)	60 (28.7)		0.069	68 (31.5)	63 (29.2)		−0.051
≥46,000	675 (35.2)	95 (45.5)		0.173	74 (34.3)	72 (33.3)		−0.020
Charlson/Deyo Score			.219				.495	
0	1638 (82.0)	178 (82.4)		0.012	176 (81.5)	178 (82.4)		0.024
1	277 (13.9)	34 (15.7)		0.050	32 (14.8)	34 (15.7)		0.025
2	84 (4.1)	4 (1.9)		−0.171	8 (3.7)	4 (1.9)		−0.137
Facility Academic Status			.001				.701	
Academic	642 (32.1)	93 (43.1)		0.219	87 (40.3)	93 (43.1)		0.056
Comprehensive community cancer	815 (40.8)	63 (29.2)		−0.260	71 (32.9)	63 (29.2)		−0.081
Community cancer or other	540 (27.0)	60 (27.8)		0.021	58 (26.9)	60 (27.8)		0.021
Insurance Type			<.001				.884	
Private	856 (42.9)	122 (56.5)		0.278	120 (55.6)	122 (56.5)		0.019
Medicaid	320 (16.0)	33 (15.3)		−0.018	35 (16.2)	33 (15.3)		−0.026
Medicare	576 (28.8)	51 (23.6)		−0.130	54 (25.0)	51 (23.6)		−0.033
Uninsured	189 (9.5)	4 (1.9)		−0.555	4 (1.9)	4 (1.9)		0.000
Other or unknown	56 (2.8)	6 (2.8)		−0.006	3 (1.4)	6 (2.8)		0.084
Year of Diagnosis			<.001				.594	
2004-2008	911 (45.6)	64 (29.6)		−0.348	59 (27.3)	64 (29.6)		0.051
2009-2013	1086 (54.4)	152 (70.4)		0.348	157 (72.7)	152 (70.4)		−0.051
Hormone Receptor (HR, Estrogen, and Progesterone Receptor) and HER2 Status			<.001				.297	
Triple-negative	220 (11.0)	37 (17.1)		0.160	30 (13.9)	37 (17.1)		0.086
HR$^+$/HER2$^-$	361 (18.1)	40 (18.5)		0.012	56 (25.9)	40 (18.5)		−0.190
HR$^-$/HER2$^+$	104 (5.2)	20 (9.3)		0.140	13 (6.0)	20 (9.3)		0.112
HR$^+$/HER2$^+$	135 (6.8)	22 (10.2)		0.112	22 (10.2)	22 (10.2)		0.000
Data unavailable	1177 (58.9)	96 (44.9)		−0.280	95 (44.0)	96 (44.9)		0.019
Distant Site Surgery Performed			<.001				<.001	
No	1833 (92.1)	174 (80.6)		−0.286	202 (93.5)	174 (80.6)		−0.327
Yes	131 (6.6)	38 (17.6)		0.291	0 (0.0)	4 (1.9)		0.118
Unknown	27 (1.4)	4 (1.9)		0.004	14 (6.5)	52 (17.6)		0.291

Data are presented as n (%) except where otherwise noted.

Abbreviations: HR = hormone receptor, referring to either estrogen or progesterone receptor positivity; SMD = standardized mean difference; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

Table 2 Univariate Survival

Covariate	Unmatched Sample		Matched Sample	
	Overall Survival Hazard Ratio (95% CI)	*P*	Overall Survival Hazard Ratio (95% CI)	*P*
Treatment Modality				
WBRT	Reference		Reference	
SRS	0.575 (0.487-0.679)	<.001	0.682 (0.547-0.851)	.001
Age at Diagnosis, y	1.02 (1.015-1.023)	<.001	1.018 (1.009-1.027)	<.001
Ethnicity				
White	Reference		Reference	
Black	1.160 (1.036-1.298)	.010	1.235 (0.918-1.661)	.163
Asian	0.778 (0.556-1.088)	.143	0.963 (0.526-1.765)	.904
Hispanic	0.763 (0.622-0.936)	.009	0.574 (0.340-0.969)	.038
Other	0.656 (0.448-0.960)	.030	0.714 (0.352-1.446)	.349
Median Income Quartile, $				
<30,000	Reference		Reference	
30,000-35,999	0.980 (0.858-1.119)	.760	1.049 (0.734-1.501)	.791
36,000-45,999	0.820 (0.720-0.933)	.003	0.860 (0.622-1.189)	.361
≥46,000	0.683 (0.597-0.781)	<.001	0.665 (0.479-0.923)	.015
Insurance Status				
Private	Reference		Reference	
Medicaid	1.084 (0.948-1.240)	.239	0.986 (0.715-1.360)	.932
Medicare	1.629 (1.461-1.816)	<.001	1.982 (1.530-2.567)	<.001
Uninsured	1.229 (1.037-1.456)	.018	1.072 (0.440-2.608)	.879
Other or unknown	1.087 (0.812-1.455)	.574	0.587 (0.187-1.838)	.360
Year of Diagnosis				
2004-2008	Reference		Reference	
2009-2013	0.867 (0.791-0.951)	.002	1.010 (0.796-1.282)	.933
Facility Academic Status				
Academic	Reference		Reference	
Comprehensive community cancer	1.256 (1.128-1.398)	<.001	1.322 (1.020-1.713)	.035
Community cancer or other	1.142 (1.014-1.287)	.029	1.118 (0.853-1.467)	.419
Hormone Receptor (HR, Estrogen, and Progesterone Receptor) and HER2 status				
Triple-negative	Reference		Reference	
HR$^+$/HER2$^-$	0.562 (0.472-0.668)	<.001	0.475 (0.327-0.690)	<.001
HR$^-$/HER2$^+$	0.559 (0.440-0.710)	<.001	0.647 (0.401-1.045)	.075
HR$^+$/HER2$^+$	0.377 (0.296-0.480)	<.001	0.399 (0.245-0.649)	<.001
Data unavailable	0.692 (0.599-0.799)	<.001	0.607 (0.441-0.835)	.002
Surgery Performed to Distant (Nonprimary, Nonregional) Site				
No	Reference		Reference	
Yes	0.741 (0.622-0.883)	.001	0.857 (0.610-1.203)	.371
Unknown	1.054 (0.721-1.542)	.785	1.796 (0.668-4.828)	.246

Abbreviations: HR = hormone receptor, referring to either estrogen or progesterone receptor positivity; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

ratio, 0.692; 95% CI, 0.599-0.799; all *P* < .001). Having a surgical resection to a distant site was associated with lower mortality compared to having no distant site resection (hazard ratio, 0.741; 95% CI, 0.622-0.883; *P* = .001).

Multivariate analysis (Table 3) and Kaplan−Meier survival curve also showed longer overall survival in patients who received SRS compared with those who received WBRT (hazard ratio, 0.633;

95% CI, 0.535-0.750; *P* < .001). Median survival for those who received SRS was 21.68 months (95% CI, 17.86-25.51) compared with 11.2 months for WBRT (95% CI, 10.36-11.96; *P* < .001; Figure 2). Survival was greater in patients with a median income of $36,000-45,999 (hazard ratio, 0.863; 95% CI, 0.754-0.988; *P* = .033) and $46,000 or greater (hazard ratio, 0.740; 95% CI, 0.641-0.854; *P* < .001), and patients with HR$^+$/HER2$^-$ (hazard ratio,

Table 3	Multivariate Survival				
	Unmatched Sample			**Matched Sample**	
Characteristic	**Overall Survival Hazard Ratio (95% CI)**	**P**		**Overall Survival Hazard Ratio (95% CI)**	**P**
Treatment Modality					
WBRT	Reference				
SRS	0.633 (0.535-0.750)	<.001		0.608 (0.483-0.765)	<.001
Ethnicity					
White	Reference			Reference	
Black	1.095 (0.967-1.239)	.152		1.118 (0.804-1.556)	.507
Asian	0.805 (0.571-1.135)	.217		0.580 (0.308-1.094)	.093
Hispanic	0.857 (0.693-1.060)	.155		0.628 (0.368-1.070)	.087
Other	0.707 (0.482-1.038)	.077		0.723 (0.351-1.490)	.380
Year of Diagnosis					
2004-2008	Reference			Reference	
2009-2013	0.906 (0.790-1.039)	.158		1.026 (0.731-1.442)	.880
Facility Academic Status					
Academic	Reference			Reference	
Comprehensive community cancer	1.165 (1.042-1.302)	.007		1.321 (1.008-1.731)	.043
Community cancer or other	1.112 (0.985-1.256)	.087		1.015 (0.763-1.351)	.917
Insurance Status					
Private	Reference			Reference	
Medicaid	1.039 (0.903-1.196)	.590		0.876 (0.625-1.228)	.442
Medicare	1.545 (1.381-1.727)	<.001		1.958 (1.484-2.584)	<.001
Uninsured	1.119 (0.938-1.335)	.210		0.972 (0.392-2.409)	.951
Other or unknown	0.937 (0.695-1.262)	.668		0.631 (0.197-2.019)	.438
Median Income Quartile, $					
<30,000	Reference			Reference	
30,000-35,999	1.007 (0.878-1.155)	.918		1.255 (0.850-1.853)	.254
36,000-45,999	0.863 (0.754-0.988)	.033		0.995 (0.697-1.421)	.978
≥46,000	0.740 (0.641-0 .854)	<.001		0.727 (0.504-1.048)	.088
Hormone Receptor (HR, Estrogen, and Progesterone Receptor) and HER2 Status					
Triple-negative	Reference			Reference	
$HR^+/HER2^-$	0.535 (0.448-0.638)	<.001		0.401 (0.272-0.593)	<.001
$HR^-/HER2^+$	0.552 (0.434-0.703)	<.001		0.660 (0.405-1.077)	.096
$HR^+/HER2^+$	0.392 (0.307-0.500)	<.001		0.414 (0.251-0.684)	.001
Data unavailable	0.615 (0.515-0.735)	<.001		0.584 (0.392-0.868)	.008
Surgery Performed to Distant (Nonprimary, Nonregional) Site					
No	Reference			Reference	
Yes	0.794 (0.664-0.949)	.011		0.939 (0.661-1.333)	.724
Unknown	1.032 (0.698-1.526)	.875		2.427 (0.861-6.844)	.094

Abbreviations: HR = hormone receptor, referring to either estrogen or progesterone receptor positivity; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

0.535 [0.448-0.638]), $HR^-/HER2^+$ (hazard ratio, 0.552 [0.434-0.703]), and $HR^+/HER2^+$ (hazard ratio, 0.392 [0.307-0.500], all with $P < .001$) cancers compared to triple negative cancers. Surgical resection to a distant site was associated with lower mortality as well (hazard ratio, .0794 [0.664-0.949], $P = .011$). Overall survival was lower in patients with Medicare (hazard ratio, 1.545 [1.381-1.727]; $P < .001$), and in those receiving care at comprehensive community cancer centers (hazard ratio, 1.165 [1.042-1.302]; $P = .003$).

Two-hundred-sixteen cases from each cohort were matched successfully, using 1:1 matching. Table 1 illustrates adequate balance between baseline characteristics between each group after matching. Median survival after matching was 21.68 months in the SRS group (CI 17.855-25.505) compared to 14.39 months (CI 11.16-17.62) in the WBRT group ($P = .001$; Figure 3). Using unadjusted cox-regression analysis, treatment with SRS (hazard ratio, 0.682 [0.547-0.851]; $P = .001$), Hispanic race (hazard ratio,

Figure 2   Kaplan—Meier Survival Curve for Unmatched Subjects

Abbreviations: SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

Figure 3   Kaplan—Meier Survival Curve for Matched Subjects
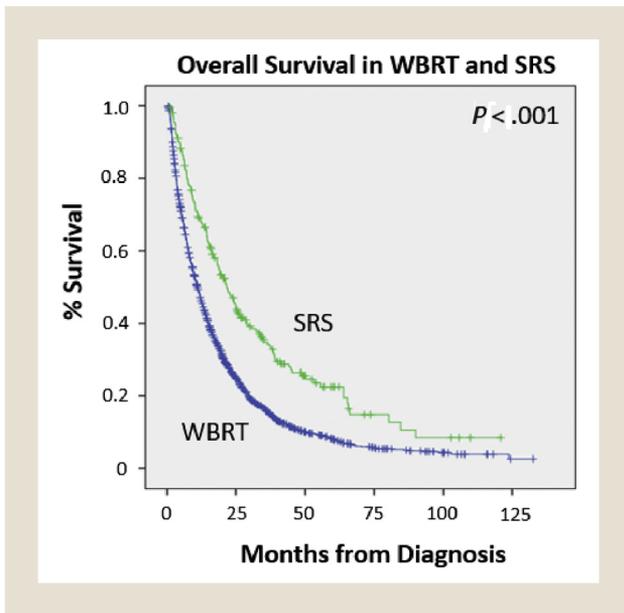
Abbreviations: SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

0.574 [0.340-0.969]; $P = .038$), and income of \$46,000 or greater (hazard ratio, 0.665 [0.479-0.923]; $P = .015$) were associated with greater overall survival. Higher age (hazard ratio, 1.018 [1.009-1.027]; $P < .001$), Medicare insurance (hazard ratio, 1.982 [1.530-2.567]; $P < .001$), and treatment at a comprehensive community cancer center (hazard ratio, 1.322 [1.020-1.713]; $P = .035$) were associated with poorer survival. On multivariate analysis, treatment with SRS (hazard ratio, 0.608 [0.483-0.765]; $P < .001$) was significantly associated with greater survival, as were HR$^+$/HER2$^-$ (hazard ratio, 0.401; 95% CI, 0.272-0.593; $P < .001$), HR$^+$/HER2$^+$ (hazard ratio, 0.414; 95% CI, 0.251-0.684; $P = .001$), and cancers without receptor status information available (hazard ratio, 0.584; 95% CI, 0.392-0.868; $P = .008$) compared with triple-negative cancers. Only Medicare insurance (hazard ratio, 1.958; 95% CI, 1.484-2.584; $P < .001$) and treatment at comprehensive community cancer centers (hazard ratio, 1.321; 95% CI, 1.008-1.731; $P = .043$) were associated with worse survival.

Discussion

Metastases to the brain are an especially devastating consequence from primary breast cancer, because they are associated with the shortest survival compared with other sites of metastasis.[14] Although WBRT is still widely chosen as a treatment for BM from breast cancer, this study shows increasing use of SRS in later years of diagnosis. This is likely because of increasing accessibility to SRS technology and evidence showing a reduction in cognitive decline without adverse effects on survival. These results revealed significant differences in the populations who received the differing treatment modalities. Those with higher income quartiles, private insurance, or academic treatment centers were more likely to receive SRS. This apparent difference in socioeconomic characteristics highlights
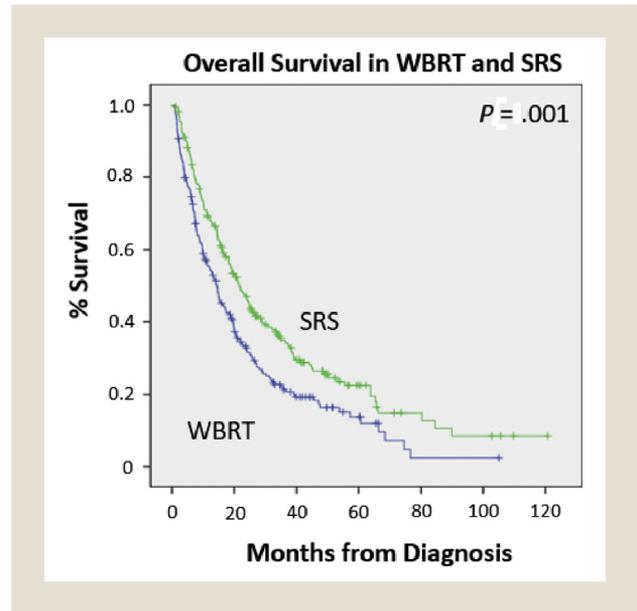
disparities between selection for radiation treatment modality. Although there is not likely a survival advantage with the use of SRS, recent data have shown a significant reduction in neurocognitive quality of life with WBRT administration. This detriment might be further amplified as new systemic therapies result in longer quantity of life. Research into disparities of access to care in radiation oncology is relatively new; most studies have been published since the beginning of 2014. However, a review of 58 published articles investigating the topic showed that disparities were prevalent in cancer treatment across many different organ systems, and are usually related to patient race and/or insurance status.[15,16] Similarly, the results of our study further reflect this trend. Because debate on insurance coverage and access to health care has intensified in recent years, the American Society for Radiation Oncology has urged lawmakers to be mindful of access to care and the unique needs of cancer patients when implementing change. The situation will be important to monitor, and efforts must be made to reduce current disparities.

Previous studies have not shown a difference in survival after eliminating WBRT. When examining all patients treated for BM, these results show longer overall survival in patients selected for SRS with a median survival nearly twice as long in that group compared with the group that received WBRT. After propensity score-matching, the overall survival benefit of SRS was less dramatic, but still with a 7-month improvement. This likely represents patient selection, rather than the treatment modality involved. A patient chosen for SRS typically includes individuals with a good performance status, limited number of BM, and low systemic burden. In recent years, there has been a treatment paradigm shift in many disease sites, for more aggressive treatment when a limited number of distant metastatic sites are identified. A popular noninvasive local treatment is stereotactic delivery of radiation.[17] Although there are

multiple factors influencing survival, the benefit in the SRS cohort likely represents the use of SRS for patients with a limited number of metastatic sites. Although difficult to tease out in a population study, further research might be warranted to determine if close surveillance to identify a higher number of patients with oligometastatic disease, followed by aggressive treatment of oligometastatic sites, leads to superior survival in breast cancer patients. This might have contributed to the improved survival noted in patients treated in the latter half of the study, with improved imaging techniques and a trend for more frequent use of stereotactic radiation in recent years. Other factors were also associated with survival benefit, including higher income, private insurance, and treatment in academic centers, whereas triple-negative cancers, black race, Medicare insurance, and treatment in nonacademic centers were associated with worse survival. This further emphasized the link between socioeconomic status and potential outcomes in treatment for intracranial metastases from breast cancer primary.

Because previous studies have indicated less cognitive decline in patients who received SRS, this study supports the trend of moving away from WBRT for treatment of BM. If SRS provides equivalent survival, in addition to fewer negative side effects, then it would assert itself as the first-line radiation treatment in the appropriately selected patient population. Furthermore, the increase in overall survival, as noted in the latter half of the analyzed time interval, supports the notion that patients with BM are living longer and would likely experience neurocognitive deficits associated with WBRT. Although there remains room for significant improvement in treatment of BM, this increase in survival with time is encouraging for the treatment of patients suffering from a devastating disease.

Limitations

This study has several limitations by nature. The SRS cohort was relatively small compared with the WBRT after eliminating subjects with inadequate or erroneous data. Furthermore, because of the available variables, it was not feasible to control for number or size of metastases and extent of systemic disease, factors that clearly have great effect on survival. As would be expected in a large population database, there was no information on cognitive testing and thus we could not examine differences in neurocognitive outcomes. Furthermore, the NCDB does not record the sequencing of treatment to differentiate postoperative, salvage, or primary treatment with radiation therapy. As such, the survival data must be interpreted with the assumption that many factors influencing survival could not be adequately controlled.

Conclusion

Evaluation of our data regarding surgical resection in addition to stereotactic radiation therapy showed a survival benefit in univariate analysis. However, when this group was propensity matched no significant difference in survival was noted. This might be attributed to lack of specific data regarding the NCDB definition of surgery at a distant site, specifically no measured data of intracranial versus spinal surgeries. This is likely the case, because 2 prospective randomized studies have shown improved survival with the combination of surgery and radiation, compared with radiation therapy alone.[3,17] Alternatively, having surgery could have been confounded

by an additional factor used for propensity matching. Ultimately, WBRT would unlikely be affected by surgery, because of the small proportion (6.5%) who undergo both therapies. However, 17.6% of patients treated with SRS underwent surgery and it might potentially be a confounding factor.

Additionally, although HR/HER2 status was independently associated with treatment modality and survival differences, most patients analyzed were missing information on HR/HER2 status, and so the variable was not used in the propensity score matching. Interestingly, group differences in HR/HER2 status were no longer significant after propensity score matching.

Clinical Practice Points

- Brain metastasis are associated with a poor prognosis in patients with system cancer, and they have traditionally been treated with either WBRT or, more recently, SRS, and recent studies suggest that omission of whole-brain therapy does not affect survival and might eliminate undesirable side effects such as neurocognitive decline.
- After multivariate analysis and propensity score matching, our data suggest that patients chosen for SRS tend to have improved overall survival. This likely correlates with patient selection and emphasizes the importance of early detection of BM and subsequent treatment with SRS to avoid known neurocognitive side effects associated with WBRT.
- Furthermore, the results indicate important socioeconomic differences between patients selected for SRS versus WBRT and highlights disparities in access to modern radiation techniques across the United States. With continued technological advances in radiation oncology, this socioeconomic disparity has the potential for a widening health care chasm that might result in not only quality but quantity of life.

Disclosure

The authors have stated that they have no conflicts of interest.

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