



Outcomes following stereotactic radiosurgery or whole brain radiation therapy by molecular subtype of metastatic breast cancer

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ABSTRACT

Background: This study quantified clinical outcomes by molecular subtype of metastatic breast cancer (BC) following whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS). Doing so is important for patient counseling and to assess the potential benefit of combining targeted therapy and brain radiotherapy for certain molecular subtypes in ongoing trials.

Materials and methods: The National Cancer Database was queried for BC (invasive ductal carcinoma) cases receiving brain radiotherapy (divided into WBRT and SRS). Statistics included multivariable logistic regression to determine factors associated with SRS delivery, Kaplan-Meier analysis to evaluate overall survival (OS), and Cox proportional hazards modeling.

Results: Of 1,112 patients, 186 (16.7%) received SRS and 926 (83.3%) underwent WBRT. Altogether, 410 (36.9%), 195 (17.5%), 162 (14.6%), and 345 (31.0%) were ER+/HER2-, ER+/HER2+, ER-/HER2+, and ER-/HER2-, respectively. In the respective molecular subtypes, the proportion of subjects who underwent SRS was 13.4%, 19.4%, 24.1%, and 15.7%. Respective OS for WBRT patients were 12.9, 22.8, 10.6, and 5.8 months; corresponding figures for the SRS cohort were 28.3, 40.7, 15.0, and 12.9 months ($p < 0.05$ for both). When comparing OS between treatment different histologic subtypes, patients with ER-/HER2+ and ER-/HER2- disease had worse OS than patients with ER+/HER2- disease, for both patients treated with SRS and for patients treated with WBRT.

Conclusions: Molecular subtype may be a useful prognostic marker to quantify survival following SRS/WBRT for metastatic BC. Patients with HER2-enriched and triple-negative disease had the poorest survival following brain irradiation, lending credence to ongoing studies testing the addition of targeted therapies for these subtypes.

Key words: breast cancer; brain metastasis; radiation therapy; stereotactic radiosurgery

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Introduction

Brain metastases (BM) will be diagnosed in 15-35% of patients with breast cancer (BC) [1-3]. The

occurrence of BM is also linked to tumor biology; BM are more common in patients with triple negative BC (TNBC) and those positive for the human epidermal growth factor receptor 2 (HER2) [4-5].

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Management of BM requires strong multidisciplinary coordination, as options include resection, systemic therapy, and/or radiation therapy (RT). With regard to the latter, the historic standard of care has been whole brain RT (WBRT), which addresses microscopic foci of disease not apparent on diagnostic imaging. However, its utility is beginning to be gradually replaced by stereotactic radiosurgery (SRS), which can deliver ablative doses for potentially higher local control, and significantly reduces the neurocognitive deterioration observed with use of WBRT [6]. Chemotherapy agents have traditionally not been utilized for primary therapy of brain disease, as penetration through the blood-brain barrier is generally low. Targeted agents such as trastuzumab, poly ADP ribose polymerase inhibitors, tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs) show modest central nervous system (CNS) activity, but may not reduce the incidence of BM [7].

Given the multitude of options for BC patients with various molecular subtypes, expected outcomes following WBRT or SRS for each subtype are important to quantify. In addition to having implications on patient counseling, it may also serve to assess the potential benefit of combining targeted therapy and brain RT for certain subtypes. There are two ongoing randomized phase II trials of the latter concept: Radiation Therapy Oncology Group (RTOG) 1119 is evaluating lapatinib in HER2 patients undergoing WBRT/SRS (NCT01622868), and Southwest Oncology Group (SWOG) 1416 is examining veliparib for TNBC with or without BM (NCT02595905). In order to accomplish this goal, we evaluated the large, contemporary National Cancer Database (NCDB).

Materials and methods

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population [8]. All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The data used in the study were derived from a de-identified

NCDB file (2005–2014). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

Inclusion criteria for this study were women with invasive ductal carcinoma with Stage IV (M1) breast cancer (International Classification of Disease–0–3 code 8500) who received RT to the brain. Additionally, because the goal of this study was to evaluate outcomes by molecular subtype, subjects were required to have available information regarding estrogen receptor (ER) and HER2 status. The patients were divided into two cohorts based on type of radiation delivered: SRS or WBRT. Based on criteria used in existing studies [9–11], patients included in the SRS cohort were those who were coded as received “gamma knife radiosurgery”, “LINAC radiosurgery,” or “stereotactic radiosurgery, NOS (not otherwise specified);” or, those receiving a daily fraction dose ≥ 6 Gy in ≤ 5 fractions. All other patients were categorized as the WBRT cohort. In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data.

All statistical tests were two-sided, with a definition of $p < 0.05$ for statistical significance, and were performed using STATA (version 14, College Station, TX). Multivariable logistic regression modeling determined characteristics predictive for SRS administration. Overall survival (OS, the interval between the date of diagnosis of brain metastasis and the date of death, or censored at last contact) analysis was per the Kaplan-Meier method, with group comparisons done with the log-rank test. Survival was separately calculated when dividing patients by histologic subtype for both WBRT and SRS. Following univariate analysis to determine factors associated with overall survival, Cox multivariate analysis included variables that were either significant or showed a strong trend to statistical significance on univariate analysis. Patients without complete survival information were censored from the survival analyses. The proportional hazards assumption was checked graphically using log-log plots.

Results

A complete patient selection diagram is shown in Figure 1. Overall, 1,112 patients met selection criteria (Tab. 1); 186 (16.7%) underwent SRS and 926 (83.3%) received WBRT. Altogether, 410 (36.9%), 195 (17.5%), 162 (14.6%), and 345 (31.0%) of the patients had ER+/HER2-, ER+/HER2+, ER-/HER2+, and ER-/HER2- disease, respectively.

Over the study period, utilization of SRS and WBRT by molecular subtype is given in Figure 2; 16.7% of the overall cohort received SRS, and 83.3% WBRT. In the respective molecular subtypes, the proportion of subjects who underwent SRS was 13.4%, 19.4%, 24.1%, and 15.7%. SRS was more often administered to ER-/HER2+ cases, at academic centers, in more recent time periods, and to privately-insured subjects (rela-

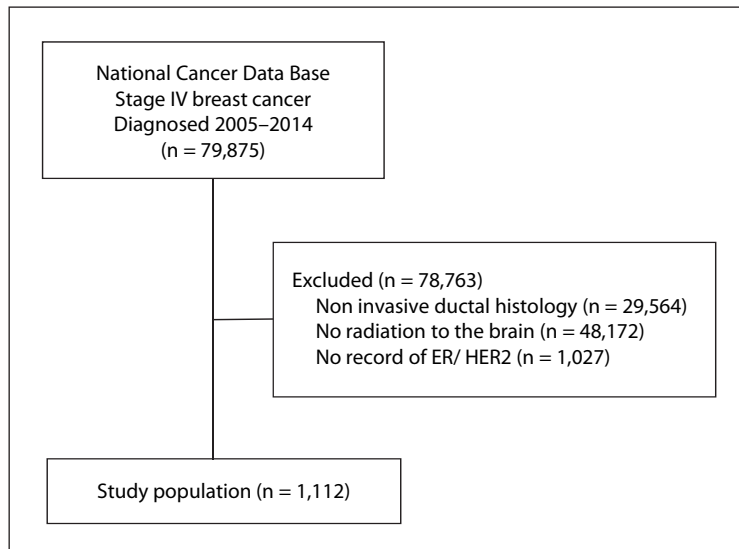


Figure 1. Patient selection diagram

Table 1. Demographic and clinical characteristics for all patients

Characteristic	Stereotactic radiosurgery (n = 186)	Whole brain radiation (n = 926)	p-value
Age			
≤ 50	58 (31.2%)	235 (25.4%)	0.215
51-65	85 (45.7%)	76 (51.4%)	
66-75	27 (14.5%)	55 (16.7%)	
≥ 76	16 (8.6%)	60 (6.5%)	
Molecular subtype			
ER+HER2-	55 (29.6%)	355 (38.3%)	0.013
ER+HER2+	38 (20.4%)	157 (17.0%)	
ER-HER2+	39 (21.0%)	123 (13.3%)	
ER-HER2-	54 (29.0%)	291 (31.4%)	
Race			
White	147 (79.0%)	711 (76.8%)	0.376
Black	26 (14.0%)	164 (17.7%)	
Other	13 (7.0%)	51 (5.5%)	



Table 1. Demographic and clinical characteristics for all patients

Characteristic	Stereotactic radiosurgery (n = 186)	Whole brain radiation (n = 926)	p-value
Charlson Deyo Score			
0	158 (85.0%)	762 (82.2%)	0.639
1	20 (10.8%)	122 (13.2%)	
≥ 2	8 (4.3%)	43 (4.6%)	
Median Income			
≤ 62999 USD	133 (71.5%)	684 (73.9%)	0.633
≥ 63000 USD	52 (28.0%)	233 (25.2%)	
Not recorded	1 (0.5%)	9 (1.0%)	
Facility type			
Academic	78 (41.9%)	24 (30.7%)	0.005
Nonacademic	92 (49.5%)	576 (62.2%)	
Not reported	16 (8.6%)	66 (7.1%)	
Chemotherapy			
Yes	129 (69.4%)	571 (61.7%)	0.106
No	41 (22.0%)	236 (25.5%)	
Not recorded	16 (8.6%)	119 (12.9%)	
Grade			
Well differentiated	5 (2.7%)	20 (2.2%)	0.318
Moderately differentiated	42 (22.6%)	242 (26.1%)	
Poorly differentiated/anaplastic	104 (55.9%)	528 (57.0%)	
Not recorded	35 (18.8%)	136 (14.7%)	
Year of diagnosis			
2005–2011	63 (33.9%)	404 (43.6%)	0.014
2012–2014	123 (66.1%)	522 (56.4%)	
Insurance			
Private	95 (51.1%)	370 (40.0%)	0.001
Medicaid	30 (16.1%)	202 (21.8%)	
Medicare	55 (29.6%)	246 (26.6%)	
Not insured	5 (2.7%)	87 (9.4%)	
Other/not recorded	1 (0.5%)	21 (2.3%)	
Surgery			
No surgery	143 (76.9%)	766 (82.7%)	0.020
Lumpectomy	10 (5.4%)	62 (6.7%)	
Mastectomy	33 (17.7%)	98 (10.6%)	

tive to Medicaid/uninsured) ($p < 0.05$ for all) (Tab. 2).

Figure 3A displays OS by molecular subtype in patients status post WBRT. The median OS for each molecular group amongst patients treated with

WBRT was 12.9, 22.8, 10.6, and 5.8 months for patients with ER+HER2–, ER+HER2+, ER–HER2+, and ER–HER2– disease, respectively. When comparing OS amongst patients receiving WBRT, those with ER+HER2+ disease had the greatest median OS when

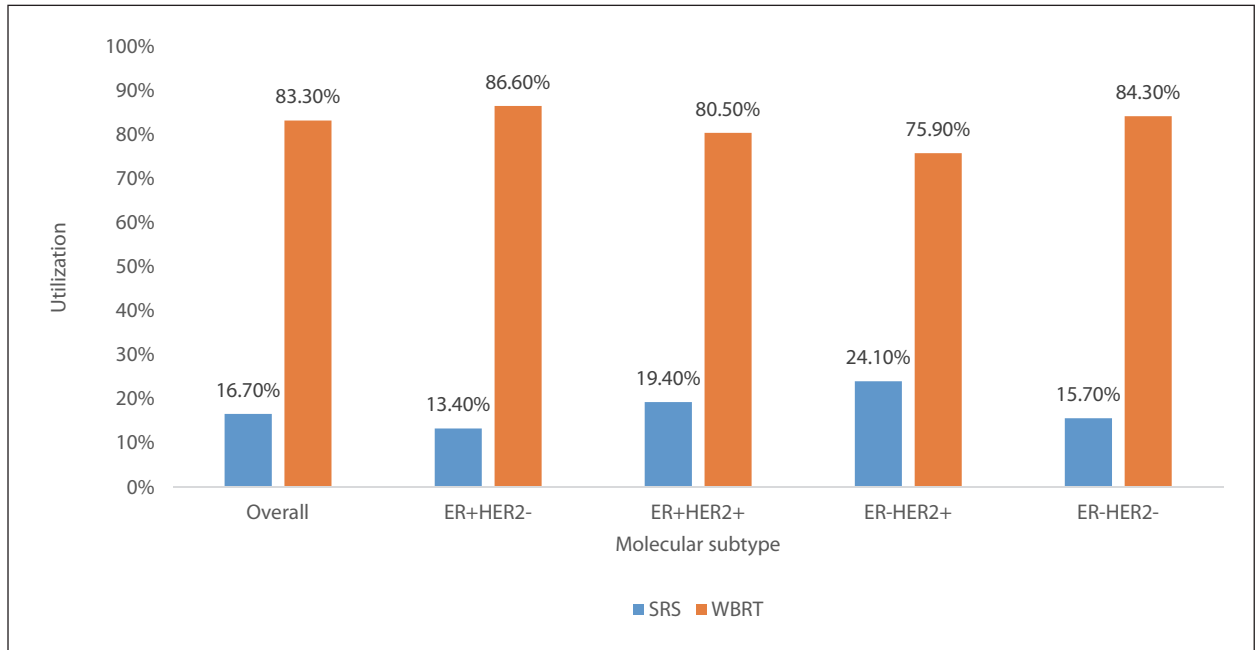


Figure 2. Utilization of stereotactic radiosurgery (SRS) by histologic subtype

Table 2. Multivariable logistic regression analysis for factors predictive of receiving stereotactic radiosurgery

Characteristic	Odds ratio	95% confidence interval	p-value
Age			
≤ 50	1 (reference)		
51–65	0.680	0.440–1.050	0.082
66–75	0.555	0/274–1.124	0.102
≥ 76	0.906	0.398–2.065	0.814
Molecular subtype			
ER+HER2–	1 (reference)		
ER+HER2+	1.493	0.912–2.446	0.111
ER–HER2+	1.944	1.154–3.276	0.012
ER–HER2–	1.219	0.774–1.921	0.392
Race			
White	1 (reference)		
Black	0.845	0.523–1.364	0.490
Other	1.187	0.608–2.320	0.616
Charlson Deyo Score			
0	1 (reference)		
1	0.746	0.438–1.269	0.280
≥ 2	0.908	0.399–2.069	0.818
Median income			
≤ 62999 USD	1 (reference)		
≥ 63000 USD	1.001	0.688–1.455	0.997
Not recorded	0.718	0.086–6.011	0.760

Table 2. Multivariable logistic regression analysis for factors predictive of receiving stereotactic radiosurgery

Characteristic	Odds ratio	95% confidence interval	p-value
Facility type			
Academic	1 (reference)		
Nonacademic	0.555	0.390–0.789	0.001
Not reported	0.656	0.327–1.316	0.235
Chemotherapy			
Yes	1 (reference)		
No	0.939	0.598–1.475	0.785
Not recorded	0.783	0.423–1.425	0.423
Grade			
Well differentiated	1 (reference)		
Moderately differentiated	0.635	0.218–1.854	0.406
Poorly differentiated/anaplastic	0.595	0.208–1.701	0.332
Not recorded	0.849	0.285–2.530	0.769
Year of diagnosis			
2005–2011	1 (reference)		
2012–2014	1.493	1.055–2.113	0.024
Insurance			
Private	1 (reference)		
Medicaid	0.582	0.366–0.925	0.022
Medicare	1.168	0.671–2.032	0.583
Not insured	0.245	0.095–0.630	0.004
Other/not recorded	0.223	0.029–1.171	0.149
Surgery			
No surgery	1 (reference)		
Lumpectomy	1.029	0.501–2.111	0.938
Mastectomy	1.805	1.122–2.903	0.015

compared to any other histologic subtype ($p < 0.005$ for all). In the SRS cohort (Fig. 3B), respective OS were 28.3, 40.7, 15.0, and 12.9 months. Patients with ER+HER2+ disease had greater median OS

In the overall cohort, there were several predictors of OS (Tab. 3) such as age, facility type, any local surgery, use of SRS, and chemotherapy receipt ($p < 0.05$ for all). Notably, as compared to ER+/HER2- disease, ER-/HER2- and ER-/HER2+ cases were associated with poorer OS ($p \leq 0.001$ for both).

Discussion

Management of BM, especially from BC, continues to evolve. This study of a large, contempo-

rary national database quantifies survival by molecular subtype following SRS or WBRT. Patients with HER2-enriched disease and ER-HER2- had the poorest survival following brain irradiation, lending credence to multiple ongoing randomized phase II studies testing the addition of targeted therapies for these high-risk subtypes.

Our results support other data demonstrating that molecular subtypes of BC represent distinct biological entities with distinct areas of metastases, patterns of failure, and survival [4–5, 12]. Moreover, it supports the disease-specific graded prognostic assessment posited by Sperduto and colleagues, as well as the recent update describing improved OS in patients with HER2 disease, although that study

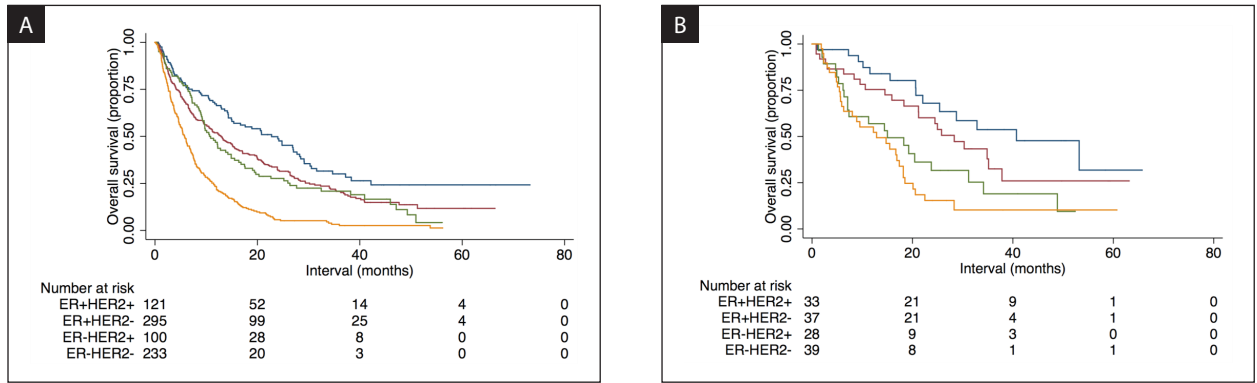


Figure 3. Kaplan-Meier curves comparing overall survival. **A.** All patients following whole brain radiation therapy. **B.** All patients following stereotactic radiosurgery

Table 3. Univariate and multivariate Cox analysis for factors predictive of overall survival

Characteristic	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value
Radiation type						
SRS	1 (reference)			1 (reference)		
Whole brain	1.709	1.366–2.138	<0.001	1.673	1.325–2.111	< 0.001
Age						
≤ 50	1 (reference)			1 (reference)		
51–65	1.221	1.015–1.470	0.034	1.109	0.901–1.364	0.330
66–75	1.760	1.393–2.224	<0.001	1.188	0.846–1.667	0.319
≥ 76	2.702	1.976–3.696	<0.001	2.297	1.536–3.435	< 0.001
Molecular subtype						
ER+HER2–	1 (reference)			1 (reference)		
ER+HER2+	0.638	0.501–0.812	<0.001	0.805	0.625–1.036	0.092
ER–HER2+	1.115	0.886–1.405	0.353	1.515	1.179–1.948	0.001
ER–HER2–	2.133	1.783–2.553	<0.001	2.684	2.200–3.273	<0.001
Race						
White	1 (reference)			–	–	–
Black	1.106	0.913–1.340	0.302	–	–	–
Other	0.838	0.597–1.174	0.304	–	–	–
Charlson Deyo Score						
0	1 (reference)			1 (reference)		
1	1.249	1.004–1.553	0.046	0.907	0.724–1.137	0.397
≥ 2	2.254	1.575–3.226	<0.001	1.348	0.927–1.959	0.118
Median income						
≤ 62 999 USD	1 (reference)			1 (reference)		
≥ 63 000 USD	0.756	0.631–0.905	0.002	0.835	0.693–1.006	0.058
Not recorded	2.407	1.243–4.664	0.009	1.798	0.912–3.544	0.090



Table 3. Univariate and multivariate Cox analysis for factors predictive of overall survival

Characteristic	Hazard ratio	95% confidence interval	p-value	Hazard ratio	95% confidence interval	p-value
Facility type						
Academic	1 (reference)			1 (reference)		
Nonacademic	1.186	1.010–1.394	0.038	1.179	1.001–1.389	0.049
Not reported	0.754	0.528–1.077	0.120	1.771	1.381–2.271	< 0.001
Chemotherapy						
Yes	1 (reference)			1 (reference)		
No	1.408	1.182–1.677	<0.001	1.466	1.191–1.804	<0.001
Not recorded	1.828	1.451–2.304	<0.001	1.771	1.381–2.271	<0.001
Grade						
Well differentiated	1 (reference)			–	–	–
Moderately differentiated	1.161	0.646–2.087	0.617	–	–	–
Poorly differentiated/ anaplastic	1.604	0.903–2.850	0.107	–	–	–
Not recorded	1.345	0.739–2.450	0.332	–	–	–
Year of diagnosis						
2005–2011	1 (reference)			–	–	–
2012–2014	0.931	0.800–1.085	0.360	–	–	–
Insurance						
Private	1 (reference)			1 (reference)		
Medicaid	1.093	0.894–1.336	0.387	1.024	0.834–1.258	0.820
Medicare	1.763	1.463–2.123	<0.001	1.279	0.966–1.694	0.086
Not insured	1.371	1.042–1.805	0.024	1.150	0.868–1.522	0.330
Other/not recorded	1.406	0.835–2.368	0.200	1.152	0.675–1.964	0.604
Surgery						
No surgery	1 (reference)			1 (reference)		
Lumpectomy	1.035	0.766–1.398	0.824	0.680	0.498–0.928	0.015
Mastectomy	0.703	0.558–0.886	0.003	0.679	0.533–0.866	0.002

SRS — stereotactic radiosurgery

did not stratify for receipt of WBRT versus SRS [13, 14]. Although not provided by the NCDB, it would certainly be useful to further elucidate the rate of distant brain failure (DBF) following SRS for each molecular subtype. Reducing the rate of DBF is the strength of WBRT over SRS [15–17], but comes at the expense of greater neurocognitive dysfunction. For these purposes, approaches such as hippocampal-sparing WBRT have been developed (NCT02360215), but in order to evaluate judicious utilization, studies on the risk of DBF for each molecular subtype may further sharpen patient selection for these new technological approaches.

Likewise, because DBF may be differentially likely based on a molecular subtype, the ongoing debate of SRS versus WBRT may also be differentially applicable. Although most data on SRS have utilized up to 3–4 BM [15–17], an argument for treating up to 10 tumors can certainly be made [18] in the sense that survival following SRS of 2–4 BM and 5–10 BM is statistically similar. To this extent, the trend towards higher DBF in patients initially presenting with higher numbers of BM may simply lead to a higher re-treatment rate but no change in outcomes; however, this notion has not been studied to date for each BC molecular subtype.

The NCDB contains adequate information for an OS comparison between SRS and WBRT. In the present study, use of SRS was associated with an improved OS when compared to WBRT in both univariate and multivariate analysis. However, this does not necessarily mean that the improved OS was due to use of SRS. There are other confounding factors at play in the selection of SRS versus WBRT, including both the number of brain metastases, patient performance status, extracranial disease status, and technology available at the treatment facility, which can also have an impact on clinical outcome. Additionally, the finding that any local surgery, including either lumpectomy or mastectomy, was associated with improved OS when compared to no local surgery is in line with the findings of other published reports [19, 20]. Again, this finding may also be confounded by selection bias, in which more healthy patients with metastatic disease may have been more likely to undergo surgical therapy. Indeed, an early report of a randomized trial comparing local therapy to no local therapy in patients with newly diagnosis Stage IV breast cancer showed no OS benefit with the use of local therapy [21].

Although a major shortcoming of the NCDB is the lack of information regarding specific targeted agents (e.g. trastuzumab or lapatinib, which could explain why the ER+/HER2+ patients had numerically higher OS than the ER+/HER2- cases), an emerging modality for management of BM are immune checkpoint inhibitors (ICIs). A dedicated phase II study of ipilimumab for melanoma metastases showed a 24% intracerebral response rate for asymptomatic BM [22]. Additionally, there is data now supporting a combination therapy of ICIs with ipilimumab and nivolumab that can control BM and potentially improve OS for these patients [23]. Although these data cannot be extrapolated to the BC setting, they have often been utilized as justification to defer SRS pending greater necessity, or spare the patient of WBRT-related neurocognition. However, we posit that the response rate remains altogether low even for small, asymptomatic lesions, far lower than for SRS (or WBRT) alone, which must be weighed against the substantially increased cost of ICIs as compared to RT [24–25]. A retrospective multicenter study studying up-front TKIs versus intracranial RT for EGFR-mutated

non-small cell lung cancer showed a detriment to OS and trend towards a detriment to intracranial progression-free survival if intracranial RT was not delivered up-front [26]. Moreover, a recent study demonstrated that tucatinib, an oral TKI selective for HER2, can improve OS in patients with HER2+ breast cancer and BM, though future studies will be required to determine how best to incorporate intracranial RT and tucatinib to maximize OS while minimizing neurocognitive toxicity in this patient cohort [27].

The NCDB has numerous shortcomings [28–32], and the reader is advised that these data are merely hypothesis-generating and not intended to substitute for randomized evidence. This includes a lack of information regarding the size/volume and location of brain and systemic metastases, symptomatology, graded prognostic assessment class, diagnostic and follow-up workup (including magnetic resonance imaging), performance status, specific systemic therapy agents/dose/tolerance, salvage therapies, and other non-OS endpoints. This study also did not evaluate timing of SRS/WBRT from diagnosis, which could also alter conclusions. The sample sizes were also relatively small, especially in the SRS group, preventing robust matched OS analysis. Lastly, although the NCDB includes data for 70% of the US population, only CoC-accredited facilities contribute data; as a result, these findings may not necessarily be representative of the entire United States population.

Conclusions

Management of BM, especially from BC, continues to evolve. This study of a large, contemporary national database quantifies survival by molecular subtype following SRS or WBRT. Patients with HER2-enriched disease and TNBC had the poorest survival following brain irradiation, lending credence to multiple ongoing randomized phase II studies testing the addition of targeted therapies for these high-risk subtypes.

Conflict of interest

All authors declare that conflicts of interest do not exist.

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