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CLINICAL TRIAL

Breast cancer subtype and intracranial recurrence patterns after brain-directed radiation for brain metastases

Daniel N. Cagney[1] · Nayan Lamba[2] · Sofia Montoya[1] · Puyao Li[1] · Luke Besse[1] · Allison M. Martin[1] · Rachel H. Brigell[1] · Paul J. Catalano[3,4] · Paul D. Brown[5] · Jose P. Leone[6] · Shyam K. Tanguturi[1] · Daphne A. Haas-Kogan[1] · Brian M. Alexander[1] · Nancy U. Lin[6] · Ayal A. Aizer[1]

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Abstract

Purpose Brain metastases from breast cancer are frequently managed with brain-directed radiation but the impact of subtype on intracranial recurrence patterns after radiation has not been well-described. We investigated intracranial recurrence patterns of brain metastases from breast cancer after brain-directed radiation to facilitate subtype-specific management paradigms.

Methods We retrospectively analyzed 349 patients with newly diagnosed brain metastases from breast cancer treated with brain-directed radiation at Brigham and Women's Hospital/Dana-Farber Cancer Institute between 2000 and 2015. Patients were stratified by subtype: hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−), HER2+ positive (HER2+), or triple-negative breast cancer (TNBC). A per-metastasis assessment was conducted. Time-to-event analyses were conducted using multivariable Cox regression.

Results Of the 349 patients, 116 had HR+/HER2− subtype, 164 had HER2+ subtype, and 69 harbored TNBC. Relative to HR+/HER2− subtype, local recurrence was greater in HER2+ metastases (HR 3.20, 95% CI 1.78–5.75, $p < 0.001$), while patients with TNBC demonstrated higher rates of new brain metastases after initial treatment (HR 3.16, 95% CI 1.99–5.02, $p < 0.001$) and shorter time to salvage whole brain radiation (WBRT) (HR 3.79, 95% CI 1.36–10.56, $p = 0.01$) and salvage stereotactic radiation (HR 1.86, 95% CI 1.11–3.10, $p = 0.02$).

Conclusions We identified a strong association between breast cancer subtype and intracranial recurrence patterns after brain-directed radiation, particularly local progression for HER2+ and distant progression for TNBC patients. If validated, the poorer local control in HER2+ brain metastases may support evaluation of novel local therapy-based approaches, while the increased distant recurrence in TNBC suggests the need for improved systemic therapy and earlier utilization of WBRT.

Keywords Breast cancer · Brain metastases · Recurrence · Subtype · HER2 · Radiation

Introduction

Brain metastases are common in patients with advanced breast cancer, [1–3] particularly patients with human epidermal growth factor receptor 2-positive (HER2+) and

Daniel N. Cagney and Nayan Lamba have contributed equally to this work.

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✉ Daniel N. Cagney
dcagney@bwh.harvard.edu

[1] Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

[2] Harvard Medical School, Boston, MA, USA

[3] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[4] Department of Biostatistics, and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA

[5] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA

[6] Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

triple-negative breast cancer (TNBC) subtypes [4–8]. Despite the extracranial efficacy of many systemic therapies for patients with breast cancer [9], the blood–brain barrier limits penetration of many systemic agents into the brain [10, 11], placing patients at risk for development of brain metastases, subsequent intracranial progression, and ultimately neurologic death [12, 13]. Therefore, radiation-based approaches have historically represented a key component of therapy for patients with breast cancer and brain metastases [14, 15].

Despite the intracranial efficacy of radiation at early timepoints after treatment, many patients ultimately progress locally and in previously uninvolved (distant) regions of the brain [15, 16]. Moreover, while most patients with metastatic breast cancer and brain metastases die of systemic disease progression [17], a significant percentage of such patients will die of intracranial progression, and neurologic death in patients with breast cancer and brain metastases represents a greater problem than in other cancers such as non-small cell lung cancer [1, 18–20].

While several studies have described differences in overall survival by breast cancer subtype in patients with brain metastases [21–24], the association between subtype and recurrence patterns after initial brain-directed radiation remains poorly characterized. An increased risk of local recurrence might suggest the need for more aggressive local management, including surgery, alterations to radiation doses, improved systemic therapies with central nervous system (CNS) activity, and/or evaluations of novel radiosensitizers. The propensity to recur in the uninvolved brain supports the need for improvements in systemic therapy given the strong association between systemic progression and development of new brain metastases [25], and/or a lower threshold to consider WBRT over localized approaches, such as surgery or stereotactic radiosurgery [14, 26].

We therefore conducted a retrospective cohort study of patients with breast cancer and newly diagnosed brain metastases managed with radiotherapy to evaluate the association between breast cancer subtype and intracranial recurrence patterns as well as other oncologic outcomes. Our hypothesis was that patients with HER2+ subtype experience more local recurrences, particularly at later time points, relative to other subtypes.

Methods

Patient population and study design

We identified 349 patients with newly diagnosed brain metastases treated with brain-directed radiation at Brigham and Women's Hospital/Dana-Farber Cancer Institute between 2000 and 2015. Patients were stratified by subtype: HER2+ (regardless of hormonal receptor status), hormone receptor-positive/HER2-negative (HR+/HER2−), and TNBC. In cases where intracranial pathology was not available for subtype information, subtype classification stemmed from tissue that was felt to be most representative of the brain metastasis, with metastatic sites preferred over locoregional sites and/or use of the most contemporary tissue among patients with multiple biopsies. Information regarding tissue site used for assessment of receptor expression status is available in Supplementary Table 1. All patients were managed with brain-directed radiation. Patients receiving WBRT generally received 30 Gy in 10 fractions, 35 Gy in 14 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions, at the discretion of the treating clinician. Stereotactic radiation was generally administered to a dose of 18–20 Gy in one fraction with a 0–1 mm planning target volume (PTV) for intact lesions, although tumors greater than 2.5–3.0 cm in maximal unidimensional size or those abutting/involving the brainstem or optic pathways were typically managed with stereotactic radiotherapy, administered as 25–30 Gy in 5 fractions, also with a 0–1 mm PTV. Some patients received upfront neurosurgical resection prior to radiation, particularly if neurologic symptoms refractory to steroids were present. Post-operative cavities generally received stereotactic radiotherapy to 25–30 Gy in 5 fractions with a PTV margin that generally ranged from 0 to 2 mm. All data collection were conducted by two radiation oncologists specializing in the management of central nervous system tumors (DC, AA).

We sought to characterize the relationship between breast cancer subtype and intracranial recurrence patterns, as well as other oncologic outcomes, after initial, brain-directed radiotherapeutic management. Outcomes of interest included local recurrence, distant intracranial recurrence (i.e., new brain metastases), receipt of additional brain-directed radiation, salvage craniotomy, development of leptomeningeal disease, seizures, neurologic death, and all-cause mortality. The primary outcome measure for the study was local recurrence after brain-directed radiation, which was assessed per-metastasis for up to six brain metastases per patient. Local recurrence was defined either by the use of salvage treatment following radiation for a growing intracranial lesion, or radiographically based on whether a lesion displayed definitive radiographic enlargement consistent with tumor progression. Enlarging tumors attributed to radiation necrosis were not counted as local recurrences [27]. Lesions initially treated by stereotactic radiation that were radiographically stable but who then received whole brain radiation or central nervous system-active systemic therapy for intracranial progression elsewhere were censored at the time of salvage brain-directed treatment. Direct review of post-treatment magnetic resonance imaging (MRI) of the brain by a radiation oncologist specializing in central nervous system disease (DC,

AA) was mandated for inclusion in this analysis; all pre- and post-treatment MRI studies were fused on a per-patient level in Mim® Software to ensure the consistency of evaluation. Neurologic death was defined by marked radiographic progression in the brain accompanied by corresponding neurologic symptomatology in the absence of systemic disease progression/systemic symptoms of a life-threatening nature.

Statistical methodology

Normally distributed continuous covariates were compared by subtype using ANOVA; non-normally distributed continuous covariates were assessed with the Kruskal–Wallis test. Categorical covariates were compared using the Chi Square test or Fisher's exact test. All time-to-event analyses were conducted using Kaplan–Meier plots, log-rank tests, and Cox regression. Covariates included in per-metastasis modeling for local recurrence after brain-directed radiation included unidimensional tumor size pre-treatment, radiotherapeutic management strategy (stereotactic radiation versus WBRT), and whether preceding surgery was performed; per-patient models were adjusted for the latter two covariates. Intra-patient correlations in per-metastasis models were accounted for using a sandwich estimator. The assumption for proportional hazards was tested and met for all models except those for development of new brain metastases and seizures after initial brain-directed radiation for which the stereotactic radiation versus WBRT and craniotomy versus no craniotomy covariates, respectively, violated the assumption; in such cases, the interaction between the culprit covariate and log time was included in the model. All p values were two-sided. All analyses were conducted in SAS v9.4 (Cary, NC). This study was approved by the institutional review board at our institution.

Results

Baseline demographic and general oncologic patient characteristics by subtype are presented in Table 1. Apart from a difference in patient age ($p=0.008$) and extracranial disease status ($p=0.04$), no other significant differences in demographic or general oncologic covariates were noted (all $p>0.05$). Initial intracranial presentation and management by subtype is presented in Table 2. No significant differences in the size or number of brain metastases at diagnosis were noted when comparing the three groups (both $p>0.05$). There were significant differences among subgroups with respect to the presence of neurologic symptoms at initial presentation (85, 84, and 66% for HR+/HER2−, TNBC, and HER2+, respectively, $p<0.001$), seizures at presentation (23, 32, and 6% for HR+/HER2−, TNBC, and HER2+, respectively, $p<0.001$), and leptomeningeal involvement at diagnosis of intracranial involvement (18, 14, and 5% for HR+/HER2−, TNBC, and HER2+, respectively, $p=0.002$). There was no difference in the use of whole brain radiation (66, 74, and 68%, respectively, $p=0.51$), stereotactic radiation as monotherapy (25, 19, and 21%, respectively, $p=0.61$), or craniotomy at diagnosis of brain metastases (15, 16, and 23%, respectively, $p=0.17$) among the three groups.

In total, 661 metastases were evaluated for local recurrence after radiation, including 204, 337, and 120 metastases in patients with HR+/HER2−, HER2+, and triple-negative

Table 1 Baseline characteristics among patients with newly diagnosed brain metastases secondary to breast cancer by subtype

Clinical parameter	HR+/HER2− ($N=116$)	HER2+ ($N=164$)	TN ($N=69$)	p
Age (years), mean (SD)	54 (12)	50 (10)	54 (12)	0.008
Race, no. (%)				
White	89 (77)	142 (87)	59 (86)	0.39
African American	7 (6)	8 (5)	6 (9)	
Hispanic	5 (4)	3 (2)	2 (3)	
Asian	4 (3)	3 (2)	1 (1)	
Other	3 (3)	4 (2)	0 (0)	
Unknown	8 (7)	4 (2)	1 (1)	
Gender, no. (%)				
Male	4 (3)	5 (3)	1 (1)	0.84
Female	112 (97)	159 (97)	68 (99)	
Marital status, no. (%)				
Unmarried	39 (34)	59 (36)	26 (38)	0.71
Married	74 (64)	104 (63)	42 (61)	
Unknown	3 (3)	1 (1)	1 (1)	
Location of management prior to development of brain metastases, no. (%)				
BWH/DFCI	104 (90)	153 (93)	61 (88)	0.34
Outside institution	12 (10)	11 (7)	8 (12)	
Tumor stage at initial diagnosis of cancer, no. (%)				
1	35 (30)	41 (25)	12 (17)	0.16
2	40 (34)	57 (35)	35 (51)	
3	36 (31)	52 (32)	17 (25)	
4	5 (4)	14 (9)	5 (7)	
Nodal stage at initial diagnosis of cancer, no. (%)				
0	40 (34)	47 (29)	17 (25)	0.44
1	35 (30)	59 (36)	30 (43)	
2	21 (18)	36 (22)	15 (22)	
3	20 (17)	22 (13)	7 (10)	
Extracranial disease status at time of initial breast cancer diagnosis				
Absent	8 (7)	23 (14)	5 (7)	0.04
Present	105 (91)	141 (86)	64 (93)	
Unknown	3 (3)	0 (0)	0 (0)	

BWH Brigham and Women's Hospital, *DFCI* Dana-Farber Cancer Institute, *HER2+* HER2-positive, *HR+/HER2−* hormone receptor-positive/HER2-negative, *No.* number, *SD* standard deviation, *TN* Triple negative

Table 2 Intracranial presentation and management of patients with brain metastases secondary to hormone receptor-positive/HER2-negative, HER2-positive, and TN breast cancer

Clinical parameter	HR+/HER2− (*N* = 116)	HER2+ (*N* = 164)	TN (*N* = 69)	*p*
Patient characteristics at time of diagnosis of brain metastases				
Years from primary diagnosis to development of BM, median (IQR)	6.4 (3.3–10.9)	3.9 (1.9–6.9)	2.1 (1.2–3.7)	< 0.001
KPS				
Median (IQR)	80 (80–90)	80 (80–90)	80 (80–90)	0.02
Largest BM diameter (mm)				
Median (IQR)[a]	14 (8–27)	17 (11–29)	20 (10–29)	0.27
Patients with metastases > 3 cm, no. (%)[a]	20 (18)	29 (18)	13 (19)	0.98
Number BM, median (IQR)[b]	3 (1–8)	3 (1–8)	5 (1–14)	0.08
Patients with > 4 BM, no. (%)[b]	42 (38)	53 (33)	36 (53)	0.02
Neurologic symptoms at diagnosis, no. (%)	99 (85)	108 (66)	58 (84)	< 0.001
Seizures at diagnosis, no. (%)[c]	27 (23)	10 (6)	22 (32)	< 0.001
Leptomeningeal disease at diagnosis, no. (%)[c]	21 (18)	9 (5)	10 (14)	0.002
Brainstem involvement, no. (%)	9 (8)	15 (9)	4 (6)	0.76
Initial treatment[d]				
WBRT, no. (%)	76 (66)	111 (68)	51 (74)	0.51
Stereotactic radiation as monotherapy, no. (%)	29 (25)	35 (21)	13 (19)	0.61
Craniotomy, no. (%)	17 (15)	38 (23)	11 (16)	0.17

BM brain metastases, *IQR* interquartile range, *HER2+* HER2-positive, *HR+/HER2−* hormone receptor-positive/HER2-negative, *KPS* Karnofsky performance status, *mm* millimeter, *No.* number, *TN* triple negative, *WBRT* whole brain radiation

[a]Excludes patients with missing data = 13 patients

[b]Excludes patients with missing data = 9 patients

[c]Excludes patients with missing data = 1 patient

[d]Sum of percentages exceeds 100, because some patients received both WBRT and craniotomy

subtypes, respectively. Differences in local recurrence rates by subtype after brain-directed radiation were noted with HER2+ metastases displaying the lowest control rates ($p < 0.001$, Fig. 1). Freedom from local recurrence was 72.7, 79.1, and 89.9% at 1 year and 50.8%, 79.1%, 82.2% at 2 years for HER2+, TN, and HR+/HER2− subtypes, respectively. After adjusting for unidimensional tumor size pre-treatment, radiotherapeutic management strategy, and whether preceding surgery was performed versus not, metastases secondary to HER2+ as opposed to HR+/HER2− breast cancer displayed increased rates of local recurrence (HR 3.20, 95% CI 1.78–5.75, $p < 0.001$, Table 3).

Distant intracranial recurrence and salvage treatment-based intracranial outcomes stratified by breast subtype are presented in Table 4. Following adjustment for the same factors mentioned above, patients with TNBC displayed the poorest clinical outcomes (all HR below reflect TNBC versus HR+/HER2− breast cancer): time to development of new brain metastases after initial treatment of existing brain metastases (HR 3.16, 95% CI 1.99–5.02, $p < 0.001$), time to salvage whole brain radiation in patients receiving upfront brain-directed stereotactic radiation (HR 3.79, 95% CI 1.36–10.56, $p = 0.01$), time to salvage stereotactic radiation after initial radiotherapeutic management (HR 1.86, 95% CI 1.11–3.10, $p = 0.02$), and time to development of seizures in patients without seizures at diagnosis (HR 2.43, 95% CI 1.06–5.57, $p = 0.04$; Fig. 2). The median time to development of new brain metastases after initial treatment of existing brain metastases was 1.91 years, 1.43 years, and 0.58 years for patients with HR+/HER2−, HER2+, and TNBC, respectively, while the median survival from the time of diagnosis of brain metastases among patients was 1.23 years, 2.17 years, and 0.69 years ($p < 0.001$), respectively. There was no difference in the percentage of patients who experienced neurologic death among the three groups (32, 44, and 32%, respectively, $p = 0.12$).

Discussion

We identified associations between breast cancer subtype and intracranial recurrence patterns after initial brain-directed radiation among patients with breast cancer and brain metastases. Compared to patients with HR+/HER2− breast cancer, patients with HER2+ metastases displayed poorer local control, whereas those with triple-negative breast cancer were more likely to recur distantly in the brain (i.e., previously uninvolved brain). Notably,

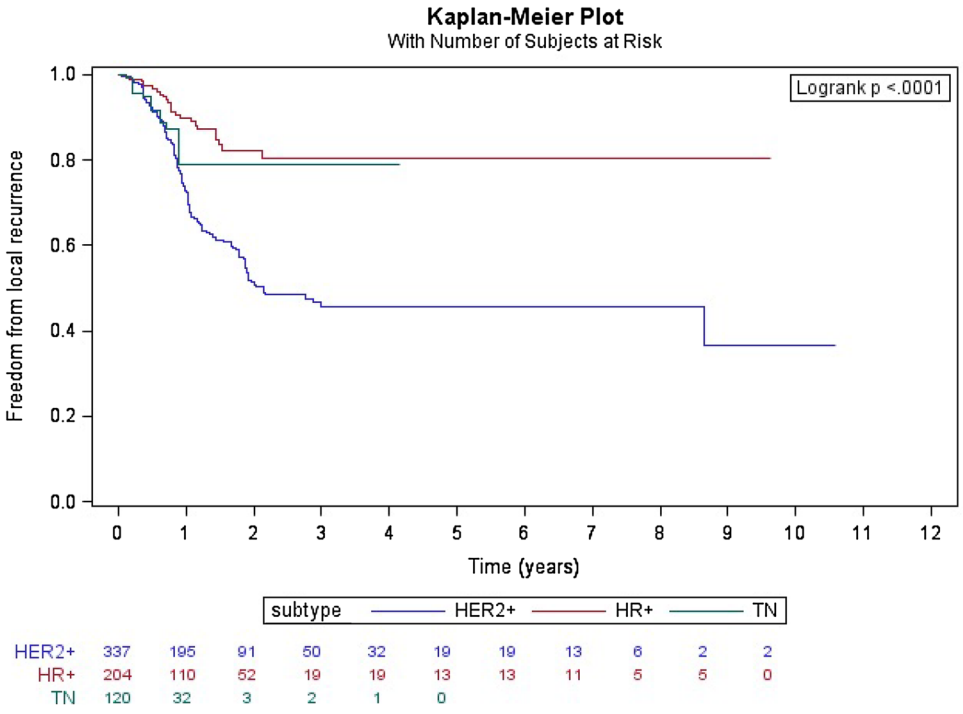

Fig. 1 Freedom from local recurrence among patients with breast cancer and newly diagnosed brain metastases managed with upfront brain-directed radiation, as stratified by subtype. *HR+* hormone receptor-positive/HER2-negative, *HER2+* HER2-positive, *TN* triple negative

Table 3 Multivariable Cox model for local recurrence following brain-directed radiation therapy on a per-metastasis level

Covariates	Multivariable HR (95% CI)	*p*
Size of metastasis, per mm increase	1.04 (1.01–1.06)	< 0.001
Initial BM management		
WBRT	REF	
Stereotactic radiation	0.40 (0.24–0.67)	< 0.001
Craniotomy before radiation		
No	REF	
Yes	0.72 (0.31–1.69)	0.45
Subtype		
HR+/HER2−	REF	
HER2+	3.20 (1.78–5.75)	< 0.001
TN	1.71 (0.71–4.13)	0.23

BM brain metastasis, *CI* confidence interval, *HER2+* HER2-positive, *HR* hazard ratio, *REF* reference, *TN* triple negative, *WBRT* whole brain radiation

the intracranial presentation and initial management of all three subtypes were relatively comparable, suggesting that the outcomes observed in our study are more likely reflective of differences in subtype aggressiveness and responsiveness to radiation and systemic therapy, as opposed to differences in initial presentation or management. These novel results, if validated by others, support investigation of additional therapeutic measures to improve local control in patients with HER2+ breast cancer and distant intracranial control in patients with TNBC.

Limited prior studies have evaluated the association between breast cancer subtype and local intracranial control in patients with brain metastases after brain-directed radiation. Vern-Gross et al. and Grubb et al. found no association between breast cancer subtype and local recurrence after radiosurgery [28, 29]. The authors deserve credit for publishing sentinel studies on this topic. It is possible that we found an association between HER2+ subtype and local recurrence after brain-directed radiation, whereas Vern-Gross et al. did not, given our per-metastasis analysis, which may have increased the power of our study to detect a significant difference. In addition, given that approximately half of the patients in the study by Vern-Gross et al. received prior WBRT, whereas all patients in our study were naive to brain-directed radiation, the populations evaluated in the two studies were different. While Grubb et al. did perform a per-metastasis analysis, sample size differences in patient populations ($N = 48$ vs. 349) might account for differing potential to detect a significant difference. An additional difference between our studies is that all patients in the Vern-Gross et al. and Grubb et al. studies underwent radiosurgery as treatment, while most patients in our study received WBRT. Radionecrosis almost never occurs after WBRT alone, so an enlarging lesion post-WBRT almost always reflects tumor progression, in contrast to patients managed with radiosurgery in which tumor progression versus radionecrosis can be challenging to delineate [30]. Moreover, technical factors related to treatment, such as dose, margin, and setup uncertainty, can impact local recurrence after radiosurgery but generally do not vary significantly when WBRT is

Table 4 Intracranial outcomes of patients with brain metastases secondary to hormone receptor-positive/HER2-negative, HER2-positive, and TN breast cancer after initial brain-directed radiation

Time to endpoint	HR+/HER2− negative ($n=116$)	Multivariable HR (95% CI)			
		HER2+ ($n=164$)	p	TN ($n=69$)	p
Development of new BM	REF	1.01 (0.70–1.45)	0.97	3.16 (1.99–5.02)	<0.001
Salvage WBRT (in patients receiving upfront brain-directed stereotactic radiation)	REF	1.08 (0.47–2.47)	0.86	3.79 (1.36–10.56)	0.01
Salvage brain-directed stereotactic radiation	REF	1.31 (0.90–1.92)	0.16	1.86 (1.11–3.10)	0.02
Salvage craniotomy	REF	0.63 (0.31–1.27)	0.19	0.56 (0.16–2.02)	0.38
Leptomeningeal disease in patients without leptomeningeal disease at diagnosis	REF	1.03 (0.42–2.55)	0.95	1.70 (0.49–5.94)	0.41
Seizure in patients without seizures at diagnosis	REF	0.83 (0.42–1.63)	0.58	2.43 (1.06–5.57)	0.04

BM brain metastases, *CI* confidence interval, *HER2+* HER2-positive, *HR+/HER2−* hormone receptor-positive/HER2-negative, *HR* hazard ratio, *REF* reference, *TN* triple negative, *WBRT* whole brain radiation

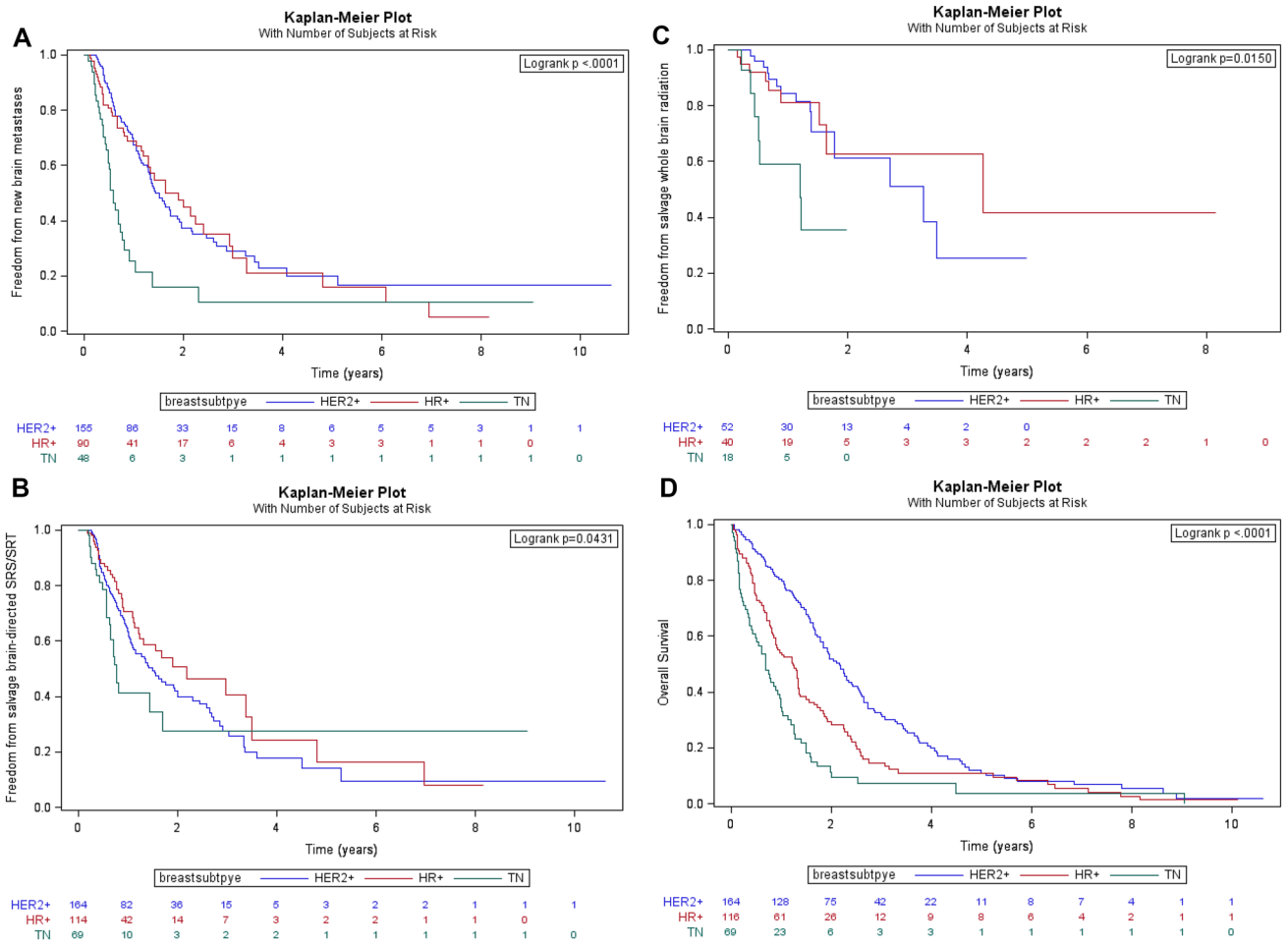

Fig. 2 Freedom from new brain metastases (**a**), salvage brain-directed stereotactic radiation (**b**), salvage whole brain radiation in patients managed with upfront stereotactic radiation (with or without preceding resection) (**c**), and all-cause mortality (**d**) among patients with breast cancer and newly diagnosed brain metastases managed with upfront brain-directed radiation, as stratified by subtype. **d** Reflects entire cohort; **a**–**c** reflect patients meeting entry criteria for the analysis who were devoid of missing data for the endpoint of interest. *HR+* hormone receptor-positive/HER2-negative, *HER2+* HER2-positive, *SRS* stereotactic radiosurgery, *SRT* stereotactic radiotherapy, *TN* triple negative

utilized. The fact that most of our patients underwent WBRT as opposed to stereotactic radiation limits the influence of these additional factors on our detected rates of intracranial recurrence.

One potential way to improve local control in patients with HER2+ breast cancer receiving brain-directed radiation would be evaluation of dose escalation [31] or the use of novel radiosensitizers. In this regard, a novel gadolinium-based radiosensitizer is being evaluated in conjunction with radiation in several clinical trials [32]. Our finding that patients with TNBC are more likely to experience distant intracranial recurrence after brain-directed radiation is consistent with a growing body of literature on this topic [28, 33]. Given the deleterious effects of new brain metastases and the treatments required to manage such patients, additional measures to minimize distant intracranial recurrence, such as more effective systemic therapy [34] and/or utilization of WBRT [35], seem warranted. Effective systemic therapy is a strong predictor of distant intracranial control among patients with brain metastases [25]. In addition, our results provide a note of caution when considering stereotactic radiation for patients with TNBC presenting with multiple brain metastases, as the likelihood of distant intracranial failure is high. While there has been a recent shift away from use of upfront WBRT due to concerns surrounding neurocognitive toxicity [16], hippocampal-avoidance WBRT has demonstrated high rates of intracranial control while minimizing neurocognitive decline in recipient patients and may be a reasonable option for patients with TNBC, particularly in the context of controlled or limited systemic disease [35].

Our study should be considered in the context of its limitations. First, our results should not be interpreted as implying causality given the retrospective nature of the study. Second, all data come from a single institution, so the study may not be generalizable to patients at other institutions given potential differences in patient populations and treatment paradigms. Third, it should also be noted that in some studies, breast cancer subtype has been reported to change with disease progression [36, 37], and it is therefore possible that brain metastases in our cohort may have been of a different subtype than the extracranial disease. We selected the most representative tissue to mitigate the impact of this limitation (i.e., brain specimen used over non-brain specimen, metastatic site preferred over locoregional site, and/or selection of most contemporary tissue among patients with multiple biopsies). Finally, it is also possible that patients with HER2+ breast cancer have other factors yielding a propensity for local recurrence other than subtype; however, factors predictive of local recurrence such as radiation modality, tumor size, and receipt of prior craniotomy were similarly distributed across subtypes, and we used a robust multivariable model to account for potential differences in the contribution of these covariates.

Conclusions

Our results suggest a strong association between HER2+ subtype and local recurrence, as well as TNBC and distant intracranial recurrence, after brain-directed radiation for brain metastases. If our results can be validated, strategies to improve local recurrence in patients with HER2+ breast cancer, such as radiosensitization or improved CNS-active systemic therapy, may be warranted. Additionally, given the very high rates of distant intracranial relapse in patients with TNBC, more effective systemic therapy options are needed to improve outcomes in this population.

Compliance with ethical standards

Conflict of interest Daniel N. Cagney is a recipient of research support from NH Theraguix. Paul Brown reports personal fees from UpToDate (current) and personal fees as DSMB member Novella Clinical (2016) outside the submitted work. Dr. Leone reports that the institution (University of Iowa) received research funding from Merck. Dr. Leone reports funding from Kazia, Lilly, and Seattle Genetics. Daphne A. Haas-Kogan is advisory board member for Cellworks and reports clinical trial support from Novartis. Dr. Lin reports research grants from Pfizer, Genentech/Roche, Novartis, Seattle Genetics, and consulting fees from Pfizer, Genentech/Roche, Novartis, Seattle Genetics, Daichii, and Puma. Dr Alexander reports personal fees from Foundation Medicine, AbbVie, Schlesinger Associates, Bristol Myers Squibb, Precision Health Economics; grants from Puma, Celgene, Eli Lilly outside the submitted work. Dr. Aizer reports research funding from Varian Medical Systems and consulting fees from Novartis. The remaining authors declare no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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