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CLINICAL STUDY

Development of new brain metastases in triple negative breast cancer

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Abstract

Background Brain metastases are common in patients with breast cancer, and those with triple negative status have an even higher risk. Triple negative status is currently not considered when managing brain metastases.

Objective To determine whether triple negative breast cancer (TNBC) patients with brain metastases have a higher burden of intracranial disease and whether WBRT has a survival benefit in this cohort of patients.

Methods We conducted a retrospective cohort study with 85 patients meeting the inclusion criteria.

Results 25% of patients had TNBC. 95% of the patients in this study received SRS and 48% received WBRT. The average number of new brain metastases from time of initial brain imaging to radiation therapy was 0.67 ± 1.1 in the non-TNBC status patients and 2.6 ± 3.7 in the triple negative status patients ($p = 0.001$). A cox proportional hazards model showed that WBRT does not significantly affect overall survival in patients with TNBC (HR 1.48; 95% CI 0.47–4.67; $p = 0.50$).

Conclusion Our findings highlight the highly aggressive intracranial nature of TNBC. The rate of new brain metastasis formation is higher in TNBC patients compared to non-TNBC patients. Furthermore, there is no survival benefit for WBRT in TNBC patients. These findings are relevant for clinicians planning brain radiation for TNBC patients as they may find more brain metastases at the time of brain radiation than they anticipated based on initial brain imaging.

Keywords Brain metastasis · Triple negative breast cancer · Breast cancer metastasis

Introduction

Brain metastases are a deadly complication of many cancers and can arise as complications of many primary carcinomas [1–3], with survival ranging from 12 to 53 months [3]. Breast cancer is the second leading cause of brain metastasis and develop in nearly 25% of women with stage IV breast cancer [4]. Furthermore, triple negative breast cancer (TNBC) is particularly devastating with a brain metastasis incidence rate of 46% [5]. While the standard of care for brain metastases is well established, there are currently no TNBC-specific guidelines despite its highly aggressive intracranial nature.

The current standard of care for brain metastases is a function of the number of brain metastases at presentation, size of metastasis, brain metastasis-related symptoms, age, and Karnofsky performance status (KPS) [6, 7]. Patients with a lower burden of intracranial pathology, good performance status, and/or significant mass effect from their brain metastases are primarily treated with surgical resection followed by stereotactic radiosurgery (SRS). Historically, patients with more numerous metastases were generally managed with whole brain radiation therapy (WBRT) either alone or in combination with SRS, however there has been a trend in recent years towards using SRS even in patients

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with numerous brain metastasis sometimes with WBRT for salvage [8–10].

The primary cancer has not traditionally been of great importance when determining the radiation treatment approach. However, mutations such as epidermal growth factor receptor (EGFR), estrogen/progesterone receptor status (ER/PR), and human epidermal growth factor receptor 2 (HER2) have started to influence systemic therapy recently [8, 11–13]. Such mutations have shown a good response to monoclonal antibody therapies, although further data is necessary to show comparable efficacy between monoclonal antibody therapy and current standard of care [14, 15]. Unfortunately, such developments have not significantly benefitted TNBC. Indeed, management of brain metastases in patients with TNBC has not been extensively studied. A recent review of this pathology reinforced the notion that, aside from the number of metastases at presentation, there is no uniform guideline governing management of TNBC brain metastases [16].

Given the aggressive nature of TNBC and the paucity of literature on managing potential intracranial metastases within this tumor subtype, we hypothesize that these patients develop metastases at a quicker rate. In this study, we conducted a single institution retrospective review of patients with breast cancer to determine whether breast cancer receptor mutational status (ER vs. PR vs. HER2) affects rate of intracranial disease progression. We also examined whether there was an increased rate of development of brain metastases in TNBC patients versus non-TNBC patients.

Methods

We conducted a single institution retrospective cohort study of patients treated for brain metastases from breast cancer by a single neurosurgeon at a tertiary medical center between 2007 and 2019. The study was institutional review board approved. Informed consent was not required given that the data collected was gathered from routine clinical care. Patients who had been diagnosed with a primary breast carcinoma that metastasized to the brain and were treated with either SRS, WBRT, or both were included. Patients who only developed osseous or dural-based metastases were not included in this study.

Data on gender, age at diagnosis, date of initial brain imaging, number of metastases on initial imaging, date of progression, mutation status (ER, PR, HER2, BRCA), KPS, date of surgical resection, timing of WBRT and/or SRS, number of metastases at radiation, and date of last follow up or death were collected from patient charts. No further distinction was made between up-front versus salvage radiation for the purposes of this study as this further sub-stratification reduced the number of patients for data analysis in each cohort. Date of progression was determined by first mention of progression or recurrence of the intracranial metastasis on an imaging report or documented clinical progression by a provider in a clinical note. KPS was calculated from clinic notes. The primary outcome, OS, was defined as the time between date of initial brain metastasis diagnosis to date of last follow-up or death.

Demographics between cohorts were compared using a Student's *t* test for continuous variables and a Fisher's exact test for categorical variables. Variables with $p < 0.10$ on univariate analysis were included as covariates in multivariate Cox regression analysis. All analyses were calculated using STATA SE 14 (StataCorp, College Station, TX, USA) and the cutoff for statistical significance was $p \leq 0.05$.

Results

A total of 85 patients met the inclusion criteria for this study and the baseline clinical characteristics for these patients are detailed in Table 1. The mean age of the patients in this study was 47 ± 11.2 years, and 83 of 85 (97%) patients were female. The mean number of intracranial metastasis on initial brain imaging was 2.6, and the mean KPS at initial brain imaging was 83 ± 9.1. With respect to breast cancer mutational status, 42% of patients were positive for ER, 40% were positive for PR, 53% were positive for HER-2, and 25% of patients had triple negative status. Furthermore, 16% of patients had either a BRCA1 or BRCA2 gene mutation. With

Table 1 Baseline patient characteristics

Variable	Value
Age, *years*, *mean (sd)*	47 (11.2)
Gender (female), *n (%)*	83 (97%)
Number of metastases on initial imaging, *mean (sd)*	2.6 (2.3)
Initial KPS, *mean (sd)*	83 (9.1)
Estrogen receptor positive status, *n (%)*	36 (42%)
Progesterone receptor positive status, *n (%)*	34 (40%)
HER2 receptor positive status, *n (%)*	45 (53%)
BRCA mutation positive status, *n (%)*	13 (16%)
Triple negative status, *n (%)*	21 (25%)
Surgical resection, *n (%)*	48 (57%)
Stereotactic radiosurgery, *n (%)*	81 (95%)
Number of metastases at initial radiation, *mean (sd)*	3.5 (3.4)
WBRT, *n (%)*	41 (48%)
Number of new metastases, *mean (sd)*	1.1 (2.1)
Time from brain imaging to radiation, *days, mean (sd)*	38 (42.8)
KPS at last follow-up, *mean (sd)*	61 (22.3)

KPS Karnofsky performance status, *HER2* human epidermal growth factor receptor 2, *BRCA* breast cancer gene, *WBRT* whole brain radiation therapy

respect to treatment modality, 57% of patients underwent surgical resection, 95% of patients received SRS, and 48% of patients received WBRT. Patients who received WBRT were not always excluded surgery or SRS. Indeed, of the patients who received WBRT, 93% had also received SRS and 28% had underwent surgical resection. The mean number of new metastasis between initial brain metastasis imaging and radiation therapy was 1.1 ± 2.1. The mean number of days between initial diagnosis of brain metastasis on brain imaging and start of radiation therapy was 38 ± 42.8 days. The mean KPS at last known follow-up was 61 ± 22.3.

A univariate analysis of patients with and without triple negative status was performed to evaluate for significant differences in patient characteristics between the two cohorts (Table 2). The mean age of patients without TNBC was 47 ± 11 years compared to 49 ± 11.9 years in patients with TNBC ($p = 0.35$). There was likewise no difference in gender between the two cohorts ($p = 0.31$). The number of brain metastases on initial imaging was 2.5 ± 2.5 in the non-TNBC cohort and 2.8 ± 1.6 in the TNBC cohort ($p = 0.68$). The initial KPS in the non-TNBC cohort was 84 ± 7.7 compared to 81 ± 12 in the TNBC cohort ($p = 0.25$). There was no significant difference in KPS at last known follow-up between the two cohorts ($p = 0.32$). There was a significant difference in percentage of patients with a BRCA gene mutation between the two cohorts (12% for non-TNBC vs. 29% for TNBC, $p = 0.01$). There was no difference between the cohorts with respect to the percentage of patients who received surgical resection, SRS, or WBRT ($p = 0.35$, $p = 0.23$, $p = 0.66$ respectively). Patients in the non-TNBC cohort developed an average of 0.67 ± 1.1 new brain metastases between initial brain imaging and radiation simulation, whereas, patients in the TNBC cohort developed an average of 2.6 ± 3.7 new metastases during this time frame ($p = 0.001$). The amount of time between initial brain imaging and initial radiation therapy was not significantly different between the two cohorts (35.8 ± 35.8 days for non-TNBC patients vs. 45.7 ± 59.2 days for TNBC patients; $p = 0.36$).

Given the finding that patients with TNBC developed significantly more metastases than non-TNBC patients (2.6 ± 3.7 vs. 0.67 ± 1.1, $p = 0.001$) in the time between initial brain imaging and radiation therapy, we evaluated whether having a receptor mutation (ER, PR, HER2) affected rate of new intracranial brain metastases between initial brain imaging and imaging for radiation therapy (Table 3). We found that patients with the ER mutation had 0.5 ± 0.88 new metastases whereas patients without the ER mutation had 1.49 ± 2.56 new metastases ($p = 0.054$). Patients with the PR mutation had significantly fewer new metastases than patients without the PR mutation in the interval from initial brain imaging to imaging for radiation therapy (0.44 ± 0.75 vs. 1.5 ± 2.55, $p = 0.04$). Patients with both an ER and PR mutation had an average of 0.42 ± 0.78 new metastases, whereas patients without both mutations had an average of 1.44 ± 2.47 new metastases ($p = 0.052$). Patients with the HER2 mutation had an average of 0.18 ± 1.17 new metastases whereas patients without the HER2 mutation had an average of 1.68 ± 2.9 new metastases ($p = 0.052$).

Finally, given that patients with TNBC develop more brain metastasis, a cox regression analysis was performed on the 21 patients with TNBC to determine whether WBRT in this subset of patients is beneficial for OS. For the 21 TNBC patients, we determined which patients received surgical resection, SRS, and WBRT. TNBC patients who received WBRT were not always exclude from surgery or SRS. Of the TNBC patients who received WBRT, 82% also received SRS and 64% also underwent surgical resection. We furthermore included patient age and initial KPS

Table 2 Univariable analysis of patients with and without triple negative breast cancer

Admission variables	Non-triple negative status ($N = 64$)	Triple negative status ($N = 21$)	*p* value
Age, *years*, *mean (sd)*	47 (11.0)	49 (11.9)	0.35
Gender (female), *n (%)*	61 (95%)	21 (100%)	0.31
Number of metastases on initial imaging, *mean (sd)*	2.5 (2.5)	2.8 (1.6)	0.68
Initial KPS, *mean (sd)*	84 (7.7)	81 (12.4)	0.25
BRCA mutation positive status, *n (%)*	7 (12%)	6 (29%)	0.01[a]
Surgical resection, *n (%)*	38 (59%)	10 (48%)	0.35
Stereotactic radiosurgery, *n (%)*	62 (97%)	19 (91%)	0.23
Number of metastases at initial radiation, *mean (sd)*	3.0 (2.9)	5.1 (4.5)	0.03[a]
WBRT, *n (%)*	30 (47%)	11 (52%)	0.66
Number of new metastases, *mean (sd)*	0.67 (1.1)	2.6 (3.7)	0.001[a]
Time from brain imaging to radiation, *days, mean (sd)*	36 (35.8)	46 (59.2)	0.36
KPS at last follow-up, *mean (sd)*	63 (22.2)	57 (22.4)	0.32

[a]Variables with significant difference between the two cohorts ($p < 0.05$)

Table 3 Number of new brain metastases from initial brain imaging to initial radiation therapy sub-divided by receptor mutation status

	ER+	ER−	PR+	PR−	ER+/PR+	ER−/PR−	HER2+	HER2−	TNBC	Non-TNBC
Mean ± st. dev	0.50 ± 0.88	1.49 ± 2.56	0.44 ± 0.75	1.5 ± 2.55	0.42 ± 0.78	1.44 ± 2.47	0.68 ± 1.17	1.68 ± 2.91	2.6 ± 3.68	0.67 ± 1.11

ER estrogen receptor, PR progesterone receptor, *HER2* human epidermal growth factor receptor 2, *TNBC* triple negative breast cancer, *st. dev.* standard deviation

Table 4 Multivariable Cox regression analysis of triple negative breast cancer patients with whole brain radiation therapy as a predictor of overall survival (n = 21)

Characteristic	Hazard ratio [95% CI]	*P*-value
Whole brain radiation	1.48 [0.47–4.67]	0.50
Age, *per year*	0.99 [0.94–1.04]	0.71
Initial KPS	0.99 [0.95–1.03]	0.67
Stereotactic radiotherapy	1.12 [0.20–6.13]	0.90
Surgical resection	1.05 [0.35–3.18]	0.93

KPS Karnofsky performance status

*$P < 0.05$ indicates statistical significance

in our analysis. We found that WBRT did not significantly decrease the hazard of death for patients with TNBC (HR 1.48; 95% CI 0.47–4.67; p = 0.50) (Table 4).

Discussion

The current management paradigm for patients with brain metastasis is a combination of surgical resection and radiation therapy. Radiation therapy has been well-established as a cornerstone of the management of brain metastasis. Beginning in the 1950s, WBRT has been employed as a critical component of such therapy [17]. Initial studies demonstrated symptom alleviation with tolerable toxicity [18]. Since then, there have been several advances in radiation technology and a more localized approach to radiation, SRS, was beginning to be adopted in Germany and the US in the 1970s. By the 1990s, SRS was used routinely for patients with intracranial metastasis. Recent studies comparing combination SRS with WBRT to SRS alone have found similar local control rates, no additional benefit to overall survival when WBRT was added to SRS, and fewer treatment-related side effects in SRS-only cohorts [19–22]. As a result, there has been a trend towards management of brain metastasis with SRS over WBRT in most patients. WBRT is typically reserved for patients with 3 or more metastases [6].

The literature suggests that TNBC is more aggressive than non-TNBC. TNBCs tend to be larger, more invasive, and more likely to metastasize to visceral organs such as lung and brain [23–25]. Additionally, these patients do not respond as well to adjuvant therapy and have a lower overall survival [26, 27]. In keeping with this aggressive nature, we have now shown that the rate of intracranial progression is significantly higher in TNBC patients compared to non-TNBC patients (2.6 ± 3.7 vs. 0.67 ± 1.1, p = 0.001). Of note, there was no significant difference in the time between initial discovery of brain metastasis and start of radiation between the two cohorts (35.8 ± 35.8 days vs. 45.7 ± 59.2 days, p = 0.36). Furthermore, our results show a trend toward

fewer new brain metastases in this time interval for patients with either ER+, ER/+PR+, or HER2+ mutation compared to patients without these mutations respectively ($p=0.054$, $p=0.052$, $p=0.052$ respectively). Patients with the PR mutation did have significantly fewer new brain metastases compared to the patients without the PR mutation in this time interval ($p=0.04$). It is important for clinicians to be aware that TNBC patients may harbor more metastases at the time of radiation simulation than at time of diagnosis, as this could affect management. For instance, our results suggest patients with TNBC may require more frequent brain imaging or more aggressive management of intracranial disease given the higher rate of progression. Further studies are required to specifically assess if these additional interventions in TNBC patients with brain metastases are efficacious. Likewise, our results suggest there is possibly a lower rate of intracranial progression in patients with ER+, PR+, ER+/PR+, or HER2+ mutations as there is a lower likelihood of finding significantly more new metastases at the time of radiation therapy compared to initial brain imaging.

Given the increased number of new metastases in TNBC patients and more aggressive intracranial progression, we evaluated whether there is a role for WBRT in all TNBC patients regardless of number of brain metastasis on initial brain imaging. Our cox proportional hazards model found no additional survival benefit for TNBC patients who received WBRT compared to TNBC patients who did not receive WBRT ($p=0.50$). These results are not surprising given that studies have indicated that TNBCs are especially resistant to radiotherapy compared to non-TNBC [28, 29]. Genomic studies conducted over the last year in an attempt to build a radiation-resistant TNBC model to determine a molecular basis for the decreased radiosensitivity seen in these patients revealed that increased superoxide dismutase 2 (SOD2) and cyclin dependent kinase inhibitor 1A (CDKN1A) expression may be responsible for TNBC radiation resistance [30]. These genes are involved in managing oxidative stress and mediating apoptosis, respectively [30]. These findings suggest that TNBC cells may be able to better respond to radiation stress and damage. Further studies will need to be conducted to determine whether this ability to respond to radiation in TNBC cells can be mitigated or reversed.

Limitations

This study is limited by its small sample size as well as its retrospective nature. Additionally, all patients in this database were treated by a single surgeon at a single institution which could potentially limit the generalizability of our findings. This study is meant to highlight important differences and trends between non-TNBC and TNBC with respect to intracranial disease progression given the sparse literature on this topic.

Conclusion

This study evaluated the intracranial tumor burden in TNBC compared to non-TNBC. We found that patients with TNBC develop new brain metastases at a significantly higher rate in the time interval from initial diagnosis of brain metastases to initiation of radiation therapy. Furthermore, we assessed a role for WBRT in improving OS in all TNBC brain metastasis patients. We conclude that clinicians should be aware that there is a high likelihood that patients with TNBC may present with additional new brain metastasis at time of intracranial radiation. Given the small number of patients with TNBC in this study and the limitations inherent to a retrospective study, further research on the modality and timing of radiation for TNBC patients is warranted.

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Compliance with ethical standards

Conflict of interest Dr. Chetan Bettegowda is a Consultant for Depuy-Synthes and Bionaut Laboratories. Dr. Michael Lim receives research support from Arbor, BMS, Accuray, DNAtrix, Tocagen, Biohaven, and Kyrin-Kyowa and is a consultant for Tocagen, VBI, and Stryker.

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