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Phase II trial of brain MRI surveillance in stage IV breast cancer

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Abstract

Background. Screening of asymptomatic stage IV breast cancer with brain MRIs is currently not recommended by National Comprehensive Cancer Network Guidelines. The incidence of asymptomatic brain metastasis is not well documented.

Methods. The study is designed as a single-arm, phase II trial, with the goal of investigating surveillance brain MRIs in neurologically asymptomatic patients with metastatic breast cancer. Breast cancer patients were classified into triple-negative (TN), HER2+, and hormone receptor (HR)+/HER2–. Patients underwent a surveillance brain MRI and a second brain MRI at 6 months if the baseline MRI was negative. Asymptomatic, stage IV breast cancer patients, ECOG ≤ 2, and life expectancy ≥ 6 months were eligible. The primary objective was to determine the frequency of asymptomatic brain metastasis in metastatic breast cancer. Clinical trial information: NCT05115474.

Results. A total of 101 patients completed the surveillance brain MRI including 40 HR+/HER2–, 33 HER2+, and 28 TN patients. The overall frequency of brain metastasis on initial surveillance brain MRI was 14% ($n = 14$) with rates of 18%, 15%, and 10% in TN, HER2+, and HR+/HER2– patients, respectively. Following the 6-month MRI, the cumulative rates of brain metastasis increased to 25% in TN, 24% in HER2+, and 23% in HR+/HER2– patients.

Conclusions. The highest frequency of brain metastases at baseline was in TN and HER2+ breast cancer. Following the 6-month MRI, the cumulative frequency was approximately a quarter across all subtypes. These results warrant confirmatory trials to refine brain MRI surveillance recommendations for neurologically asymptomatic stage IV breast cancer.

Key Points

- A phase II trial of brain MRI surveillance in stage IV breast cancer was conducted.
- On initial surveillance brain MRI, the frequency of brain metastases was 14%.
- Following the 6-month MRI, the cumulative rate of brain metastasis was 24%.

It is believed that approximately 15%–30% of all metastatic breast cancer patients develop brain metastases, a devastating cause of morbidity and mortality.[1] Compared with other sites of metastatic spread, the development of brain metastases portends a particularly poor prognosis. Several recent advancements in systemic therapy have extended the survival for breast cancer patients with metastatic disease, likely increasing the number of patients at risk to develop brain metastasis.[2,3] In addition, a number of systemic agents have now revealed efficacy in the management of brain metastases, improving intracranial control and overall survival in these patients.[4–6]

Importance of the Study

Screening of asymptomatic stage IV breast cancer patients with brain MRIs is currently not recommended by the National Comprehensive Cancer Network (NCCN) Guidelines. We conducted a single-arm, nonrandomized, phase II trial, with the goal of investigating surveillance brain MRIs in neurologically asymptomatic patients with metastatic breast cancer. A total of 101 patients enrolled and completed the surveillance brain MRI. The overall frequency of brain metastasis on initial surveillance brain MRI was 14% across subtypes with the highest rate in triple-negative. Following the 6-month MRI, essentially a quarter of each subtype was noted to have brain metastases. Given improvements in systemic and local management of breast cancer brain metastases, these results warrant confirmatory trials to refine current NCCN Guidelines for brain MRI surveillance in stage IV breast cancer.

Screening brain MRIs are currently recommended for patients with stage ≥II non-small cell lung cancer (NSCLC), as well as stage IIIB–IV melanoma due to the prevalence of brain metastasis in these populations.[7,8] However, brain MRIs are only recommended in advanced breast cancer patients when neurologic symptoms are present per National Comprehensive Cancer Network (NCCN) Guidelines.[9] Patients with early screen-detected brain metastases are more likely to receive stereotactic radiosurgery (SRS), which has been demonstrated to have fewer side effects and a decreased risk of neurocognitive decline compared to patients receiving whole brain radiation therapy (WBRT).[10–12] In addition, following the diagnosis of brain metastases, brain MRIs are recommended at 2–4 month intervals per NCCN Guidelines allowing for the early detection of intracranial progression.[13]

In our prior, retrospective institutional experience of 959 patients with brain metastases,[14] we noted more advanced brain metastases presentations in breast cancer patients compared to NSCLC and melanoma which may be due to current NCCN brain MRI screening recommendations. In the study, at brain metastases diagnosis, breast cancer patients were more likely to have concurrent systemic metastasis (breast cancer 77%, NSCLC 42%, melanoma 69%, $p < .0001$), at least 5 brain metastases (breast cancer 27%, NSCLC 14%, melanoma 13%, $P = .0004$), and leptomeningeal disease (LMD) (breast cancer 23%, NSCLC 6%, melanoma 6%, $P < .0001$). Patients with breast cancer were significantly more likely to receive WBRT (breast cancer 58%, NSCLC 37%, melanoma 22%, $P < .0001$) and less likely to receive SRS (breast cancer 26%, NSCLC 48%, melanoma 58%, $P < .0001$) following initial brain metastasis diagnosis. Although overall survival has many contributing factors including extent and treatment of systemic disease, median overall survival following brain metastasis diagnosis was the shortest for breast cancer (ie, breast cancer 9.9 months, NSCLC 10.3 months, melanoma 13.7 months, $P = .0006$). Cagni et al. have reported similar findings in a series of 1008 breast cancer and NSCLC patients with brain metastases noting higher rates in the use of WBRT and neurologic death in breast cancer patients.[15] Given these findings, the current phase II trial was undertaken.

In this prospective, single-arm, nonrandomized, phase II trial, we sought to determine the asymptomatic frequency of brain metastases in stage IV breast cancer in subtypes of HER2+, triple-negative breast cancer (TNBC), and hormone receptor positive (HR)+/HER2– and assess the presentation and management of asymptomatic brain metastasis patients.

Methods

Study Design and Participants

The study is designed as a prospective, single-arm, phase II clinical trial, with the goal of investigating the role of surveillance brain MRIs in neurologically asymptomatic patients with metastatic breast cancer. The study enrolled patients at Moffitt Cancer Center, a single NCI Designated Comprehensive Cancer Center in Tampa, FL. Clinical trial information: NCT05115474. Patients were prescreened for eligibility and those that met inclusion criteria were approached by the clinical trial coordinator regarding enrollment. Investigators obtained informed consent from each participant and study procedures were approved by the local Institutional Review Board and Protocol Monitoring Committees.

Patients with histologically proven metastatic breast cancer ≥18 years, life expectancy ≥6 months, with an Eastern Cooperative Oncology Group Performance Status 0–2 were included in this study. Patients with HR+/HER2– breast cancer should have progressed on at least 1 line of therapy in the metastatic setting. TNBC and HER2+ patients could enroll regardless of their line of therapy. HR+ was defined as ER and/or PR ≥ 10%. To be classified as HER2+ disease, overexpression of HER2 by either IHC or in situ hybridization was necessary as defined by the ASCO/CAP Guidelines.[16] Key exclusion criteria included prior diagnosis or treatment of brain metastases or LMD. Patients with prior history of nonbreast cancer malignancies needed to have no evidence of disease ≥2 years. Other exclusion criteria included neurologic symptoms warranting a standard screening brain MRI in the judgement of the treating physician, indications warranting brain MRIs for other neurologic conditions at time of study entry, contraindication towards MRIs with contrast, or chronic kidney disease stage IV or V or end-stage renal disease (CrCl < 30 mL/min).

Procedures

Following study enrollment, patients underwent a baseline brain MRI with and without contrast. Patients

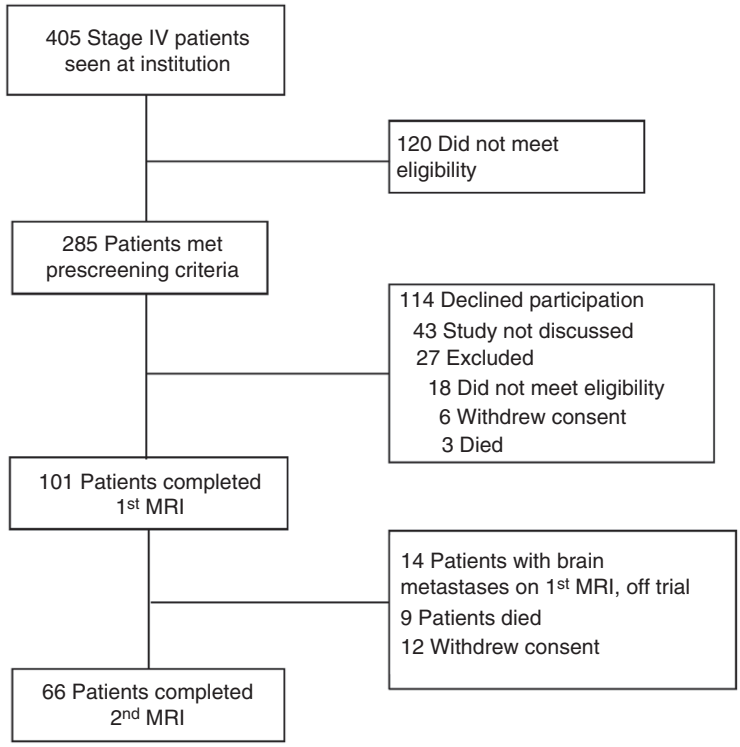


Figure 1. CONSORT Diagram.

were imaged on a 1.5T or 3T MRI. A 3D MPRAGE post-gadoliniumT1-weighted sequence with 1-mm slice resolution was completed in all patients and in patients scanned on the 3T MRI the 3D FSET1-weighted scan was also completed. Scans were reviewed by a neuroradiologist with multiplanar sequences. If patients were noted to have brain metastases or LMD, standard-of-care treatment was delivered at the discretion of the treating team, and patients came off the study. If patients were not noted to have brain metastases a repeat brain MRI with and without contrast 6 months following the baseline MRI was conducted.

Statistical Analysis

A total of 100 stage IV patients were planned for enrollment with an enrollment of 40% HR+/HER2–, 30% TNBC, and 30% HER2+. The primary objective was to determine the frequency of asymptomatic brain metastasis in metastatic breast cancer by subtype. Secondary objectives included evaluation of treatment characteristics of patients diagnosed with brain metastases and overall survival following brain metastasis diagnosis. Events were summarized descriptively using frequencies and percentages. Demographics and baseline patient characteristics were summarized using descriptive statistics for all participants. The Kaplan–Meier method was used to estimate overall survival following brain metastasis diagnosis with differences assessed via log-rank. Statistical analysis was carried out using JMP v17.

Results

Patient Characteristics

Between January 2022 and December 2023, a total of 101 patients completed the baseline surveillance brain MRI including 40 HR+/HER2–, 28 TNBC, and 33 HER2+ patients (Figure 1). Patient characteristics according to breast cancer subtype at time of enrollment are detailed in Table 1. Median patient age was 60, 60, and 54, respectively. Median prior lines of systemic therapy in the stage IV setting was 4, 2, and 2, respectively. Lung metastases were noted in 28%, 38%, and 19%; liver metastases in 48%, 29%, and 39%; and bone metastases in 78%, 39%, and 59%, respectively.

Frequency of Brain Metastasis

The overall frequency of brain metastasis on initial surveillance brain MRI was 14% ($n = 14$) with rates of 18%, 15%, and 10% in TNBC, HER2+, and HR+/HER2– patients, respectively (Figure 2). Of the 87 patients eligible to complete the second brain MRI, 66 patients completed the MRI. Reasons for not completing the 6-month brain MRI included death ($n = 9$) and consent withdrawal ($n = 12$). Following the 6-month MRI, the cumulative rates of brain metastasis increased to 25% in TNBC, 24% in HER2+, and 23% in HR+/HER2– patients (Figure 2). Ten patients (15%) had a negative baseline MRI with interval development of brain

Table 1. Patient Characteristics by Subtype

	HR+/HER2–		TNBC		HER2+	
Variable	*N*	%	*N*	%	*N*	%
Completed first MRI	40		28		33	
Completed second MRI	26		14		26	
Sex						
Female	40	100%	28	100%	32	97%
Male	0	0	0	0	1	3%
Median age (range)	60	(41–87)	60	(29–79)	54	(28–74)
ECOG performance status						
0	12	30%	14	50%	17	52%
1	24	60%	14	50%	15	45%
2	4	10%	0	0	1	3%
Race						
White	35	88%	23	82%	29	89%
Black	0	0	3	11%	2	6%
Asian	0	0%	0	0	2	6%
American Indian or Alaskan Native	1	3%	0	0	0	0
Native Hawaiian or Other Pacific Islander	2	5%	0	0	0	0
Unknown	2	5%	2	7%	0	0
Ethnic group						
Hispanic or Latino	4	10%	5	23%	1	3%
Non-Hispanic or Non-Latino	36	90%	23	79%	32	97%
ER or PR positivity (%)						
0–9	0	0%	28	100%	16	48%
10, 50	8	20%	0	0%	4	12%
51–100	32	80%	0	0%	13	39%
Primary tumor grade						
1	3	8%	0		1	3%
2	18	45%	6	21%	8	24%
3	12	30%	21	75%	22	67%
Unavailable	7	18%	1	4%	2	6%
BRCA1/2 mutation						
Y	2	5%	3	11%	1	3%
N	30	75%	21	75%	16	48%
Unknown	8	20%	4	14%	16	48%
Median prior lines of therapy in stage IV setting (range)	4	(1–8)	2	(0–5)	2	(1–7)
Number of lines of therapy in stage IV setting						
0	0	0	1	4%	0	0
1	3	8%	6	21%	10	30%
2	7	18%	10	36%	8	24%
3	7	18%	4	14%	7	21%
4	11	28%	5	18%	3	9%
5	4	10%	2	7%	3	9%
6 or more	8	20%	0	0	2	6%
Sites of extracranial metastases						
Lung metastasis, %	11	28%	11	38%	6	19%
Liver metastasis, %	19	48%	8	29%	13	39%
Bone metastasis, %	31	78%	11	39%	19	59%

Table 1. Continued

Variable	HR+/HER2–		TNBC		HER2+	
	N	%	*N*	%	*N*	%
Median number of organs with metastases (range)	2	(1–5)	2	(0–5)	1	(0–4)
Median interval between stage IV diagnosis and enrollment, months (range)	40.4	(1.3–122.4)	17.6	(2.8–49.7)	25.7	(1.1–119.9)
Median interval between breast cancer diagnosis and enrollment, months (range)	103.7	(19.3–390.1)	57.7	(6.7–383.3)	41.8	(1.3–252.5)

Abbreviations: *N*, number of patients; HR+, hormone receptor; TNBC, triple-negative breast cancer.

metastases on the 6-month MRI. Most of these patients also demonstrated systemic progression ($n = 6$; 60%).

Older TNBC patients were less likely to have brain metastasis (odds ratio: 0.92; 95% confidence interval [CI]: 0.84–0.99; $P = .03$). However, no differences were noted between the number of prior therapies, BRCA1/2 mutational status, number of organs with metastasis, and sites of extracranial metastasis with the development of brain metastases (Supplementary Figures 1–3).

Treatment and Outcomes Following Brain Metastasis Diagnosis

The majority of patients with detected brain metastasis were treated with focal, stereotactic radiation, 67% ($n = 16$) (Table 2). SRS administration details are included in Supplementary Table 1. One patient underwent surgical resection following preoperative SRS. Three patients (13%) were treated with hippocampal avoidance WBRT and 2 with conventional WBRT. A total of 4 patients were diagnosed with LMD; 2 HR+/HER2–, and 2 HER2+ patients. In 9 of 24 patients (38%), the diagnosis of brain metastases contributed to changes in systemic therapy; 3 of these patients, all of whom were HER2+, had no systemic disease that contributed to the change. Changes to systemic therapy were most common in HER2+ patients in which 4 of 8 (50%) diagnosed patients underwent a change in their systemic therapy following the diagnosis of brain metastases.

Median OS since diagnosis of brain metastases has been a median of 19.9 months (95% CI: 9.1–Not Reached) in all patients. Median OS by subtypes is not reached in HER2+, 14.6 months in HR+/HER2–, and 9.7 months in TNBC, $P = .07$, Figure 3.

Discussion

In this study of brain MRI surveillance in stage IV breast cancer, we note several findings, first the highest rate of brain metastases on the initial surveillance MRI was in TNBC and HER2+ patients; however, the cumulative frequency at 6 months was essentially equal with approximately a quarter of all subtypes having brain metastases. Second, early detection of brain metastases led to the majority of patients receiving focal, stereotactic radiation at the time of diagnosis with lower rates in the use of WBRT compared to our historical data[14] and data of other groups.[15] These results warrant larger prospective trials to refine brain MRI surveillance recommendations for stage IV breast cancer.

The frequency of breast cancer brain metastases (BCBM) is believed to be increasing when compared with historic series.[17] Improved efficacy of systemic therapy may be contributing to this increase.[17] A recent meta-analysis of largely retrospective series using current NCCN symptom-directed brain imaging noted an incidence of 31%, 32%, and 15% for HER2+, TNBC, and HR+/HER2– patients.[18] Survival by phenotype, without consideration of performance status, is on the order of 6 months for TNBC, 20 for HER2+, and 10 months for HR+/HER2– BCBM patients.[19,20] The frequency of asymptomatic brain metastases is not well documented.

Recent advancements in systemic therapy for stage IV breast cancer have extended survival but given this improvement, more patients are likely at risk of intracranial metastases.[2,3] In addition, promising recent developments in the systemic treatment for BCBM have improved the prognosis for many patients with intracranial disease.[4,21,22] Treatments with blood–brain barrier (BBB) penetration most notably include tyrosine kinase inhibitors,[4,23] antibody drug conjugates,[6,24] and the CDK 4/6 inhibitor abemaciclib.[5] Advances in radiation therapy techniques have also made focal SRS more common in the management of patients with up to 15 brain metastases.[25,26] Multiple studies have found patients treated with limited intracranial disease have superior clinical outcomes compared to those with more extensive intracranial disease.[27–29] In addition, patients with asymptomatic melanoma brain metastases have been shown to have better outcomes to immunotherapy compared to those that are symptomatic.[30] Early diagnosis of brain metastases now means earlier access to these improved treatment strategies, which may enhance both overall survival and quality of life (QoL). In our study, we found that 9 of the 24 patients (38%) diagnosed with brain metastases underwent a change in their systemic therapy following brain metastasis diagnosis, most commonly in the HER2+ subtype (50%). These findings represent changes in clinical practice reflective of our institution and patterns may differ at other institutions.

Our prior institutional data indicated current NCCN screening paradigms may be leading to more advanced disease presentation in breast cancer patients.[14] Overall survival following diagnosis of brain metastases in the

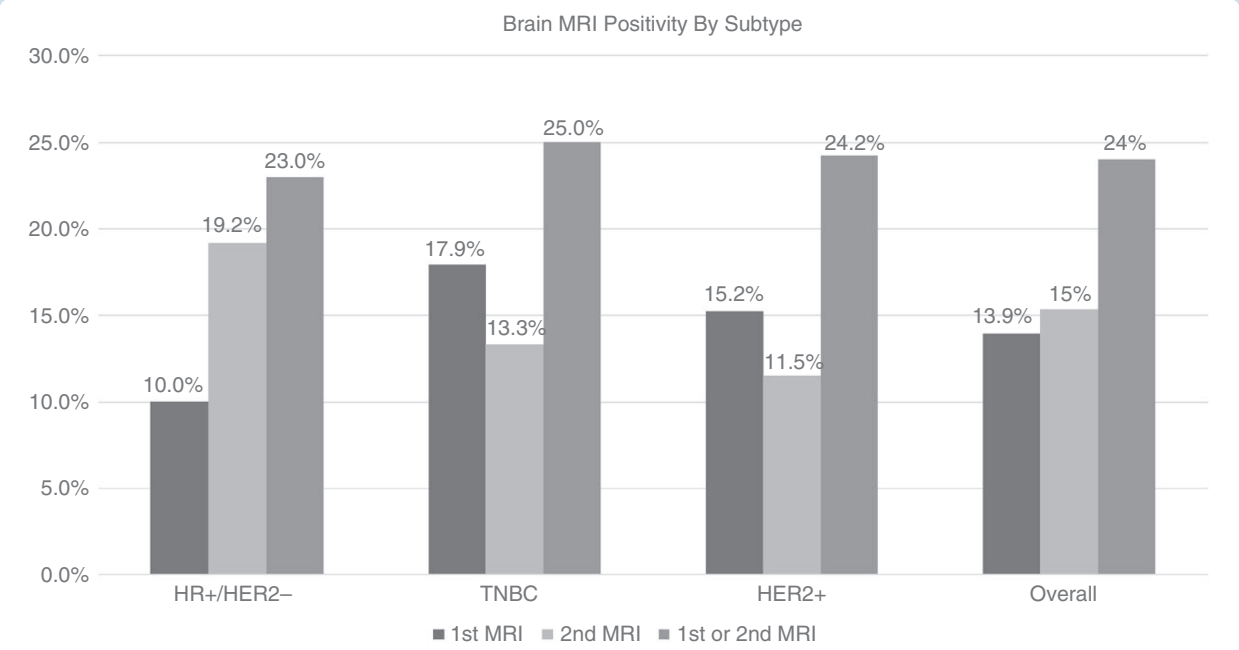


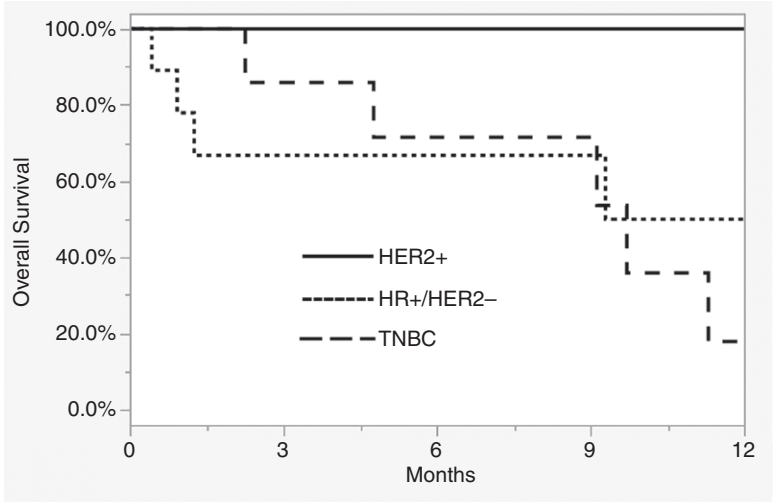
Figure 2. Frequency of brain metastases by subtype at time of first MRI, second MRI, and cumulative.

Table 2. Disease and Treatment Characteristics

	HR+/HER2–		TNBC		HER2+	
Variable	*N*	%	*N*	%	*N*	%
Brain metastasis on first MRI	4	10%	5	18%	5	15%
Brain metastasis on first or second MRI	9	23%	7	25%	8	24%
Number of brain metastases at diagnosis						
1	1	11%	2	29%	3	38%
2–5	5	56%	2	29%	1	13%
6–15	1	11%	0		1	13%
>15	2	22%	3	43%	3	38%
Leptomeningeal disease	2	22%	0		2	25%
Treatment delivered						
SRS or fSRS	7	78%	4	57%	5	63%
HA WBRT	0		2	29%	1	13%
WBRT	1	11%	1	14%	0	
CSI	0		0		2	25%
None	1	11%	0		0	
Diagnosis of brain metastases leading to change in systemic therapy						
Y	4	44%	1	14%	4	50%
N	5	56%	6	85%	4	50%

Abbreviations: CSI, craniospinal irradiation; fSRS, fractionated stereotactic radiosurgery; HA WBRT, hippocampal avoidance whole brain radiation therapy; HR+, hormone receptor; *N*, number of patients; SRS, stereotactic radiosurgery; TNBC, triple-negative breast cancer.

current study appears to be improved over our historical results for BCBM patients diagnosed via current NCCN Screening recommendations,[14] although the reasons for this may be multifactorial. In our prior series, we noted the highest rates of WBRT receipt at brain metastasis diagnosis to be in breast cancer patients, 57%, compared to 37% in NSCLC and 21% in melanoma in which surveillance MRIs are conducted. The majority of patients in our trial



No. at Risk					
HER2+	8	8	7	6	3
HR+/HER2–	9	7	7	5	3
TNBC	7	7	5	5	2

Figure 3. Kaplan–Meier overall survival following brain metastasis diagnosis by subtype.

were treated with focal SRS, 67% ($n = 16$). Only 29% of patients in our trial required WBRT or CSI. As breast cancer patients live longer due to improved systemic management options, improving QoL is essential. Limiting the use of WBRT also means a decreased chance of cognitive decline.[10–12] In addition, more frequent screenings in breast cancer patients also means that progression of intracranial disease can be detected earlier with earlier access to medications with intracranial activity. Furthermore, given the lack of symptoms at the time of brain metastasis diagnosis, only 1 patient underwent surgical resection following preoperative SRS. The rate of surgical resection in the initial management of BCBM was 24% in our historical series.[14] Surgical resection of brain metastases is typically indicated in the setting of solitary, symptomatic, larger brain metastases,[17] given the lack of symptoms at presentation in our series, surgery was only recommended in 1 patient. Surgery has also been shown to potentially increase the risk of subsequent LMD in the management of BCBM.[31]

Essentially a quarter of each of the subtypes was found to have brain metastases in our study. It should be noted, we selected to only include those HR+/HER2– patients that had progressed past first-line therapy, given these patients have been historically thought to have less of a risk of brain metastases and the frequency of detection in this subtype was thought to be lower.[17] TN and HER2+ patients were enrolled regardless of their line of therapy. There is a lack of data on brain metastasis risk with receipt of previous lines of therapy. In the current study, we did not find a correlation with the number of lines of therapy or sites of systemic metastases with brain metastases. However, younger TN patients were more likely to be diagnosed with brain metastases likely an indicator of more aggressive disease. The majority of patients diagnosed with brain metastases at the 6-month MRI were also noted to have systemic progression (60%). Although further inquiry is needed to determine the exact time interval at which brain MRIs should be repeated in higher-risk breast cancer patients, studies have revealed systemic progression to also play a potential role in intracranial progression.[32]

Given improvements in the systemic management of BCBM[4,21,22] as well as improved local therapies,[33–35] the time may be appropriate to reconsider current NCCN Guidelines[9] for the asymptomatic surveillance of breast cancer brain metastases. Our phase II data reveal the highest percentage of brain metastases on the initial MRI to be in TNBC and HER2+ patients but by 6 months, the rate was approximately a quarter across all subtypes leading to changes in systemic therapy and receipt of local therapies for brain metastases management. Future studies will be needed to confirm the results from this trial and provide external validation. These trials should consider inclusion to be restricted by line of therapy to more clearly define recommended changes to the current NCCN Guidelines.[9]

Limitations of the current study include a lack of collected QoL data. When introducing a new regimen of brain MRI surveillance, the benefits of early detection must also be weighed against the potential harms of overtreatment and anxiety related to imaging.[36] The cost of surveillance brain MRIs must also be considered. The study was not randomized which could have led to potential biases. In addition, although we enrolled 101 patients, the number of patients by subtype was smaller with variability in the number of lines of prior therapy received by patients making firm conclusions for each breast cancer subtype more difficult. Furthermore, our institution has both 1.5T and 3T MRIs, and both were utilized for study imaging. The results may not be generalizable across all institutions given the variability in MRI equipment,[37] radiologist interpretation, and patient presentation. Future prospective evidence will be needed to determine the appropriate interval for brain MRI surveillance in breast cancer. However, given improved

options for systemic therapies that can cross the BBB[4–6] and improved radiotherapy techniques,[25,26] an earlier diagnosis of brain metastases can provide access to these treatment strategies.

In conclusion, we report results from the first prospective study of brain MRI surveillance in stage IV breast cancer. The highest frequency of brain metastases at baseline was in TN and HER2+ breast cancer. Following the 6-month MRI, essentially a quarter of all subtypes developed brain metastases. Early detection of brain metastases meant most patients were eligible for SRS with the diagnosis of brain metastases also leading to changes in systemic therapy. Further prospective evaluation is warranted to confirm these results and potentially modify current brain MRI surveillance guidelines.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

brain metastases | brain MRI | stage IV breast cancer | surveillance

Conflict of Interest

P.A.F. has received research funding from Pfizer and Celgene and is on the advisory boards of Novocure, BTG, Inovio, AbbVie, Ziopharm, Tocagen, and Pfizer. H.S. serves as a consultant for Astrazeneca, Celgene, Novartis, PUMA, and Eisai, is on advisory boards for Novartis, Eisai, PUMA, Eli Lilly, Astrazeneca, and received speaker fees from Merck. H.S.H. declares research funding from Abbvie, Arvinas, Celcuity, Ellipses, Pfizer, Mersana, Quantum Leap Healthcare Collaborative, Zymeworks, and is on advisory boards for Pfizer and Arvinas. K.A.A. has received research funding from Bristol-Myers Squibb, Eli Lilly, and Genentech. M.E. has received honoraria from OncLive. R.C. has received honorariums from Gilead, Pfizer, Athenex, Immunomedics, Daiichi Sankyo, and Astrazeneca. M.R. is a consultant for Astrazeneca. Roberto Diaz is a consultant for Lumicell.

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Authorship statement

K.A.A., Y.K., J.A.A., and H.S.H. designed the study. K.A.A., Y.K., H.S.H., and R.A.D. contributed to data collection. K.A.A. and Y.K. performed the statistical analysis. K.A.A., Y.K., A.J.A., J.A.A., R.L.C., R.A.D., K.T.L., L.L., H.H.S., A.E.S., and H.S.H. contributed to data analysis and interpretation. K.A.A., Y.K., A.J.A., J.A.A., R.L.C., B.J.C., R.D., R.A.D., M.E., P.A.F., K.T.L., L.L., M.N.M., V.H.P., M.R., H.H.S., C.S.S., I.R.W., A.E.S., and H.S.H. assisted with data analysis, data interpretation, manuscript editing, and review.

Data availability

Summary data will be made available upon reasonable request by email to the corresponding author.

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