

ORIGINAL ARTICLE

A prospective study for brain metastasis imaging screening in patients with advanced HER2-positive or triple-negative breast cancer[☆]

G. M. Kim^{1†}, M. H. Kim^{1†}, H. S. Park², J. H. Kim³, K. H. Kim¹, S.-G. Kim⁴, J. Y. Kim⁵, H. S. Park⁵, S. Park⁵, S.-K. Lee⁶, Y. B. Kim⁷, J. H. Chang⁸, S. I. Kim⁵ & J. Sohn^{1*}

¹Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul; ²Division of Medical Oncology, St Vincent's Hospital, The Catholic University of Korea, Seoul; ³Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul; ⁴Division of Hematology and Oncology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam; ⁵Division of Breast Surgery, Department of Surgery, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul; Departments of ⁶Radiology; ⁷Radiation Oncology, Yonsei Cancer Center; ⁸Neurosurgery, Yonsei University College of Medicine, Seoul, Republic of Korea



Available online xxx

Background: Current guidelines for advanced breast cancer do not recommend routine brain imaging in neurologically asymptomatic patients. Prospective clinical evidence on the effectiveness of screening for early detection of brain metastasis (BM) remains limited. We conducted a prospective cohort study to evaluate the utility of magnetic resonance imaging (MRI) screening in patients with advanced human epidermal growth factor receptor 2-positive (HER2+) or triple-negative breast cancer (TNBC).

Patients and methods: In this single-arm, prospective study, screening brain MRI was carried out at diagnosis in asymptomatic patients with advanced HER2+ or TNBC. Patients without BM on baseline MRI were monitored for the development of neurologic symptoms. Follow-up brain MRI studies were carried out at the initiation of second- and third-line systemic therapy. The primary endpoint was the detection rate of BM on screening MRI.

Results: MRI detected asymptomatic BM in 11/112 (9.8%) patients at baseline; the cumulative detection rates increased to 17.0% and 19.6% by the initiation of second- and third-line therapy, respectively. Through this serial screening strategy, two-thirds of all BM cases (22/33) were identified at an asymptomatic stage. Patients with baseline metastatic involvement of three or more organ sites outside the central nervous system had an increased risk of BM (hazard ratio 3.38), and 38.5% of patients in this subgroup were diagnosed with BM by MRI screening. Stereotactic radiosurgery (66.7%) was the most common initial treatment for BM, and the median overall survival after BM diagnosis was 23.3 months.

Conclusions: Two-thirds of BM cases in patients with advanced HER2+ or TNBC were diagnosed at an asymptomatic stage in this prospective serial brain MRI screening program.

Key words: MRI screening, brain metastasis, triple-negative breast cancer, HER2-positive breast cancer, early detection

INTRODUCTION

Breast cancer is the most common cancer among women worldwide and the second most frequent cause of metastatic brain tumors, accounting for ~15% of cases.¹ Several molecular pathways have been implicated in promoting organotropism to the brain,² and clinical cohort studies

have demonstrated that patients with advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer and triple-negative breast cancer (TNBC) are at high risk of brain metastasis (BM).^{3,4} The overall incidence of BM in these breast cancer subtypes is ~30%, and BM is an independent poor prognostic factor, increasing the risk of death 2.5- to 3-fold.⁵⁻⁷ The conventional treatment mainstay for BM has been local treatment modalities, including radiotherapy and surgery. However, recent clinical trials have also revealed significant intracranial activity of targeted agents in patients with HER2-positive breast cancer. Therefore systemic therapy alone or in combination with local therapies is now an effective strategy for selected patient groups.

As the expected overall survival (OS) of patients with advanced breast cancer (ABC) increases, the management

*Correspondence to: Prof. Joohyuk Sohn, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. Tel: +82-2-2228-8127; Fax: +82-2-393-3652
E-mail: oncsohn@yuhs.ac (J. Sohn).

[†]These authors contributed equally to this study as co-first authors.

[☆]Note: Previous presentation: Poster presentation in the San Antonio Breast Cancer Symposium 2023.

2059-7029/© 2026 The Authors. Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

strategy for BM is becoming increasingly important for patient survival and quality of life. As the extent of intracranial disease at the time of diagnosis is a well-established prognostic factor,^{8,9} researchers are interested in whether early detection of BM through imaging surveillance in asymptomatic patients offers survival benefits. Early detection of smaller lesions may allow for more effective and less toxic interventions, potentially resulting in improved intracranial outcomes. However, current guidelines for ABC [National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and ABC-06,07¹⁰⁻¹²] do not recommend routine brain imaging for neurologically asymptomatic patients with breast cancer, in contrast to those for lung cancer or melanoma, owing to the lack of prospective clinical evidence supporting the effectiveness of early detection and intervention for BM in patients with ABC. The European Society for Medical Oncology—European Association of Neuro-Oncology (ESMO—EANO) guidelines suggest that brain magnetic resonance imaging (MRI) screening may be considered for patients with metastatic TNBC and HER2-positive breast cancer, allowing for potential subtype-oriented screening for BM.

A previous imaging study revealed similar OS between patients with symptomatic and those with occult BM.^{4,13} Therefore the impact of treatment for occult central nervous system (CNS) disease on survival remains questionable. Advances in local and systemic treatment options for BM may benefit patients in whom BM is detected at an early stage. Stereotactic radiotherapy (SRS) and MRI-guided navigation surgery reportedly alleviate complications of local treatment,^{14,15} and newer antibody—drug conjugates and brain-penetrating tyrosine kinase inhibitors exhibit significantly improved activity against BM.^{16,17} With the introduction of treatment modalities associated with low neurologic toxicities and better intracranial and extracranial disease control, improved survival and neurologic outcomes are expected among patients in whom BM is detected in an early stage.

Based on this clinical background, we conducted a prospective study of brain MRI screening in neurologically asymptomatic patients with advanced TNBC or HER2-positive breast cancer to evaluate the effectiveness of a serial brain MRI screening program for BM detection in these high-risk patients (NCT03617341). Here, we report the primary findings from a cohort of 112 treatment-naive patients with ABC who were serially screened from the time of ABC diagnosis to the initiation of up to third-line systemic therapy. The aim was to assess the BM detection rate and clinical outcomes after detection, and to identify patient subgroups for whom routine brain MRI screening may offer the greatest benefit.

PATIENTS AND METHODS

Patients

This prospective single-arm study was conducted to evaluate the clinical usefulness of brain MRI surveillance in

patients with ABC (see the study scheme in [Supplementary Figure S1](#), available at <https://doi.org/10.1016/j.esmooop.2026.106892>) at Yonsei Cancer Center. Eligible patients were aged ≥ 19 years and were diagnosed with advanced HER2-positive breast cancer or advanced TNBC according to the ASCO—College of American Pathologists (ASCO—CAP) guidelines. Patients were excluded if they had a history of prior BM, were neurologically symptomatic during the screening period, or had previously received third- or later-line systemic treatments (including endocrine therapy). Patients enrolled from October 2018 to July 2023 who had not yet received first-line systemic therapy (treatment-naive) for ABC were included in this analysis. Patients were enrolled if they met the eligibility criteria and provided informed consent. The study population was not a consecutive cohort and did not include all patients with advanced HER2-positive and TNBC in Yonsei Cancer Center during the enrollment period. The Consolidated Standards of Reporting Trials (CONSORT) diagram for patient enrollment is presented in [Supplementary Figure S2](#), available at <https://doi.org/10.1016/j.esmooop.2026.106892>. This study was approved by the Institutional Review Board of Severance Hospital (approval number 4-2018-0254; approval date: 2 May 2018) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from all patients at enrollment. All procedures were carried out in compliance with relevant laws and institutional guidelines.

Brain MRI screening and treatment for BM

Screening brain MRI was carried out before the initiation of systemic therapy in asymptomatic patients with HER2-positive ABC or TNBC (i) at baseline and (ii) at the initiation of second- and third-line systemic therapy following disease progression on prior treatment ([Supplementary Figure S1](#), available at <https://doi.org/10.1016/j.esmooop.2026.106892>). If no BM was detected on baseline brain MRI, patients were monitored for the development of neurologic symptoms suggestive of brain involvement (e.g. headache, nausea, or vomiting). If such symptoms occurred during any line of chemotherapy, a brain MRI was carried out at the discretion of the treating physician. Patients diagnosed with symptomatic BM were withdrawn from the remainder of the study; however, we collected data on their subsequent treatment, including local therapies, as well as survival outcomes. If BM was not identified on baseline brain MRI screening and no BM was diagnosed during systemic therapy, a follow-up brain MRI was carried out at the initiation of second- or third-line systemic therapy after disease progression on prior treatment. For patients diagnosed with BM, treatment was determined through multidisciplinary consultation between neurosurgeons and radiation oncologists. Surgical resection was considered for patients with one or two surgically accessible and symptomatic metastases. For patients with up to four metastases measuring ≤ 3 cm each, SRS (e.g. gamma

Table 1. Baseline characteristics of patients in this study			
Characteristics		First-line patients (final analysis set; n = 112)	All patients (n = 138)
Enrollment line, n (%)	First line	112 (100)	112 (81.2)
	Second line	0 (0)	24 (17.4)
	Third line	0 (0)	2 (1.4)
Age (years), median (Q1-Q3)		52 (43-59)	50 (29-80)
Sex, n (%)	Female	111 (99.1)	137 (99.3)
	Male	1 (0.9)	1 (0.7)
Subtype, n (%)	HR–HER2+	35 (31.3)	42 (30.4)
	HR+HER2+	23 (20.5)	28 (20.3)
	TNBC	54 (48.2)	68 (49.3)
ECOG performance status, n (%)	0	102 (91.1)	124 (89.9)
	1	10 (8.9)	14 (10.1)
Disease status, n (%)	Recurrent	70 (62.5)	90 (65.2)
	<i>De novo</i> stage IV	42 (37.5)	48 (34.8)
Visceral metastasis, n (%)	No	29 (25.9)	42 (30.4)
	Yes	83 (74.1)	96 (69.6)
Number of organ metastatic sites (non-CNS), n (%)	<3	86 (76.8)	108 (78.3)
	≥3	26 (23.2)	30 (21.7)
Brain metastasis detection, n (%)	No	79 (70.5)	93 (67.4)
	Yes	33 (29.5)	45 (32.6)
Brain metastasis detection, n (%)	No	79 (70.5)	93 (67.4)
	By screening MRI	22 (19.6)	26 (18.8)
	By symptoms	11 (9.8)	19 (13.8)
Brain metastasis treatment, n (%)	Surgery	3 (2.7)	6 (4.3)
	GKS	26 (23.2)	33 (23.9)
	WBRT	18 (16.1)	24 (17.4)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GKS, gamma knife surgery; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MRI, magnetic resonance imaging; Q, quartile; TNBC, triple-negative breast cancer; WBRT, whole-brain radiation therapy.

knife surgery or CyberKnife radiation therapy) was considered.

Study endpoints

The primary endpoint was the detection rate of BM by screening brain MRI. The secondary endpoints were as follows: (i) the incidence of brain oligometastasis (four lesions or fewer) confirmed by brain MRI; (ii) intracranial progression-free survival (PFS) after treatment for BM; (iii) OS after diagnosis of BM; (iv) the time from diagnosis to treatment for BM; and (v) cognitive impairment after BM.

Cognitive function assessment by questionnaires

In patients diagnosed with BM either by screening MRI or MRI carried out due to symptoms, a baseline assessment of cognitive function was conducted using the Korean version of the Mini-Mental State Examination (MMSE-K), before treatment for BM, such as surgical resection, stereotactic radiosurgery, or whole-brain radiotherapy (WBRT). A follow-up MMSE was carried out 6 months after completion of BM therapy.

Statistical analysis

This was a prospective observational study, and no formal statistical hypothesis testing was planned for the primary endpoint. Continuous variables were compared using Student's *t*-test, and categorical variables were compared using the chi-square test. Time to BM was calculated from the date of ABC diagnosis (*de novo* stage IV or recurrent) to the date of BM detection on brain MRI. The cumulative

incidence of BM was estimated using Kaplan–Meier curves and compared using the log-rank test. OS was defined as the time from diagnosis of BM to death from any cause and was compared using the log-rank test. Intracranial PFS was defined as the time from the first BM diagnosis to progression of intracranial disease or death from any cause. Univariate and multivariable Cox regression analyses were carried out to evaluate the impact of baseline characteristics on BM incidence. Statistical analyses were carried out using IBM SPSS Statistics version 28.0 (IBM Corp) and GraphPad Prism (GraphPad Software). Competing risk analysis was carried out using the *cmprsk* package in R (version 4.3.3). All *P* values are two-sided.

RESULTS

Baseline characteristics of patients

Among the 138 patients with advanced HER2-positive breast cancer or TNBC who were enrolled in the prospective brain MRI screening study, 112 patients who were at the initial diagnosis of ABC and had not yet undergone first-line treatment were included in the final analysis set (Supplementary Figures S1 and S2, available at <https://doi.org/10.1016/j.esmoop.2026.106892>). Patients enrolled before the initiation of second- (*n* = 24) or third-line (*n* = 2) treatment were excluded from the analysis. Contrast-enhanced brain MRI was carried out before the start of systemic treatment to screen for BM. The median age of the 112 patients was 52 years, and most had a good performance status [Eastern Cooperative Oncology Group (ECOG) 0, *n* = 102, 91.1%; Table 1]. The breast cancer

Table 2. Incidence of BM according to breast cancer subtype

BM detection	All subtypes (N = 112), n (%)	TNBC (n = 54), n (%)	HER2+ (n = 58), n (%)
Detection via MRI screening	22 (19.6)	13 (24.1)	9 (15.5)
Detection via symptoms during treatment	11 (9.8)	4 (7.4)	7 (12.1)
BM at diagnosis of MBC	11 (9.8)	7 (13.0)	4 (6.9)
BM throughout follow-up	33 (29.5)	17 (31.5)	16 (27.6)

BM, brain metastasis; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; TNBC, triple-negative breast cancer.

subtypes were TNBC ($n = 54$, 48.2%), HR-negative HER2-positive ($n = 35$, 31.3%), and HR-positive HER2-positive ($n = 23$, 20.5%). The median follow-up duration was 24.9 months up to the data cut-off date of 21 September 2023. The median OS from the diagnosis of stage IV disease was 30.7 months in patients with TNBC and was not reached in patients with the HER2-positive subtype ($P = 0.004$, log-rank test, [Supplementary Figure S3](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). The median time from ABC diagnosis to the first, second, and third brain MRI screens was 25 days, 8.8 months, and 15.2 months, respectively. First-line systemic therapy was administered to 98.1% (53/54) of patients with TNBC and 100% (58/58) of patients with HER2-positive disease. Among patients who progressed on first-line therapy, 70.5% (31/44) of those with TNBC and 90.0% (27/30) of those with HER2-positive disease received second-line therapy. Among those who progressed on second-line therapy, 91.7% (22/24) of patients with TNBC and 81.0% (17/21) of patients with HER2-positive disease received third-line therapy.

Diagnosis of BM via brain MRI screening

The proportion of patients diagnosed with BM on brain MRI screening was 19.6% (22/112) overall ([Table 2](https://doi.org/10.1016/j.esmoop.2026.106892) and [Supplementary Table S1](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>): 24.1% (13/54) among patients with TNBC and 15.5% (9/58) among patients with HER2-positive disease [22.7% for hormone receptor (HR)-positive, HER2-positive and 11.1% for HR-negative, HER2-positive patients]. Despite MRI screening before initiation of each line of systemic treatment, 9.8% (11/112) of patients were diagnosed with symptomatic BM during treatment, and the overall cumulative incidence of BM during the study period was 29.5%. Therefore two-thirds of patients diagnosed with BM (22/33, 66.7%) were identified while asymptomatic owing to the serial screening strategy. There were 12 patients with attrition before the second brain MRI and seven before the third brain MRI ([Supplementary Figure S2](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). The reasons for attrition are described in [Supplementary Table S2](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>. The median time from stage IV diagnosis to BM diagnosis was 3.3 months in patients diagnosed through asymptomatic screening and 12.9 months in those diagnosed after symptom onset. The corresponding median times are 3.6 months for TNBC and 11.1 months for HER2-positive subtypes. The cumulative

detection rate of BM via MRI screening increased over time: 9.8% (11/112), 17.0% (19/112), and 19.6% (22/112) at the first-, second-, and third-line MRI studies, respectively ([Figure 1](https://doi.org/10.1016/j.esmoop.2026.106892)). The absolute detection rates were 9.8% (11/112) at the first MRI, 18.2% (8/44) at the second MRI, and 13.0% (3/23) at the third MRI. Among the 33 patients diagnosed with BM, 51.5% (17/33) had oligometastatic disease, 45.5% (15/33) had more than four lesions, and 3.0% (1/33) exhibited leptomeningeal seeding. The detailed number, size, location, and symptoms of BM are summarized in [Supplementary Table S3](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>. Patients diagnosed with symptomatic BM ($n = 11$) tended to have larger lesions and more numerous lesions than those diagnosed through asymptomatic MRI screening; however, statistical comparisons were not feasible because of the limited sample size. In these patients, the median time from the last negative screening MRI to the onset of neurologic symptoms and subsequent BM diagnosis was 11.2 and 11.3 months, respectively. Symptoms resolved in eight patients and worsened in two after local treatment; one patient did not receive local treatment.

BM risk and the number of organ metastatic sites

The median time from ABC diagnosis to BM diagnosis was 25.1 months. The cumulative incidence of BM was 14.3% and 20.5% at 6 and 12 months after the diagnosis of stage IV disease, respectively ([Figure 2A](https://doi.org/10.1016/j.esmoop.2026.106892)). The estimated probability of BM diagnosis at 12 months using the one-minus Kaplan–Meier method was 23.4% (corresponding to a 76.6% 12-month BM-free survival; [Figure 2B](https://doi.org/10.1016/j.esmoop.2026.106892) and [Supplementary Figure S4A](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). A competing-risk analysis accounting for death as a competing event was additionally carried out, and the difference between the one-minus Kaplan–Meier method and cumulative incidence function curves was modest in our cohort ([Supplementary Figure S4B](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). The rate of BM diagnosis did not differ according to cancer subtype (TNBC versus HER2-positive breast cancer, [Supplementary Figure S5A](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). Patients with metastatic involvement of three or more non-CNS organ sites had a higher risk of BM diagnosis than those with involvement of less than three organ sites ([Supplementary Figure S5B](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>; $P < 0.001$, log-rank test). Multivariable Cox regression analysis using baseline clinical parameters revealed

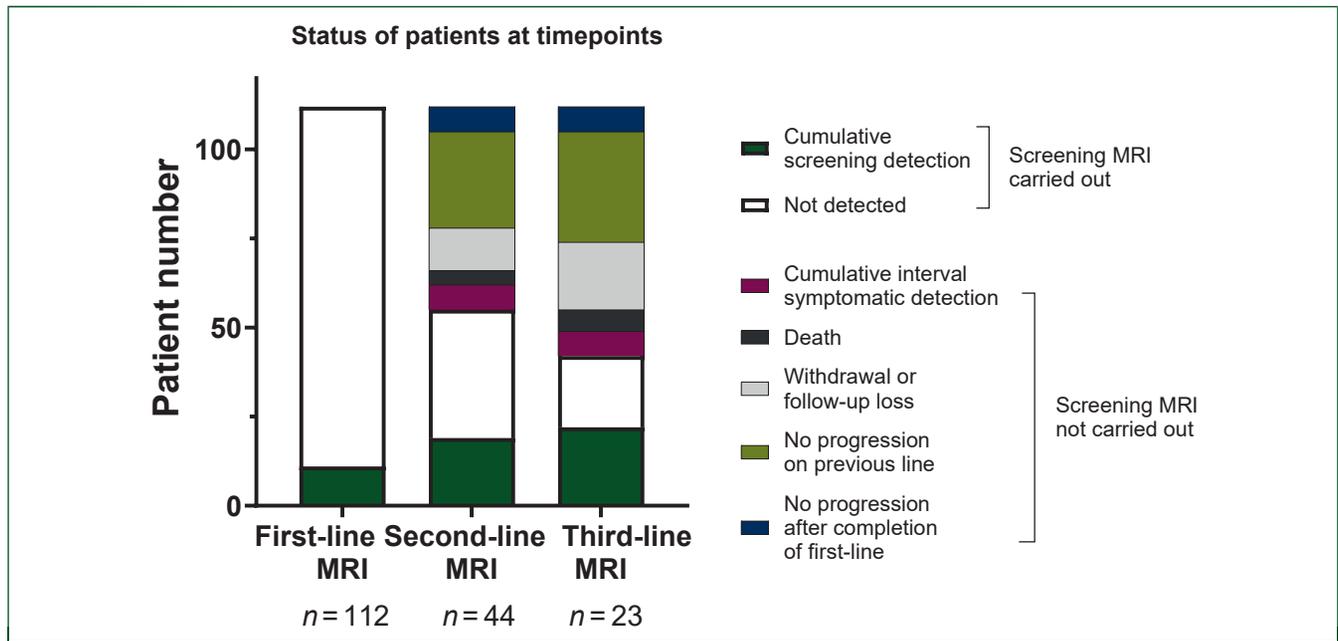


Figure 1. Brain metastasis detection at each screening timepoint. MRI, magnetic resonance imaging.

that metastatic involvement of three or more non-CNS organ sites at baseline was an independent predictive factor for BM diagnosis (hazard ratio: 3.38, 95% confidence interval: 1.55-7.34, $P = 0.002$; Table 3). Recurrent disease status also conferred a higher risk of BM than *de novo* stage IV disease (hazard ratio 3.06, 95% confidence interval 1.34-7.03, $P = 0.008$). Among patients with metastatic involvement of three or more non-CNS organ sites ($n = 26$), the incidence of BM was 46.2% during the study period, compared with 29.5% among patients with less than three non-CNS organ sites ($n = 86$). In this subgroup, 38.5% (10/26) of patients were diagnosed with BM via brain MRI screening, whereas the corresponding rate

was 14.0% (12/86) among those with less than three non-CNS organ sites (Supplementary Tables S4 and S5, available at <https://doi.org/10.1016/j.esmooop.2026.106892>). Notably, 83.3% (10/12) of BM diagnoses in patients with three or more non-CNS organ sites were identified through brain MRI screening (Supplementary Table S5, available at <https://doi.org/10.1016/j.esmooop.2026.106892>).

BM treatment

SRS in the form of gamma knife surgery was the most common initial local treatment modality for patients

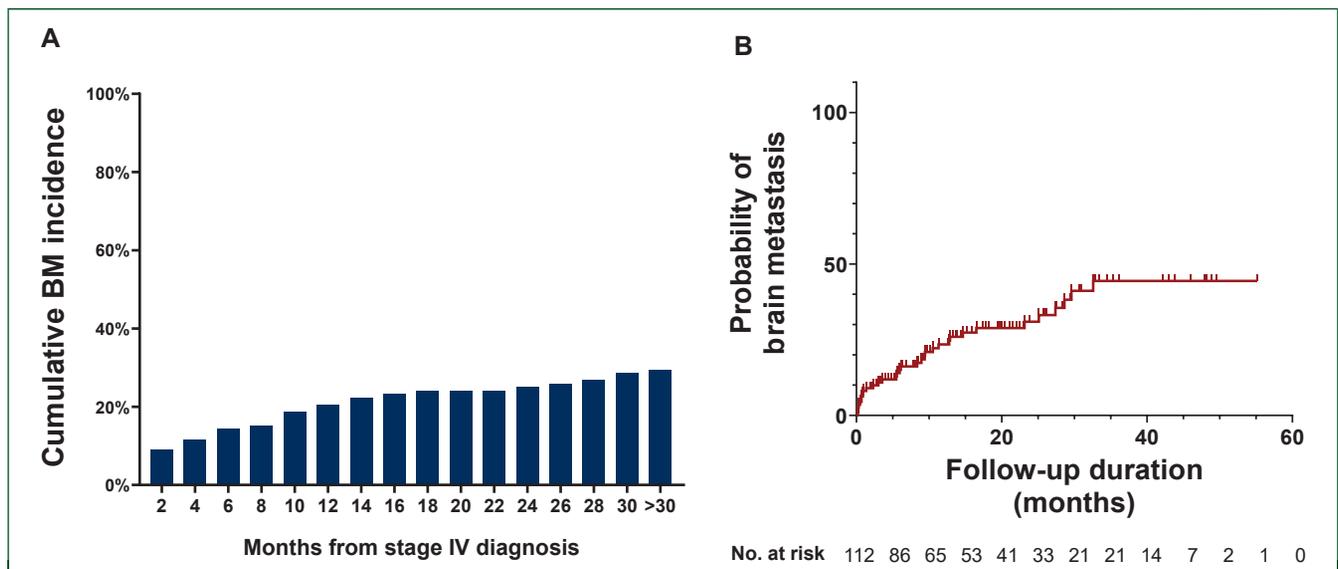


Figure 2. Cumulative incidence and estimated probability of brain metastasis (BM) diagnosis. (A) Bar graph illustrating the observed cumulative incidence of BM among all patients ($n = 112$) over time from stage IV breast cancer diagnosis. (B) One minus Kaplan–Meier curve depicting the estimated probability of BM diagnosis from the time of stage IV breast cancer diagnosis in the overall cohort.

Table 3. Cox regression analysis for brain metastasis diagnosis for patients enrolled before first-line treatment (N = 112)

Factors	Univariate Cox regression			Multivariable Cox regression		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
ECOG performance status (0 versus 1)	0.79	0.28-2.24	0.651	0.76	0.26-2.22	0.620
Disease status (recurrent versus <i>de novo</i> stage IV)	2.26	1.01-5.04	0.046	3.06	1.34-7.03	0.008
Number of non-CNS organs involved (≥ 3 versus < 3)	3.09	1.50-6.36	0.002	3.38	1.55-7.34	0.002
Visceral metastasis (yes versus no)	2.54	0.89-7.24	0.080	1.76	0.58-5.37	0.321
Subtype (TNBC versus HER2+)	1.25	0.63-2.49	0.520	0.92	0.45-1.86	0.812
Age (> 50 versus ≤ 50 years)	0.54	0.26-1.05	0.068	0.61	0.30-1.26	0.183

CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

diagnosed with BM (22/33, 66.7%; [Supplementary Table S6](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). WBRT was carried out in 9/33 (27.3%) patients, and the remaining 2 (6.1%) patients did not receive any treatment for BM. Among patients who underwent local treatment for BM ($n = 31$), WBRT was more commonly used in patients with TNBC (6/15, 40.0%) than in those with HER2-positive breast cancer (3/16, 18.8%). None of the patients underwent surgery as the initial treatment for BM. After the initial gamma knife surgery, three HER2-positive subtype patients (two symptomatically and one through asymptomatic screening) subsequently underwent surgical resection for BM at 15.4, 17.5, and 20.1 months after the first BM diagnosis, respectively. The median OS following a diagnosis of BM ($n = 33$) was 23.3 months ([Supplementary Figure S6A](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). OS after BM diagnosis did not significantly differ according to the mode of detection ([Supplementary Figure S6B](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). Patients with TNBC had a shorter OS (11.9 months) than those with HER2-positive breast cancer (27.4 months; [Supplementary Figure S7](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). The median intracranial PFS was 6.5 months for all patients with BM ($n = 33$; [Supplementary Figure S8A](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). Intracranial PFS did not differ between patients with screening-detected ($n = 22$) and those with interval symptomatic detection ($n = 11$; $P = 0.182$; [Supplementary Figure S8B](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>). Intracranial PFS also did not differ according to subtype (TNBC versus HER2+, $P = 0.182$; [Supplementary Figure S8C](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>).

Systemic treatment

The systemic treatment regimens received as first-, second-, and third-line therapy are summarized in [Supplementary Table S7](https://doi.org/10.1016/j.esmoop.2026.106892), available at <https://doi.org/10.1016/j.esmoop.2026.106892>. For patients diagnosed with BM on the first screening MRI at the time of stage IV disease diagnosis ($n = 11$), systemic therapy was initiated concurrently with the diagnosis of BM. Among patients diagnosed with BM on the second ($n = 8$) or third ($n = 3$) screening MRI, which were carried out at the time of systemic disease progression, the

systemic treatment regimen was changed in all patients ($n = 11$). Among patients diagnosed with symptomatic BM during the interval period ($n = 11$), systemic therapy was maintained in two patients, both of whom were receiving an trastuzumab + pertuzumab + docetaxel regimen. By contrast, systemic therapy was modified in six patients following the diagnosis of BM, while three patients did not receive further systemic treatment due to clinical deterioration.

Cognitive function evaluation by MMSE

MMSE scores were collected for 16 patients (12 screening-detected BM and 4 with interval symptomatic detection). MMSE scores were obtained at the time of BM diagnosis in all 16 patients and at 6 months after BM diagnosis in 12 patients. The MMSE score did not differ between the time of BM diagnosis (29.58 ± 0.79) and 6 months after BM diagnosis and brain radiotherapy (29.58 ± 0.90). Cognitive function in patients with screening-detected BM did not differ from that in patients diagnosed with interval symptomatic BM.

DISCUSSION

As the treatment landscape for breast cancer continues to evolve with the development of novel systemic therapies, researchers have shown increasing clinical interest in the detection of and management strategies for BM.¹⁸ In this prospective study, we conducted brain MRI screening at ABC diagnosis and at the initiation of each line of systemic therapy (from first to third line) in neurologically asymptomatic patients with advanced HER2-positive breast cancer or TNBC. The study screening protocol resulted in the detection of asymptomatic BM in 19.6% of patients, and the cumulative incidence increased with each subsequent line of therapy (9.8% at ABC diagnosis, 17.0% at initiation of second-line therapy, and 19.6% at initiation of third-line therapy). Notably, two-thirds of BM diagnoses were made in asymptomatic patients through this screening program. This study is one of the recently conducted prospective trials, together with the study by Ahmed et al.,¹⁹ evaluating brain MRI screening for asymptomatic BM in patients with ABC. Our study demonstrated the potential clinical utility of baseline and serial brain MRI screening in patients with newly diagnosed ABC. These results support the integration of routine

brain MRI screening into clinical practice for patients with advanced HER2-positive breast cancer or TNBC.

BM remains a critical challenge in patients with ABC and has been consistently associated with poor clinical outcomes in large-scale registry studies, including the SystHERs⁶ and registHER studies.⁷ Previous studies have reported an estimated cumulative risk of BM in patients with ABC of up to 25%, and this risk is especially pronounced in those with HER2-positive or TNBC subtypes.^{6,7,20,21} The reported median time to BM diagnosis after ABC diagnosis is 2-3 years.²⁰ Despite this substantial risk, current clinical guidelines do not recommend routine brain MRI screening in patients with ABC, largely owing to earlier studies that revealed no survival difference between patients with occult BM and those with symptomatic BM.^{4,13} However, those studies were retrospective in nature, subject to selection bias, and did not focus on high-risk subtypes (HER2-positive breast cancer and TNBC). Therefore the actual rate of BM detection via screening MRI, the impact of BM diagnosis on clinical outcomes, and the effectiveness of brain MRI screening were previously unclear. Accordingly, the practice patterns regarding brain MRI screening in asymptomatic patients vary widely among physicians, ranging from routine screening in asymptomatic patients to symptom-directed brain imaging.^{22,23} Our prospective screening study addressed this critical knowledge gap by demonstrating that a brain MRI screening program can yield a high detection rate of asymptomatic BM. These findings provide supportive evidence for considering early brain MRI screening strategies in high-risk ABC populations. However, this study was not designed to directly evaluate survival benefits, such as intracranial PFS or OS, compared with symptom-directed imaging in a randomized manner. Therefore further prospective interventional studies are warranted to establish definitive evidence for BM screening.

The BM detection rate of 19.6% among patients with HER2-positive ABC or advanced TNBC in this study is consistent with previous reports.²¹ In the SystHERs study, the BM diagnosis rate was 8.9% at the initial ABC diagnosis and 21.7% thereafter. The BM incidence observed in our study is also comparable to that in patients with non-small-cell lung cancer, for whom brain MRI screening is mandatory (10%-15% at diagnosis).²⁴ Previous studies have indicated that younger age, recurrent ABC rather than *de novo* stage IV ABC, HR-negative status, and a higher disease burden are associated with an increased risk of CNS metastasis.^{6,7} Our study also suggested that the number of metastatic non-CNS organ sites is a significant risk factor for BM diagnosis in patients with ABC (hazard ratio 3.38). Brain MRI screening was effective in these patients, with an overall BM detection rate of 38.5%; 83.3% of such BM were diagnosed via brain MRI screening. However, this result should be interpreted with caution and validated in future studies, given that this was a single-center study with a limited number of BM events ($n = 33$).

The impact of early detection of and intervention for BM in patients with ABC was uncertain in previous studies, probably because previous BM treatment modalities were

less effective than current approaches. Recent clinical advancements in therapeutic modalities have reduced their neurotoxicity and enhanced efficacy. A landmark trial (NCCTG N0574) revealed that SRS is less toxic than WBRT and yields a similar survival outcome, establishing SRS as the treatment of choice for patients with one to three BMs.^{15,25} Regarding WBRT, hippocampal avoidance combined with memantine can alleviate cognitive dysfunction in patients with low-risk BM.²⁶ Therefore outcomes of local treatment for BM have improved substantially in recent years. In our study, the median OS after BM diagnosis was favorable (23.3 months), and cognitive function, as assessed by MMSE, was preserved between baseline and 6 months after BM diagnosis.

In addition, systemic treatment has now become a feasible option for patients with previously untreated or stable BM. Unlike monoclonal antibody agents, trastuzumab deruxtecan has demonstrated robust activity against BM in the TUXEDO, DESTINY-Breast03, and DESTINY-Breast12 trials.^{17,27,28} Moreover, the HER2CLIMB trial showed significant intracranial efficacy with tucatinib-based combination treatment.¹⁶ Therefore multiple systemic treatment strategies (e.g. systemic therapy alone for active BM and continuation of systemic drug maintenance beyond progression) are now available for HER2-positive breast cancer. With these advances in BM management, not all asymptomatic patients with incidentally detected BM require immediate SRS or WBRT; some may be appropriately managed with systemic therapy. In light of these developments, the potential clinical superiority of early screening and intervention for BM, compared with symptom-driven diagnosis and treatment, warrants evaluation in a prospective interventional study.

We also note that brain-active systemic treatment options remain limited for patients with TNBC. In our study, patients with TNBC were more likely to receive WBRT than those with HER2-positive disease (40.0% versus 18.8%) because of multiple BMs or leptomeningeal seeding. This difference may reflect distinct biologic and clinical characteristics, as well as disparities in available treatment options, between the two subtypes. These findings suggest that the MRI screening platform proposed in this study may not sufficiently reduce the use of neurotoxic WBRT in patients with TNBC, underscoring the need for further advances in both BM screening strategies and brain-effective systemic therapies for this population.

A major strength of our analysis was the prospective enrollment of patients at a standardized timepoint (before first-line treatment) and systematic data collection with long-term follow-up MRI surveillance. This design enabled a more accurate estimation of BM incidence and treatment outcomes while minimizing selection bias. However, several limitations should be acknowledged. This study was limited by its small sample size, lack of randomized comparison between screening and symptom-based detection strategies, and single-institution setting. In addition, the attrition rate (19 of 112, 17.0%, patients) represents a practical challenge to implementing repeated brain MRI surveillance

in patients with ABC. Most attrition events were attributable to patient refusal of brain MRI or transfer to another institution (14 of 19, 73.7%, patients), whereas clinical deterioration accounted for 4.5% (5 of 112 patients) of the overall cohort. These findings identify patient refusal and clinical deterioration as important real-world barriers to BM screening and underscore the need for more accessible and patient-friendly approaches to early BM detection, particularly for patients with limited tolerance for MRI or declining clinical status.

Recently, Ahmed et al. reported a phase II trial evaluating brain MRI surveillance at baseline and at 6 months in patients with stage IV breast cancer.¹⁹ However, they enrolled across a wide range of treatment lines (first to eighth), which limits the generalizability of their findings. Furthermore, the study included all breast cancer subtypes, including HR-positive/HER2-negative disease, further broadening the study population. By contrast, our study focused specifically on high-risk subtypes (only those with HER2-positive breast cancer and TNBC), and implemented BM screening beginning at the time of ABC diagnosis. Jerzak et al. have also reported interim results of a randomized study comparing routine BM screening with symptom-directed brain imaging; final results are awaited.²⁹

In conclusion, our prospective brain MRI screening program detected BM in 19.6% of patients with HER2-positive ABC or advanced TNBC, with approximately two-thirds of cases (22/33) identified at an asymptomatic stage. These findings suggest that serial brain MRI surveillance may facilitate earlier detection of BM in high-risk populations. Further prospective clinical studies are warranted to determine the clinical utility and survival benefit of such a screening strategy. As therapeutic modalities for breast cancer-related BM continue to evolve, early detection and timely intervention may represent an effective approach to improving patient outcomes.

ACKNOWLEDGEMENTS

The authors thank the patients, their families, and all investigators involved in this study.

FUNDING

This work was supported by the Severance Hospital Research Fund for Clinical Excellence (SHRC) at Severance Hospital [grant number C-2019-0007].

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

The data presented in the study can be made available on request to the corresponding author.

REFERENCES

- Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep*. 2012;14(1):48-54.
- Liang Z, Mo Y, Zhang Y, Yu Y, Ji Y. Molecular mechanisms and signaling pathways related to brain metastasis in breast cancer. *Front Pharmacol*. 2025;16:1585668.
- Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol*. 2010;28(20):3271-3277.
- Miller KD, Weathers T, Haney LG, et al. Occult central nervous system involvement in patients with metastatic breast cancer: prevalence, predictive factors and impact on overall survival. *Ann Oncol*. 2003;14(7):1072-1077.
- Laakmann E, Witzel I, Neunhoffer T, et al. Characteristics of patients with brain metastases from human epidermal growth factor receptor 2-positive breast cancer: subanalysis of Brain Metastases in Breast Cancer Registry. *ESMO Open*. 2022;7(3):100495.
- Hurvitz SA, O'Shaughnessy J, Mason G, et al. Central nervous system metastasis in patients with HER2-positive metastatic breast cancer: patient characteristics, treatment, and survival from SystHERs. *Clin Cancer Res*. 2019;25(8):2433-2441.
- Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. *Clin Cancer Res*. 2011;17(14):4834-4843.
- Castaneda CA, Flores R, Rojas KY, et al. Prognostic factors for patients with newly diagnosed brain metastasis from breast cancer. *CNS Oncol*. 2015;4(3):137-145.
- Rostami R, Mittal S, Rostami P, Tavassoli F, Jabbari B. Brain metastasis in breast cancer: a comprehensive literature review. *J Neurooncol*. 2016;127(3):407-414.
- Ramakrishna N, Anders CK, Lin NU, et al. Management of advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: ASCO guideline update. *J Clin Oncol*. 2022;40(23):2636-2655.
- Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, et al. 6th and 7th International consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). *Breast*. 2024;76:103756.
- National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology*. Breast Cancer (Version 5.2025). NCCN. 2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed December 2, 2025.
- Niwinska A, Tacikowska M, Murawska M. The effect of early detection of occult brain metastases in HER2-positive breast cancer patients on survival and cause of death. *Int J Radiat Oncol Biol Phys*. 2010;77(4):1134-1139.
- Ng PR, Choi BD, Aghi MK, Nahed BV. Surgical advances in the management of brain metastases. *Neurooncol Adv*. 2021;3(suppl 5):v4-v15.
- Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA*. 2016;316(4):401-409.
- Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. 2020;38(23):2610-2619.
- Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. *Nat Med*. 2024;30(12):3717-3727.
- Raghavendra AS, Ibrahim NK. Breast cancer brain metastasis: a comprehensive review. *JCO Oncol Pract*. 2024;20(10):1348-1359.
- Ahmed KA, Kim Y, Armaghani AJ, et al. Phase II trial of brain MRI surveillance in stage IV breast cancer. *Neuro Oncol*. 2025;27(6):1550-1558.
- Darlix A, Louvel G, Fraisse J, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. *Br J Cancer*. 2019;121(12):991-1000.
- Martin AM, Cagney DN, Catalano PJ, et al. Brain metastases in newly diagnosed breast cancer: a population-based study. *JAMA Oncol*. 2017;3(8):1069-1077.
- Sammons S, Lamba N, Lin NU. Brain imaging screening in metastatic breast cancer: is it time to rethink clinical guidelines and practice? *Breast*. 2025;84:104616.

23. Matos L, van Ramshorst M, Muller V, et al. Brain imaging screening in metastatic breast cancer: patients' and physicians' perspectives. *Breast*. 2025;84:104558.
24. Waqar SN, Samson PP, Robinson CG, et al. Non-small-cell lung cancer with brain metastasis at presentation. *Clin Lung Cancer*. 2018;19(4):e373-e379.
25. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. *J Clin Oncol*. 2022;40(5):492-516.
26. Brown PD, Gondi V, Pugh S, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG oncology CC001. *J Clin Oncol*. 2020;38(10):1019-1029.
27. Hurvitz SA, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer patients with brain metastases from the randomized DESTINY-Breast03 trial. *ESMO Open*. 2024;9(5):102924.
28. Bartsch R, Berghoff AS, Furtner J, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. *Nat Med*. 2022;28(9):1840-1847.
29. Jerzak KJ, Shum M, Pond G, et al. Abstract 4798: MRI screening for brain metastases (BrM) versus SYMptom-directed brain imaging for patients with triple negative (TN) or HER2+ metastatic breast cancer (MBC): an ad-hoc interim analysis of a randomized phase II pilot study. *Cancer Res*. 2024;84(suppl 6):4798-4798.