Proactive brain screening using contrast-enhanced brain CT scans in HER2+ metastatic breast cancer

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Translational relevance

Brain metastases are a frequent complication in HER2+ metastatic breast cancer, but evidence on proactive imaging in asymptomatic patients is limited. This study provides real-world data showing that contrast-enhanced CT brain screening can reduce the occurrence of symptomatic lesions and preserve performance status. Our findings support proactive imaging by demonstrating potential benefits in reducing morbidity and possibly limiting the need for whole-brain radiotherapy, informing clinical decision-making and guideline development. These results also lay the groundwork for prospective studies to define optimal imaging modalities and timing, highlighting the significance of early detection strategies in improving outcomes for patients with HER2+ metastatic breast cancer.

Abstract

Purpose: According to recent EANO-ESMO guidelines, proactive brain imaging can be considered in asymptomatic patients with HER2+ metastatic breast cancer (mBC), due to high risk of developing brain metastases (BMs). However, optimal imaging modality and timing remain unclear. We retrospectively assessed the impact of contrast-enhanced CT screening on symptomatic BMs in HER2+ mBC patients.

Methods: Consecutive patients newly diagnosed with HER2+ mBC treated with trastuzumab-pertuzumab plus taxane (2014-2024) were retrospectively identified. Brain screening was defined as at least one contrast-enhanced brain CT scan per year without neurological symptoms during the first 2 years post-diagnosis.

Results: Among 148 identified patients, 73 underwent brain screening and 75 did not. Median number of annual brain CT scans during the first 2 years was 2.0 (IQR 1.2-2.5) and 0.0 (IQR 0.0-0.5) in the screening and non-screening groups, respectively. Thirty patients (20.3%) developed BMs during the first 2 years. Cumulative BM incidence was significantly higher in patients undergoing screening (30.6% vs 12.3%, Gray's p=0.004), but symptomatic BMs were significantly lower in patients undergoing screening (0% vs 9.5%, Gray's p=0.012). Patients undergoing screening had better preserved performance status at BM diagnosis (p=0.002) and a numerical trend toward fewer BMs (p=0.057). Treatment patterns post-BM diagnosis were similar, though WBRT was used less often in the screening group (14.3% vs 44.4%, p=0.073).

Conclusions: Brain screening with CT scans was associated with fewer symptomatic BMs and better performance status at BM diagnosis, supporting proactive imaging in HER2+ mBC. Prospective studies are warranted to define optimal timing and imaging modalities.

Keywords: breast cancer, brain metastases, brain screening, CT scan

Background

Patients with HER2-positive (HER2+) breast cancer (BC) are at high risk of developing brain metastases (BMs), with approximately 30-50% of patients with advanced HER2+ disease experiencing central nervous system (CNS) involvement at some point during their clinical history.(1–3) The management of patients with BMs requires a personalized, multimodal approach, integrating locoregional treatments (i.e. neurosurgery and radiotherapy) and systemic therapy tailored based on disease characteristics.(4–7)

Despite significant advancements in the management of BC-related BMs over the last decades, BMs remain a major source of comorbidity and a significant cause of death for BC patients.(8) The impact of BMs on metastatic BC treatment and prognosis, along with the detrimental effects of neurological symptoms on quality of life, have driven growing interest in the early identification of BMs before the onset of neurological symptoms, with the ultimate goal of reducing symptom burden in patients affected by BC-related BMs and increasing the proportion of patients which can be treated with less toxic local treatment options, such as stereotactic radiotherapy.

While current guidelines do not strongly recommend routine brain imaging in asymptomatic patients with metastatic HER2+ BC, the most recent European guidelines (EANO-ESMO) acknowledge that proactive brain imaging can be considered in high-risk patients, such as those with HER2+ and triple-negative metastatic BC.(9) However, due to the lack of evidence, no clear indication regarding the radiological technique which should be used and its timing is currently given. Indeed, while it is well-known that magnetic resonance imaging (MRI) represents the gold standard for radiological diagnosis of symptomatic BMs and contrast-enhanced (CE) brain CT scan is less sensitive in this setting, there is a lack of data regarding their relative value in proactively screening for BMs in asymptomatic patients with BC.(9,10) Moreover, the routine use of proactive brain MRI imaging in patients with metastatic BC presents significant challenges in terms of resource availability and allocation, and requires additional contrast media administration and increased time spent in the hospital, thus potentially negatively affecting patient quality of life. In this uncertain scenario, the pragmatic clinical approach of including evaluation of the brain in the thorax/abdomen CE CT scans to stage and re-evaluate patients with metastatic HER2+/TN BC has been adopted by several medical oncologists in Italy and might represent a more practical and patient-friendly approach. However, we currently lack data regarding the clinical impact of this strategy in reducing the frequency of symptomatic BM diagnosis.

To better assess the impact of surveillance brain imaging in neurologically asymptomatic patients, we retrospectively analyzed a homogeneous cohort of metastatic HER2+ BC patients who received trastuzumab-pertuzumab in combination with taxane and assessed the impact of brain screening using CE CT scans (performed by clinical practice of treating oncologist during the first 2 years following metastatic BC diagnosis) on incidence of symptomatic BMs and patients' characteristics at time of BM diagnosis.

Methods

Patients

Consecutive patients newly diagnosed with metastatic HER2+ BC and starting first line treatment with trastuzumab-pertuzumab plus taxane-based chemotherapy at Istituto Oncologico Veneto - Padova (Italy) between February 2014 and November 2024 were included.

Inclusion criteria were: histologically proven HER2+ BC, histologically or radiologically proven metastatic BC diagnosis, age ≥18 years at time of metastatic BC diagnosis, having received trastuzumab-pertuzumab plus taxane-based chemotherapy as first-line systemic treatment.

Exclusion criteria were: presence of symptomatic BMs at time of first metastatic BC diagnosis; incomplete imaging data regarding the first 2 years from metastatic BC diagnosis.

Demographic, clinicopathologic and treatment data were retrospectively collected from medical charts in a dedicated database. Hormone receptor (HR) expression was determined by immunohistochemistry; positivity was defined as immunohistochemistry staining in at least 1% of tumor cells. BC was considered HER2+ if scored 3+ by immunohistochemistry (IHC) or, in case of IHC HER2 2+ score, if HER2 amplification was observed by fluorescence or chromogenic in situ hybridization (FISH/CISH).

To allow for a more homogeneous evaluation of both the radiological re-evaluation approach adopted by the treating oncologist (proactive brain imaging versus no use of brain imaging in asymptomatic patients) and the clinical outcomes observed (in terms of cumulative rate of BM diagnosis, overall and according to presence/absence of neurological symptoms) in patients with different follow-up time and clinical pathways, we limited the observation period of this study to the first two years following the diagnosis of metastatic BC.

Therefore, data regarding brain imaging procedures performed during the first two years following the diagnosis of metastatic BC was retrospectively collected from medical charts, including radiology records, and analyzed. The observation interval of this study was defined as the first two years from metastatic BC diagnosis (or until BM diagnosis, death or last follow-up, whichever occurred first). For each patient, the number of CE brain CT scans and the number of CE brain MRI performed in the absence of neurological symptoms during that observation interval was recorded. Subsequently, the number of CE brain CT scans performed per year in the absence of neurological symptoms was calculated for each patient by dividing the absolute number of CE brain CT scans performed during the observation time by the duration of the observation interval in years.

For the purpose if this study, patients were classified as having undergone a proactive brain imaging strategy with CE brain CT scans if at least one brain CT scan per year was performed in the absence of neurological symptoms during the observation time (generally as part of routine radiological reassessment).

This study was reviewed and approved by the involved Institutional Review Board and Ethics Committee. If necessary, according to local regulation, written informed consent was obtained from participants. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using IBM SPSS (version 29) and R (version 4.3.3). Descriptive statistics were calculated for patients' demographics and clinical characteristics. The Chi-squared test ($\chi 2$) and Mann-Whitney U test were used to study association between variables, as appropriate.

Cumulative incidence of BMs during the first two years from metastatic BC diagnosis was evaluated using a competing risk methodology (Fine and Gray method(11,12)). In analyses that considered BM diagnosis as the event of interest, death without BMs was treated as a

competing risk. In analyses that considered symptomatic BM diagnosis as the event of interest, death without BMs and diagnosis of asymptomatic BMs were treated as competing risks. In analyses that considered asymptomatic BM diagnosis as the event of interest, death without BMs and diagnosis of symptomatic BMs were treated as competing risks. Patients who had not experienced an event of interest or any of the competing risk events after two years (or at last follow-up, whichever occurred first) were censored at that time.

Overall survival from BM diagnosis (OS) was defined as time from BM diagnosis to death from any cause or last follow-up. Patients alive without event at the cut-off date of this analysis (25th February 2025) were censored at the date of last follow-up.

OS was estimated using the Kaplan–Meier method and reported with its 95% confidence intervals (95% CIs). The log-rank test was used to compare OS between groups.

All reported p values were two-sided and significance level was set at 5% ($p < 0.05$).

Data availability

Data that support the findings of this study are available from the corresponding author upon request, pending on formalization of a Data Transfer Agreement and necessary ethical approvals, reinforcing the compliance with the EU privacy law. Further information is available from the corresponding author upon request.

Results

Patients' characteristics

A total of 166 patients with stage IV HER2+ BC treated with trastuzumab-pertuzumab plus taxane-based chemotherapy as first-line treatment were identified. Among them, 11 patients presented with symptomatic BMs at time of first metastatic BC diagnosis and were therefore excluded from the present study. For an additional 7 patients, complete information on imaging performed during the first two years from metastatic BC diagnosis was unavailable.

Among the remaining 148 patients, 73 had undergone proactive brain imaging by CE brain CT scans (at least one CE brain CT scan per year in absence of neurological symptoms) during the observation period of this study (first two years from metastatic BC diagnosis), while 75 had not (Figure 1).

Main clinicopathological characteristics of study cohort are reported in Table 1.

Patients undergoing and not undergoing a proactive brain imaging strategy with CE brain CT scans during the study observation period presented similar clinicopathological characteristics at BC diagnosis (Table 1). Median age at diagnosis was 54 years of age in both groups, most patients had grade 3 no special type BC (84.9%-86.7%), around 70% presented HR+ disease (67.1%-72.0%) and nearly 60% of patients had de novo stage IV disease (59.7-58.7).

As expected, since brain screening has only recently been incorporated into guidelines, patients who underwent a proactive brain imaging strategy with CE brain CT scans during the study observation period were diagnosed significantly more recently and had a significantly shorter median follow-up from both first BC diagnosis and metastatic BC

diagnosis. No significant differences were reported in terms of performance status (as evaluated by Karnofsky Performance Status [KPS]) and number of metastatic sites at metastatic BC diagnosis (p=0.231 and p=0.556, respectively).

As by definition, patients undergoing proactive imaging underwent a higher number of proactive (asymptomatic) brain CT scans per year during the observation period of the study (median 2.0 versus 0.0, p<0.001). Coherently, more patients in the proactive imaging group underwent brain imaging in absence of symptoms at time of first metastatic BC diagnosis as compared to patients not undergoing proactive imaging (65.5% vs 20%, p<0.001). In addition, although a numerically higher number of patients undergoing proactive imaging with CE brain CT scans also performed at least one brain MRI during the observation period of this study as compared to patients not undergoing proactive imaging (12.3% vs 4.0%, p=0.063), it should be highlighted that the use of brain MRI imaging in asymptomatic patients was extremely limited in both subgroups.

Among the 142 cases who did not present BMs at time of first metastatic diagnosis, 103 patients (72.5%) were still receiving trastuzumab-pertuzumab at the time of BM diagnosis or at the two-year cut-off (49 patients undergoing proactive brain imaging, 54 patients not undergoing proactive brain imaging), while 39 patients (27.5 %) had progressed.

Incidence of brain metastases

Overall, 30 (20.3%) patients developed BMs within the first two years from metastatic BC diagnosis, 21 in the group undergoing proactive brain imaging, 9 among patients not undergoing proactive brain imaging. Patients undergoing brain surveillance experienced an overall significantly higher cumulative incidence of BMs (Gray's p=0.004) at 24 months, with a 30.6% incidence compared to 12.3% among patients not undergoing brain screening (Figure 2A).

Among these 30 patients, 7 presented neurological symptoms at BM diagnosis, while 23 patients were diagnosed with BMs in the absence of neurological symptoms.

No patient was diagnosed with symptomatic BM within the first two years from metastatic BC diagnosis in the subgroup of patients undergoing proactive brain imaging. Coherently, patients undergoing proactive brain imaging experienced a significantly lower cumulative incidence of symptomatic brain metastases (Gray's p=0.012) at 24 months, with a cumulative incidence of 0% as compared to 9.5% in the subgroup of patients who did not undergo proactive brain imaging (Figure 2B).

On the other hand, a significantly higher cumulative incidence of asymptomatic brain metastases (Gray's p<0.001) was observed at 24 months in patients undergoing proactive brain imaging (30.6%) as compared to patients who did not undergo proactive brain imaging (2.7%, Figure 2C). Asymptomatic BMs were identified at time of first metastatic diagnosis in 6 (9.5%) of the 63 patients which underwent a CE brain CT scan as part of disease restaging procedures (6/48 classified as undergoing proactive brain imaging and 0/15 classified as not undergoing proactive brain imaging).Taking into account that patients undergoing proactive brain imaging were diagnosed more recently and this might have influenced access to novel HER2-targeted agents (e.g. trastuzumab deruxtecan and tucatinib) in later lines of treatment, we conducted a subgroup analysis only in patients diagnosed with metastatic BC between 2018 and 2021 (N=64, N=29 undergoing imaging and N=35 non undergoing imaging) to better isolate the effect of proactive brain imaging from the potential confounding influence of year of diagnosis. In this subgroup, proactive

imaging remained associated with a numerically higher cumulative incidence of BMs (cumulative incidence at 1-year: 18.7% vs 2.7%; cumulative incidence at 2-year: 30.3% vs 13.5%, p=0.131), a significantly higher incidence of asymptomatic BMs (cumulative incidence of asymptomatic BMs at 1-year: 19.0% vs 0.0%; cumulative incidence at 2-year: 31.2% vs 2.7%, p=0.002) and a numerically lower incidence of symptomatic BMs (cumulative incidence of symptomatic BMs at 1-year: 0.0% vs 2.7%; cumulative incidence at 2-year: 0.0% vs 10.8%, p=0.095). These findings are consistent with the results observed in the overall study cohort, although statistical power was limited by the small sample size.

Treatments and outcome after BM diagnosis

Clinical characteristics at BM diagnosis and first treatments received for brain progression are reported in Table 2.

Seven patients in the non-proactive screening group presented neurological symptoms at time of BM diagnosis: 3 patients presented with vertigo and gait instability, 1 patient with headache, 1 patient with speech impairment, 1 patient with cranial nerve deficit, and 1 patient with confusion and somnolence. Of these 7 patients, 2 (28.6%) experienced complete symptom resolution following treatment, 3 (42.9%) showed a partial improvement, and 2 (28.6%) did not show any improvement in neurological symptoms.

In addition to a significantly higher proportion of asymptomatic cases, patients who had undergone proactive brain imaging with CE brain CT scans during the observation period of the study also presented a significantly more conserved performance status at time of BM diagnosis, with 71.4% of them having a KPS of 90-100 (versus 11.1% in patients not undergoing proactive brain imaging) and only 1 patient (4.8%) having a KPS<70 (versus 55.6% in patients not undergoing proactive brain imaging) (p=0.002). Moreover, patients undergoing proactive brain imaging presented significantly smaller BMs at time of first diagnosis (median size of the largest BM 8 mm vs 25 mm, p=0.040) and a numerical trend toward a higher number of BMs was observed among patients who did not undergo brain screening (88.9% diagnosed with more than 3 BMs versus 52.4%, p=0.057).

No statistically significant differences in locoregional and systemic treatments (evaluated as change of systemic treatment versus continuation of the same systemic treatment) received after BM diagnosis were observed between the two subgroups. However, whole-brain radiotherapy (WBRT) was more frequently administered to patients who had not undergone proactive brain imaging, although the difference was not statistically significant (44.4% vs. 14.3%, p=0.073).

Regarding systemic treatment, six patients who were diagnosed with asymptomatic BMs through proactive imaging at time of first diagnosis of metastatic BC started treatment with trastuzumab-pertuzumab and taxanes after BM diagnosis. Among the remaining 24 patients, 20 were still receiving trastuzumab-pertuzumab (alone or with chemotherapy) when BMs were diagnosed, while four had transitioned to second-line treatment (T-DM1 in three patients, trastuzumab deruxtecan in one patient). After BM diagnosis, 14 patients with controlled extracranial disease did not modify their systemic therapy, and BMs were managed exclusively with locoregional treatment, with no differences in terms of change of systemic therapy between patients undergoing or not undergoing proactive brain imaging.

At a median follow-up from BM diagnosis of 26.4 months, 18 patients had died. Median OS from time of first BM diagnosis was numerically longer among patients who underwent

proactive brain imaging (28.6 months, 95%CI 15.3-36.5) compared to patients not undergoing proactive brain imaging (7.5 months, 95%CI 5.5-9.5, p=0.192; Figure 3).

Discussion

The higher incidence of BM in HER2+ disease and the growing availability of effective treatment options with relevant intracranial activity has increased interest in the potential use of surveillance brain imaging in neurologically asymptomatic patients with metastatic HER2+ BC. Acknowledging the significant clinical impact of BC-related BMs, the most recent European guidelines (EANO-ESMO) have started to consider the potential role of proactive brain screening for patients with HER2+ metastatic BC (9), while NCCN guideline currently only support the use of CE brain MRI in patients with suspicious CNS symptoms.(13)

In this context, our study retrospectively assessed the impact of brain screening using CE CT scans on incidence of BMs, and in particular symptomatic BMs, among patients newly diagnosed with HER2+ stage IV BC. In our study cohort, brain screening with CE CT scans was significantly associated with a significantly higher incidence of asymptomatic BMs and a lower incidence of symptomatic BMs. Notably, almost 10% of patients (8.2%, 6/73) undergoing baseline brain imaging were found to have asymptomatic BMs at first metastatic HER2+ BC diagnosis, highlighting the potential value of brain screening at first stage IV diagnosis. Indeed, in this study, a significant proportion of patients was diagnosed with asymptomatic BMs (mainly among patients undergoing brain screening), thus suggesting that a substantial fraction of patients diagnosed with HER2+ metastatic BC may harbor clinically silent BMs for a considerable portion of their metastatic disease course. This might potentially represent a window of therapeutic opportunity, as timely diagnosis and intervention might potentially delay or even prevent the onset of neurologically symptomatic and potentially debilitating brain involvement.

However, the implementation of proactive brain screening in asymptomatic patients with metastatic breast cancer remains controversial, with inconsistent recommendations throughout different guidelines, in the absence of clear evidence of overall survival benefit.

Nevertheless, in metastatic BC, quality of life and symptom control represent crucial clinical endpoints, even beyond OS benefit. Early detection of asymptomatic BMs might allow for earlier and less invasive treatment strategies, potentially reducing symptoms burden and maintaining quality of life and neurological functionality. Previous studies have reported that BC patients (not undergoing brain screening) were more likely to present with larger and more numerous BMs as compared to NSCLC patients (undergoing brain screening), with a higher risk of neurologic symptoms and leptomeningeal disease (LMD).(14) Although the retrospective nature of our study and the lack of quality of life data do not allow to strongly support this hypothesis, we interestingly observed significantly better KPS at time of BM diagnosis and smaller size of BMs in patients who underwent brain screening. Additionally, another key prognostic factor, BM number, also showed a trend favoring patients who underwent brain screening. Consistent with these findings, patients who did not undergo proactive brain imaging had a higher likelihood of receiving WBRT at BM diagnosis (44.4% vs. 14.3%), although this difference was not statistically significant. However, this last observation should be interpreted with caution, as screened patients were diagnosed more recently than not screened patients, thus coinciding with a more general shift from WBRT toward less toxic locoregional treatments such as stereotactic radiosurgery. Nevertheless, since lesion size is a key factor guiding local treatment decisions for BMs and toxicity of

stereotactic radiosurgery/radiotherapy increases with lesion size, our observations indirectly suggest that proactive brain imaging may be associated with less toxic local treatment options in HER2+ BC patients diagnosed with BMs. Nevertheless, these associations should be interpreted with caution given the exploratory nature of the analyses and the limited size of this subgroup.

The numerically longer median OS from BM diagnosis observed in patients who underwent proactive brain imaging (28.6 vs 7.5 months, p=0.192) should not be over-interpreted as evidence that proactive brain imaging might improve OS. This numerical difference may be easily explained by lead-time bias, as earlier detection of smaller or asymptomatic lesions inherently extends the interval between BM diagnosis and death without reflecting a true survival benefit. In addition, more recently diagnosed patients also potentially had broader access to new anti-HER2 targeted agents with intracranial activity, potentially further contributing to the apparent difference in OS. Therefore, the OS findings should be interpreted with caution and should not be directly attributed to the effect of proactive imaging.

With these significant limitations, the results of our study suggest that the use of proactive brain imaging for patients with metastatic HER2+ BC may beassociated with a reduction in symptomatic/emergency presentations and with a more preserved performance status, thus potentially ultimately resulting in better neurological and quality of life outcomes. Therefore, these results warrant confirmation in independent studies.

Indeed, up to date only a limited number of recent studies, all assessing the use of CE brain MRI, have demonstrated that proactive brain imaging can detect asymptomatic BMs in patients with stage IV BC. However, this evidence is limited to single-arm studies with small, heterogeneous patient cohorts, often including different BC subtypes and varying degrees of prior systemic therapy exposure.(15,16) Ongoing trials, including randomized studies, will help further define the role of brain surveillance in this setting (NCT04030507, NCT03881605).

While guidelines and existing literature primarily assess MRI as the gold standard for BM screening, its clinical applicability is limited by resource constraints, longer hospitalization times, and patient anxiety related to multiple scan procedures. From a patient perspective, CT scans may be better tolerated than MRIs due to their shorter duration, less confining design, and quieter environment, which might significantly reduce the stress associated with repeated imaging. Therefore, integrating brain CT imaging into routine CT-based disease re-evaluation could offer a more practical and cost-effective alternative, with a reduced impact on quality of life, on time spent in the hospital, and on potential adverse effect of contrast medium. Nevertheless, as studies directly comparing CE brain CT scan and CE brain MRI as screening techniques for asymptomatic BC-related BM are lacking, we cannot exclude that MRI might offer superior sensitivity or clinical benefit in this specific setting. For instance, in a prospective study including patients diagnosed with stage III NSCLC brain MRI was able to detect asymptomatic BMs in 5% of patients with a negative CE brain CT scan.(17) However, whether brain MRI presents higher sensitivity specifically for detecting asymptomatic breast cancer-related BM, and more importantly, whether increased sensitivity would translate into clinical benefit (such as an additional reduction in symptomatic BM), remains to be evaluated. In this context, identifying the optimal radiological surveillance technique and timing for screening asymptomatic BM in BC patients represents an important area for future research. Moreover, as a relevant critique to the implementation of proactive brain screening, even in high-risk patients, is that this might lead to unnecessary scan-related anxiety, studies assessing whether structured imaging protocols may help reduce

patient distress by offering timely interventions rather than waiting for symptom onset are warranted.(18)

This study has some limitations. First, its retrospective nature did not allow for complete data collection in certain patients. Second, differences in the year of BC diagnosis between the two groups, with screened patients being diagnosed more recently, may have influenced treatment strategies and outcomes. Third, the retrospectively nature of this study and the small size of some of the study groups warrant for a cautious interpretation of our results. Additionally, the definition of brain surveillance as at least one brain imaging per year in asymptomatic patients is arbitrary.

Nevertheless, our study also presents some notable strengths. It includes data from a relatively large and homogeneous cohort of patients all treated with first-line trastuzumab-pertuzumab, minimizing variability in systemic therapy exposure before BM diagnosis. Moreover, applying a two-year data cut-off helped reduce the potential impact of differing follow-up durations on BM detection and the potential impact of changes in standard second-line treatment over time (the large majority of patients were still receiving first-line pertuzumab-trastuzumab at time of BM diagnosis). Consistently, although interpretation is limited by the small sample size, the similar findings observed in the subgroup of patients diagnosed between 2018 and 2021 (treated within a narrower time window and who likely had comparable access to subsequent treatment options) further support that our results may be driven more by proactive brain imaging than by year of diagnosis. Finally, our study's real-world setting supports the feasibility of this surveillance strategy in clinical practice.

In conclusion, our study suggests that at least annual brain CT surveillance may be associated with a reduction in detection of symptomatic BMs in patients with stage IV HER2+ BC. This approach has a limited cost and is minimally invasive. Prospective trials are needed to define the optimal screening strategy, surveillance interval, and prognostic implications of proactive brain monitoring in advanced BC patients.

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Figure captions

Figure 1. Flow diagram of study cohort.

Figure 2. Cumulative incidence curves for diagnosis of brain metastases (A), diagnosis of symptomatic brain metastases (B), and diagnosis of asymptomatic brain metastases (C) according to brain screening practice.

Figure 3. Overall survival from brain metastasis diagnosis according to brain screening practice.

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Table 1. Clinicopathological characteristics at BC diagnosis and at metastatic BC diagnosis

	Proactive brain imaging N=73 (%)	No proactive brain imaging N=75 (%)	p-value
Median follow-up from BC diagnosis (years, 95%CI)	6.0 (4.5-7.5)	9.0 (6.8-11.2)	**0.009**
Median age at BC diagnosis (range)	54 (27-82)	54 (19-79)	0.564
Age at BC diagnosis			
≤50 years	32 (43.8)	28 (37.3)	0.421
>50 years	41 (56.2)	47 (62.7)	
Tumor histology			
No special type	62 (84.9)	65 (86.7)	
Lobular	10 (13.7)	8 (10.7)	0.867
Other	1 (1.4)	1 (1.3)	
Not available	0 (0)	1 (1.3)	
Tumor grade			
G1	0 (0)	3 (4.0)	
G2	16 (21.9)	13 (17.3)	0.190
G3	54 (74.0)	56 (74.7)	
Not available	3 (4.1)	3 (4.0)	
Hormone receptor status			
Positive	49 (67.1)	54 (72.0)	0.519
Negative	24 (32.9)	21 (28.0)	
Stage at BC diagnosis			
I-III	29 (40.3)	31 (41.3)	0.896
IV	43 (59.7)	44 (58.7)	
Year of mBC diagnosis			
2014-2017	9 (12.3)	33 (44.0)	**<0.001**
2018-2021	29 (39.7)	35 (46.7)	
2022-2024	35 (48.0)	7 (9.3)	
Median follow-up from mBC diagnosis (years, 95%CI)	3.0 (2.7-3.4)	5.9 (5.3-6.4)	**<0.001**
Median age at mBC diagnosis (range)	56 (28-82)	57 (19-79)	0.468
Age at mBC diagnosis			
≤50 years	27 (37.0)	24 (32.0)	0.523
>50 years	46 (63.0)	51 (68.0)	
KPS at mBC diagnosis			
90-100	48 (65.8)	50 (66.7)	
70-80	18 (24.7)	21 (28.0)	0.231
<70	5 (6.8)	1 (1.3)	
NA	2 (2.7)	3 (4.0)	
N of metastatic organs at mBC diagnosis			
1	28 (38.4)	33 (44.0)	0.556
2	25 (34.2)	27 (36.0)	
≥3	20 (27.4)	15 (20.0)	
Median N of proactive brain CT scans per year (IQR)*	2.0 (1.2-2.5)	0.0 (0.0-0.5)	**<0.001**

Brain imaging at initial mBC diagnosis			**<0.001**
Yes	48 (65.8)	15 (20.0)	
No	25 (34.2)	60 (80.0)	
At least one brain MRI during the observation period*			0.063
Yes	9 (12.3)	3 (4.0)	
No	64 (87.7)	72 (96.0)	

Abbreviations: BC breast cancer, KPS Karnofsky Performance Status, MRI magnetic resonance imaging

* During the observation period of the study (from metastatic BC diagnosis to two years from diagnosis or until BM diagnosis, death or last follow-up, whichever occurred first) in the absence of neurological symptoms. Patients with brain metastases at baseline (N=6) were excluded from this analysis

Table 2. Clinical characteristics at BM diagnosis and first treatments received (locoregional and systemic) after BM diagnosis

	Brain screening N=21 (%)	No brain screening N=9 (%)	p-value
Neurological symptoms			
Yes	0 (0)	7 (77.8)	**<0.001**
No	100 (100)	2 (22.2)	
KPS			
90-100	15 (71.4)	1 (11.1)	**0.002**
70-80	5 (23.8)	3 (33.3)	
<70	1 (4.8)	5 (55.6)	
Median number of BM (range)	5 (1-26)	9 (1-50)	0.164
Number of BMs			
1-3	10 (47.6)	1 (11.1)	0.057
>3	11 (52.4)	8 (88.9)	
Median size of largest BM in mm (range)	8 (4-16)	25 (5-31)	**0.040**
Extracranial status			
CR/PR/SD	12 (80.0)*	8 (88.9)	0.571
PD	3 (20.0)*	1 (11.1)	
First treatment after BM diagnosis			
No treatment	0 (0)	1 (11.1)	0.105
Locoregional treatment	8 (38.1)	6 (66.7)	
Locoregional treatment + change in systemic therapy[§]	2 (9.5)	1 (11.1)	
Change in systemic therapy[§]	11 (52.4)	1 (11.1)	
Neurosurgery			
No	21 (100)	9 (100)	1.000
WBRT			
Yes	3 (14.3)	4 (44.4)	0.073
No	18 (85.7)	5 (55.6)	
SRS			
Yes	7 (33.3)	3 (33.3)	1.000
No	14 (66.7)	6 (66.7)	
Change in systemic therapy			
Yes	7 (46.7)*	2 (22.2)	0.231
No	8 (53.3)*	7 (77.8)	

Abbreviations: KPS Karnofsky Performance Status, BM brain metastasis, CR complete response, PR partial response, SD stable disease, PD progressive disease, WBRT whole brain radiotherapy, SRS stereotactic radiotherapy

*excluding 6 patients with asymptomatic BMs diagnosed during disease staging at time of first metastatic BC diagnosis and who started first-line trastuzumab-pertuzumab plus taxane

[§]including start of first-line treated with trastuzumab-pertuzumab plus taxane in patients with asymptomatic BMs diagnosed during disease staging at time of first metastatic BC diagnosis

Figure 1

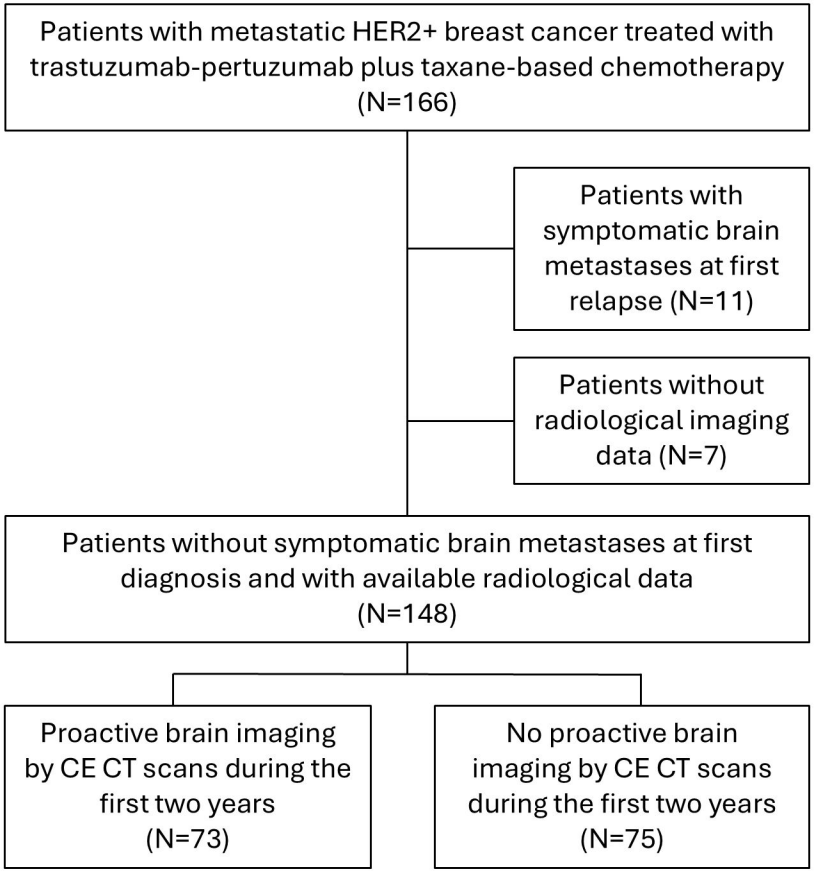

Figure 2

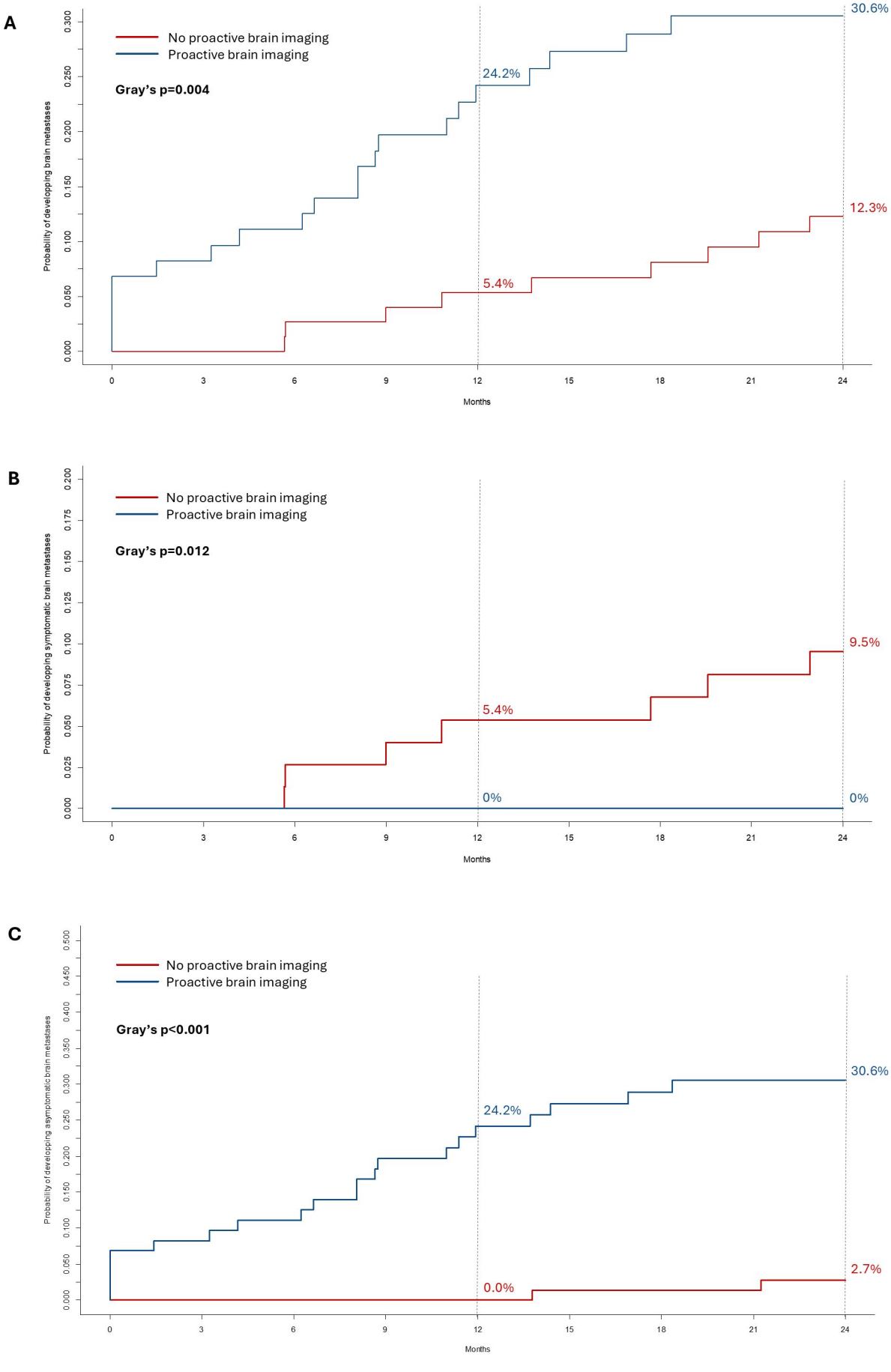

Figure 3