Brain Imaging Surveillance for Patients With Metastatic Breast Cancer: A Randomized Clinical Trial Is Required to Guide Practice

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DOI https://doi.org/10.1200/JCO-25-00356

Accepted July 1, 2025
Published August 13, 2025

J Clin Oncol 00:1-4

The topic of brain imaging surveillance among patients with metastatic breast cancer (MBC) has been a matter of debate over the past two decades, without the benefit of high-quality clinical evidence to provide resolution. Accordingly, international guidelines provide conflicting recommendations. For example, as summarized in Table 1, the advanced breast cancer (ABC) guidelines version 6 and 7[1] and current National Comprehensive Cancer Network Breast Cancer guidelines[2] do not recommend surveillance to detect asymptomatic brain metastases, whereas the European Society of Medical Oncology (ESMO) guidelines indicate that subtype-oriented surveillance may be considered for certain subtypes based on a high incidence of brain metastases among patients with human epidermal growth factor receptor 2–positive (HER2+) and triple-negative breast cancer (TNBC),[3] and the ASCO guidelines indicate that screening can be considered based on shared decision making with patients.[4]

Among patients with metastatic lung cancer and melanoma, for whom the lifetime incidence of brain metastases is up to 40% and 80%, respectively, brain imaging surveillance has been adopted into clinical practice guidelines in the absence of randomized clinical trial data. Among patients with metastatic HER2+ or TNBC, 33%-50% will develop brain metastases during their lifetime[5]; this is much higher than the approximately 15% lifetime risk of brain metastases generally reported for patients with hormone receptor–positive (HR+)/HER2-negative MBC.[5] The question remains—is a high incidence of brain metastases on its own enough to warrant a generalized brain metastasis surveillance program for patients with MBC, or would one first need to demonstrate net clinical benefit from this practice?

In the past, there was little rationale for considering brain imaging surveillance for patients with MBC because toxicities associated with available local therapies, including surgical resection and/or whole-brain radiotherapy (WBRT), were not felt to justify the possible benefit. Furthermore, brain metastases were felt to presage death, and therefore, earlier detection and treatment would not affect prognosis and only increase patient anxiety and suffering. However, in the era of focal treatment with stereotactic radiosurgery (SRS) and a growing repertoire of CNS-active systemic therapies, the balance between risk versus benefit of surveillance might have changed.[6] It is logical to hypothesize that early detection and intervention for asymptomatic brain metastases may be advantageous if modern well-tolerated SRS procedures and/or CNS-penetrant systemic therapies could prevent the development of potentially debilitating and often irreversible neurologic symptoms associated with progression. Indeed, in a retrospective cohort study of patients with breast cancer and non–small cell lung cancer (NSCLC) diagnosed with brain metastases between January 2000 and December 2015, those with MBC (n = 349) who did not typically undergo brain imaging surveillance had larger and more numerous brain metastases than patients (n = 659) with NSCLC (who did typically undergo brain imaging surveillance).[7] Patients with MBC and brain metastases were also more likely to have neurologic symptoms (75.9% *v* 60.5%; $P < .001$) than those with NSCLC.[7] Importantly, neurologic death rates were higher among patients with MBC (37.3% *v* 19.9%, $P < .001$) with the caveat of similar overall survival rates (1.45 *v* 1.09 years, respectively, $P = .06$).[7]

These data support the potential for early diagnosis of brain metastases to positively affect quality of life, especially with the advent of CNS-active agents that not only delay progression of existing metastases but also reduce the incidence of new metastases.[8] These agents may even avoid or at least delay the need for local CNS therapies, particularly for patients with HER2+

TABLE 1. International Guidelines Regarding Screening for Asymptomatic Brain Metastases

Guideline (year)	Recommendation	Rationale
ASCO (2022)	Clinicians and patients may discuss options using shared decision-making processes	Insufficient data to recommend for or against performing routine surveillance with brain MRI. The Expert Panel encourages patients to enroll in clinical trials to expand knowledge regarding MRI surveillance
ESMO (2021)	Subtype-oriented screening may be considered	High incidence of brain metastases among patients with HER2+ and triple-negative breast cancer
NCCN (2024)	Not recommended	Brain MRI with contrast only indicated for suspicious central nervous system symptoms
ABC version 6 and 7 (2024)	Not recommended	Lack of high-quality data (trials are ongoing)

Abbreviations: ABC, advanced breast cancer; ESMO, European Society for Medical Oncology; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network.

disease, as has recently been reflected upon in the current ESMO guidelines.[3] These agents include small-molecule tyrosine kinase inhibitors and antibody drug conjugates that have been studied in several important practice-changing trials. For example, the HER2CLIMB clinical trial randomly assigned patients with metastatic HER2+ disease to the combination of trastuzumab and capecitabine plus either tucatinib or placebo. Among the 174 patients who had active/previously untreated disease in the brain, 40% of the patients in the tucatinib arm remained progression-free after 1 year compared with 0% of those in the placebo arm.[8] Trastuzumab deruxtecan (T-DXd) has also demonstrated impressive intracranial activity in several clinical trials; most recently, in the DESTINY-Breast12 trial, intracranial response rates up to 82.6% were observed among patients with active and previously untreated CNS metastases.[9] This is in addition to the previously reported intracranial activity of T-DXd in the TUXEDO and DEBBRAH trials and a pooled analysis of patients with brain metastases from the DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03 trials.[10] While these CNS-active agents have significantly extended the survival of patients with HER2+ brain metastases, unfortunately, patients with HER2-negative brain metastases have continued to have a poor prognosis with real-world overall survival estimates ranging from 2.6 to 3.7 months for those with TNBC and 4.8 to 5.3 months for those with HR+/HER2-negative disease.[11,12] However, the landscape is changing in this population with CNS-active agents, such as T-DXd, demonstrating significant activity even in patients with HER2-low disease that would have otherwise been considered HER2-negative.[13] Patritumab deruxtecan showed impressive intracranial activity among patients with MBC irrespective of subtype in the TUXEDO-3 trial,[14] whereas the intracranial activity of trophoblast cell-surface antigen 2–directed agents, such as sacituzumab govitecan and datopotamab deruxtecan, is currently being evaluated in several nonrandomized clinical trials (eg, ClinicalTrials.gov identifiers: NCT03995706, NCT04484142).

There is general agreement that the value of a proposed new screening or surveillance intervention must be demonstrated, ideally in a randomized controlled trial (RCT), before its routine adoption in a health care system, to ensure that the probability of benefit exceeds the potential harms and costs and that limited resources are used wisely.[15] The optimal measure needed to determine the efficacy of CNS surveillance for patients with MBC is debatable. While a purist might insist on an improvement in overall survival, many patients and practitioners would argue that quality of life, cognition, and functional abilities (eg, outcome measures such as quality-adjusted time without symptoms of disease or toxicity) are just as important (if not *more* important) as longevity. Not only has brain imaging surveillance never been studied in a RCT, but there is also no direct evidence demonstrating that it leads to better quality of life, neurologic outcomes, or longer survival. Meanwhile, the potential downsides of brain imaging surveillance must be strongly considered: false positives or detection of incidental findings needing further workup; diagnosis of asymptomatic and quiescent brain metastases resulting in overtreatment; premature discontinuation of an active systemic therapy; patient anxiety about the possibility of brain metastases that have not yet/will never develop; exclusion from clinical trials; and, of course, costs to health care systems and patients.

Overtreatment would result if a patient's brain metastases would have remained asymptomatic until, or soon before, death from extracranial disease. In this case, the patient might experience adverse effects from treatment (surgical resection, WBRT, and/or SRS) but no benefit. The potential risks associated with a craniotomy are obvious to most physicians and patients. Data from the study by Brown et al demonstrated that WBRT (even with hippocampal sparing and use of the neuroprotective agent memantine) results in a substantial and progressive cognitive decline in a significant proportion of patients,[16] and although SRS is a safer and better tolerated focal alternative to WBRT, its use is not completely benign because of the potential for symptomatic radiation necrosis.[17] The risk of symptomatic radiation necrosis is a significant issue (typically occurs in approximately 5% of treated lesions) as technological advances are allowing for multiple metastases to be treated and, as a result, the burden of diagnosing and managing radiation necrosis will

increase.[18] Although the use of bevacizumab represents a major positive shift in the medical management of radiation necrosis, as outlined in practice guidelines from the International Stereotactic Radiosurgery Society, this agent can cause hemorrhage, perforation, and thromboses and, moreover, can interfere with the cadence of breast cancer–specific therapies.[19]

The exciting developments in CNS-active systemic therapy are also causing new challenges with respect to treatment sequencing. For patients with screen-detected brain metastases who lack or have good control of extracranial disease, a line of systemic therapy might be switched prematurely to one with greater CNS activity. This may harm patients by subjecting them prematurely to a regimen with more toxicity (eg, the not insignificant risk of pneumonitis with T-DXd) and a negative impact on otherwise controlled extracranial disease. This is why many oncologists still first consider local therapy (predominantly with SRS) upon the development of brain metastases, while reserving a switch in systemic therapy until a more appropriate downstream oncologic event is observed, especially for those patients with stable extracranial disease. Ultimately, the unprecedented array of options for managing patients with MBC and brain metastases increases the importance of multidisciplinary case discussions that incorporate CNS-specific radiation oncologists, neuro-oncologists, and oncologic neurosurgeons to assist in providing patient-specific recommendations.

One of the greatest sources of hesitation regarding surveillance imaging for any disease is the fear of inducing anxiety among patients (scanxiety). A survey of 545 patients residing in Europe revealed that 85.3% would be open to surveillance for brain metastases, even in the absence of definitive evidence to support this practice[20]; however, this positive position in support of surveillance needs to be taken into context as the survey represents a hypothetical exercise and respondents did not actually undergo magnetic resonance imaging (MRI).

Another very real concern about surveillance for brain metastases is exclusion from clinical trials. Fortunately, there is an increasing shift in trial methodology to allow for patients with active and/or treated brain metastases to be included in clinical trials.[21] This has been supported by the Friends of ASCO and the US Federal Drug Administration and has resulted in an acceleration of the development and testing of novel systemic therapies with CNS activity.

The impact of adopting a new surveillance intervention on health care systems needs to be considered through a local and global lens. There are many regions, particularly middle- and low-income countries, in which such an intervention would not be affordable. Before introducing yet another global disparity in the management of MBC, not only do randomized trials need to be performed, but also cost-benefit analyses should be embedded in the trial design. The financial burden of routine brain metastasis surveillance would be significant even for wealthy countries. For example, in Canada, approximately 30,000 Canadian women were diagnosed with breast cancer in 2024, 5% of whom (n = 1,500) had metastatic disease. Assuming a 4-year survival (weighted average across subtypes) and biannual MRI-based screening, this translates into 12,000 brain MRIs ($18,000,000 in Canadian dollars [CAD] at $1,500 [CAD] per MRI), not accounting for additional imaging to follow-up on incidental findings and treatment of confirmed brain metastases. From a technical perspective, costs may be reduced by introducing an MRI scan without the traditional exhaustive set of sequences that would diagnose malignant and nonmalignant conditions. The drawbacks of short metastasis-specific protocols include a potential legal risk associated with missing pathology and patients being called back for further scanning to establish accurate diagnoses. Therefore, the optimal set of sequences for a more tailored screening MRI program remains an area for health economic research and consensus development and where appropriate patient consent is needed if not on trial.

One common question that arises in the debate of the merits of initiating screening is patient selection, and whether it should be driven by molecular markers alone. Although the majority of clinical evidence and drug development for breast cancer brain metastases have focused on HER2+ disease, a recent phase II single-arm trial demonstrated a high incidence of asymptomatic brain metastases not only among patients with HER2+ (24%) and TNBC (25%) but also in patients with HR+/HER2− (23%) MBC whose disease progressed on first-line endocrine therapy.[22] These data confirm a substantially high risk of brain metastases across breast cancer subtypes and support the need for a definitive RCT, which includes HER2-negative breast cancer subtypes. The feasibility of a large RCT of MRI-based surveillance for detection of asymptomatic brain metastases has recently been investigated in a multicenter pilot study of patients with HER2+ or triple-negative MBC (ClinicalTrials.gov identifier: NCT06247449). Based on a priori criteria, a large multicenter RCT is likely feasible as 42% of eligible patients agreed to be randomly assigned and over 50% completed the study.[23] However, a high rate of brain imaging among patients in the control arm of the study was noted outside of the 12-month trial period.[23] As a high crossover rate from the control arm would compromise the ability of any future definitive randomized trial to evaluate the efficacy of surveillance, efforts would be needed to minimize crossover, such as excluding centers where some practitioners already consider surveillance to be the standard of care. In addition, given that the treatment landscape for patients with HER2+ MBC has changed since SYMPToM was initially designed, we recognize that research questions and control arms of future studies may need to differ for HER2+ and HER2-negative MBC populations. There are several ongoing single-arm phase II trials (eg, ClinicalTrials.gov identifiers: NCT04030507, NCT05130840, NCT00398437) of brain imaging surveillance for patients with breast cancer which incorporate brain MRIs at baseline and at variable time points thereafter. To the best of our knowledge, HER2-CNS SURVEILLANCE is the only

ongoing study examining the feasibility of a randomized trial of brain MRI surveillance, which will add to data generated in the abovementioned recently completed SYMPToM trial (ClinicalTrials.gov identifier: NCT03881605). Until additional data are available, a careful review of the potential risks and benefits should be an integral component of any patient discussion regarding surveillance for asymptomatic brain metastases.

In conclusion, the issue of brain imaging surveillance for patients with MBC has not been adequately addressed. It is our position that we can do better and we must do better than the present data-free state. Only by conducting appropriately designed RCTs that account for breast cancer subtype and integrate economic analyses, can we adequately inform clinical practice and evidence-based international guidelines.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-00356.

AUTHOR CONTRIBUTIONS

Administrative support: Arjun Sahgal
Provision of study materials or patients: Arjun Sahgal
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Honoraria: Roche, Novartis, Apobiologix, Pfizer, Eisai, AstraZeneca, Knight Therapeutics, Lilly, Amgen, Myriad Genetics, Seagen, Gilead Sciences, Merck, Daiichi Sankyo/AstraZeneca, Exact Sciences, Viatris
Consulting or Advisory Role: Roche, Novartis, Pfizer, Apobiologix, Genomic Health, Eisai, Lilly, AstraZeneca, Knight Therapeutics, Amgen, Merck, Myriad Genetics, Seagen, Gilead Sciences, Daiichi Sankyo, Viatris
Research Funding: Lilly, AstraZeneca, Seagen
Patents, Royalties, Other Intellectual Property: I am the lead inventor on a patent for the use of dronedarone and its structural derivatives as cancer therapies
Travel, Accommodations, Expenses: Agendia, AstraZeneca/Daiichi Sankyo
Other Relationship: Viatris

Jonathan P.S. Knisely
This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.
Open Payments Link: https://openpaymentsdata.cms.gov/physician/10706

Arjun Sahgal
Leadership: ISRS
Honoraria: BrainLAB, Elekta, AstraZeneca, Seagen, Cerapedics, CarboFix Orthopedics, SERVIER, Varian Medical Systems
Consulting or Advisory Role: BrainLAB, Elekta
Research Funding: Elekta (Inst), Seagen (Inst), BrainLab
Patents, Royalties, Other Intellectual Property: Clustering software for Gamma Knife treatment planning (Inst), System for Automated and Quantitative Assessments of Metastatic Spinal Stability (Inst)
Travel, Accommodations, Expenses: Elekta, BrainLAB, Cerapedics, Inc

No other potential conflicts of interest were reported.