Original Study

Incidence of Brain Metastases in Women Treated With Neoadjuvant Chemotherapy for Breast Cancer: Implications for Screening

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Abstract

Early detection of brain metastases (BM) may prevent patients from undergoing invasive and morbid treatments. Outcomes of 485 patients with breast cancer were analyzed to inform brain MRI screening for high-risk patients. Patients with breast cancer under age 40 and with lung metastases were found to have increased likelihood of BM and may benefit from screening.

Purpose: Patients with metastatic breast cancer may develop brain metastases. Our study identified high-risk patients to refine selection criteria for BM screening approaches.**Patients:** We reviewed breast cancer patients treated with neoadjuvant chemotherapy (NAC) at a single university center between 2005 and 2019. **Methods:** Competing risks analysis was performed with the Fine and Gray model to analyze the cumulative incidence of BM and loco-regional recurrence. Overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan-Meier and log-rank tests. Multivariable analysis was performed with Cox proportional hazards regression to identify factors predictive for development of BM. Statistical significance was determined as a 2-sided P value of $<.05$. **Results:** In total, 112 patients experienced distant failure (DF) and 49 patients developed BM. Twenty patients with BM (41%) presented with symptoms requiring craniotomy +/- whole brain radiation treatment. Patients with BM were significantly more likely to have local ($P < .01$) and regional ($P < .01$) failure. On multivariable analysis, age <40 years ($P = .011$), presence of lung metastases ($P < .0001$), and residual nodal disease with >4 lymph nodes positive after NAC ($P = .024$) all predicted for increased likelihood of BM. Patients with these criteria had higher likelihoods of having BM ($P = .013$) and worse PFS ($P = .044$). On multivariable analysis for OS, presence of lung metastases was the most significant predictor of poor outcome ($P < .0001$). **Conclusion:** We propose a study of screening brain MRI for young (<40 years) patients with breast cancer receiving NAC and patients who develop metastatic disease post-NAC, especially those with lung involvement.

Clinical Breast Cancer, Vol. , No.xxx, 1–6
Keywords: Age > 40 years, Craniotomy, Radiosurgery, Whole brain radiation, MRI

Introduction

Metastatic breast cancer is the second most common cause of brain metastases (BM) after lung cancer.[1,2] In patients with metastatic breast cancer, approximately 30%-50% of patients will develop BM with a median time of ~2-3 years after initial diagnosis.[1] No formal guidelines exist for obtaining a screening brain MRI in patients with breast cancer who are asymptomatic, despite many prior studies identifying breast cancer populations that are at particularly high risk of intracranial relapse.[3-6] Clinicopathologic variables that have been associated with a high risk of breast cancer BM include young age, large tumor size, lymph node metastases, no pCR after neoadjuvant chemotherapy (NAC), and HER2-positive or triple-negative subtype.[7-11]

Clinically, patients with breast cancer are more likely to present with symptomatic BM, which frequently requires hospitalization, whole brain radiation treatment (WBRT), and sometimes, craniotomy.[12] Our study aimed to identify predictors of BM in a breast cancer population treated with NAC. These predictors were used to generate a high-risk cohort whose outcomes were evaluated to propose a selective screening approach for BM. Such an approach would identify BM earlier with the goal of avoiding hospitalization, craniotomy, and WBRT, while facilitating the use of radiosurgery, which has less untoward neurologic side effects.

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Submitted: Jun 29, 2022; Accepted: Aug 8, 2022

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1526-8209/$ - see front matter
https://doi.org/10.1016/j.clbc.2022.08.002

Please cite this article as: Margaret M Kozak et al, Incidence of Brain Metastases in Women Treated With Neoadjuvant Chemotherapy for Breast Cancer: Implications for Screening, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2022.08.002

Materials and Methods

We retrospectively reviewed records of 485 women treated with NAC at a single university center between January 2005 and June 2019. All patients received anthracycline-based chemotherapy and HER2-targeted therapy if appropriate. For estrogen receptor-positive (ER+) tumors, patients received adjuvant endocrine therapy. Clinicopathologic characteristics were recorded for each patient including dates of diagnosis, chemotherapy, surgery, and radiation treatment (RT).

Timing and location of local, regional, and distant metastases were recorded for each patient. Sites of local failure (LF) included chest wall and in breast failure. Sites of regional failure (RF) included axillary, supraclavicular and/or internal mammary lymph nodes. Sites of distant failure included bone, brain, liver, lung, mediastinum, and/or soft tissue. Time to disease relapse was calculated from time of initial diagnosis. First site(s) of distant failure (DF1) as well as subsequent sites of distant failure (DF2) were recorded for each patient. Time to development of BM was recorded separately.

Competing risks analysis was performed using the Fine and Gray model to analyze the cumulative incidence of BM development and distant failure at various sites. Overall survival and progression-free survival were calculated using Kaplan-Meier and log-rank tests. Multivariable analysis was performed with Cox proportional hazards regression to identify predictive factors for development of BM. Statistical significance was determined as a 2-sided P value of $<.05$.

Results

Characteristics of Patient Population

A total of 485 women treated with NAC for breast cancer were included in this analysis. The median time of follow-up was 56 months (range: 6-175 months). Clinicopathologic characteristics are listed in Table 1 .

The median overall survival (OS) was not reached. Thirty-three patients were lost to follow-up. Five-year OS was 82%, and 10-year OS was 69% for the cohort. In total, 131 (27%) patients experienced recurrent disease, with 40 local, 53 regional, and 112 distant failures. There were 24 (21%) patients discovered to have brain metastases at the time of initial metastatic breast cancer workup, of which 8 had BM as their only site of initial metastatic disease. Ultimately, a total of 49 (46%) patients with metastatic disease developed BM at a median time of 7.5 months (range: 0-83 months) from the time of diagnosis of DF, which represents 10.1% of the entire cohort.

Imaging for the Detection of Brain Metastases

Of the 112 patients with DF, 82 received at least one brain MRI due to symptoms concerning for BM or a new diagnosis of metastatic disease. On detailed review, primary reasons provided by referring physicians for ordering a brain MRI were: 1) symptoms, including headache, ataxia, nausea, seizures, and/or weakness (n = 49; 21 found to have BM), 2) new diagnosis of metastatic disease (n = 20; 3 found to have BM), and 3) positive head CT performed in the Emergency Department for emergent neurologic symptoms requiring further investigation (n = 10; all confirmed to have BM).

Of the 22 patients with persistent symptoms despite a negative initial brain MRI, 12 were found to have brain metastases on their second MRI. For the 6 patients who received a second brain MRI as part of a metastatic workup, 2 had imaging findings of BM. New neurologic symptoms were the most common reason for repeat brain MRI, primarily headaches (n = 17). Five patients presented with changes in vision, 4 with persistent nausea/vomiting, 1 with altered mental status, and 1 following a syncopal episode. All 3 patients who underwent a second brain MRI due to concerning CT findings were found to have BM.

Initial Treatment of Brain Metastases

We evaluated initial management of the 49 patients with BM. A total of 25 patients had 5 or fewer BM, 7 patients had 5-10 BM, and the remainder had >10 at initial brain metastases diagnosis. Five patients were found to have "innumerable" BM. Of the 49 patients who had BM confirmed on MRI, 20 (40%) underwent craniotomy and 29 (58%) received WBRT. Of the 20 patients who received a craniotomy, the average size of BM was 29.8 mm (missing data for 4 patients). Eight patients required both craniotomy and WBRT. One patient was scheduled for WBRT but passed away before treatment could begin. Six patients (12%) had such extensive intracranial metastatic disease that physicians determined that craniotomy and/or WBRT would not have significant long-term benefit.

Clinical Factors Predicting for Brain Metastases

When evaluating for differences between patients who developed BM and those who did not in the cohort (n = 485), we found on univariable analysis that age <40 years (P = .002), cN stage (P = .03), breast conservation (P = .02), final pathologic stage (P = .04), total number of positive lymph nodes (P = .03), and presence of LVSI (P = .006) were associated with subsequent development of BM (Table 1). Breast cancer subtype (P = .27), tumor grade (P = .26), cT stage (P = .11), and adjuvant RT (P = .45) were not significantly different between patients who did or did not have BM. We found that women were at a higher risk of developing BM if they had LF or RF. Twenty percent of women with brain metastases had experienced LF versus only 7% of women without BM (P = .001). Similarly, 30% of women with BM had RF compared to only 9% of women without BM (P < .001).

The cumulative incidence of BM was 10% at 5 years for all patients and was 3.6%, 10%, and 13% for patients who had pCR, ypT+ypN0, and ypT+ypN+ disease, respectively (P = .05, Table 2). Patients diagnosed under age 40 had a 5-year cumulative incidence of developing BM of 17% versus 7% for patients ≥40 years (P = .01). Those with LVSI had an 18% chance of developing BM compared to 7% for patients without LVSI (P = .02). Notably, patients with lung metastases had a nearly 50% cumulative incidence of BM at 5 years compared to only 5% for patients without lung metastases (P < .0001, Figure 1).

For patients with metastatic disease (n = 112), patients with HER2+, triple negative, and luminal B breast cancer subtypes were more likely to have BM (57%, 42%, and 39%, respectively) compared to 11% of patients with luminal A subtype, though this did not reach statistical significance (P = .13).

Please cite this article as: Margaret M Kozak et al, Incidence of Brain Metastases in Women Treated With Neoadjuvant Chemotherapy for Breast Cancer: Implications for Screening, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2022.08.002

Table 1 Clinical Characteristics of Patients who did Versus did not Develop Brain Metastases (BM) Following Neoadjuvant Chemotherapy (NAC) for Breast Cancer

Variable	No Brain Metastases	Brain Metastases	*P*-value
Age at diagnosis			.002
<40 y (n = 111, %)	91 (82.0)	20 (18.0)	
≥40 y (n = 373, %)	344 (92.2)	29 (7.8)	
Unknown	1	0	
Breast cancer subtype			.272
Luminal A (n = 50, %)	49 (98.0)	1 (2.0)	
Luminal B (n = 113, %)	103 (91.2)	10 (8.8)	
ER/PR+ HER2+ (n = 75, %)	68 (90.7)	7 (9.3)	
ER/PR- HER2+ (n = 73, %)	63 (86.3)	10 (13.7)	
Triple negative (n = 163, %)	145 (89.0)	18 (11.0)	
Unknown	8	3	
Tumor grade on biopsy			.256
Grade 1 (n = 26, %)	25 (96.1)	1 (3.9)	
Grade 2 (n = 151, %)	131 (86.8)	20 (13.2)	
Grade 3 (n = 283, %)	256 (90.5)	27 (9.5)	
Unknown	24	1	
Clinical T stage			.109
cT1 (n = 54, %)	50 (92.6)	4 (7.4)	
cT2 (n = 276, %)	254 (92.0)	22 (8.0)	
cT3 (n = 110, %)	93 (84.5)	17 (15.5)	
cT4 (n = 42, %)	36 (85.7)	6 (14.3)	
Unknown	3	0	
Clinical N stage			.032
cN0 (n = 201, %)	187 (93.0)	14 (7.0)	
cN1 (n = 202, %)	179 (88.6)	23 (11.4)	
cN2 (n = 50, %)	45 (90.0)	5 (10.0)	
cN3 (n = 29, %)	22 (75.9)	7 (24.1)	
Unknown	3	0	
Type of breast surgery			.020
Mastectomy (n = 245, %)	228 (93.1)	17 (6.9)	
Lumpectomy (n = 240, %)	208 (86.7)	32 (13.3)	
Final pathologic T stage (ypT)			.024
ypT0 (n = 153, %)	146 (95.2)	7 (4.58)	
ypT1 (n = 180, %)	162 (90.0)	18 (10.0)	
ypT2 (n = 94, %)	81 (86.2)	13 (13.8)	
ypT3 (n = 46, %)	37 (80.4)	9 (19.6)	
ypT4 (n = 9, %)	8 (88.9)	1 (11.1)	
Final pathologic N stage (ypN)			.146
ypN0 (n = 309, %)	283 (91.6)	26 (8.4)	
ypN1 (n = 109, %)	96 (88.1)	13 (11.9)	
ypN2 (n = 49, %)	80 (81.6)	9 (18.4)	
ypN3 (n = 17, %)	16 (94.1)	1 (5.9)	
Final pathologic classification			.041
pCR (ypT0/Tis ypN0) (n = 121, %)	116 (95.9)	5 (4.1)	
ypT+ ypN0 (n = 188, %)	167 (88.8)	21 (11.2)	
ypN+ (n = 172, %)	150 (87.2)	22 (12.8)	
Unknown	3	1	
Lymphovascular invasion			.006
No (n = 356, %)	328 (92.1)	28 (7.9)	
Yes (n = 99, %)	82 (82.8)	17 (17.2)	
Unknown	26	4	
Adjuvant RT			.452
Yes (n = 405, %)	362 (89.4)	43 (10.1)	
No (n = 77, %)	71 (92.2)	6 (7.8)	
Unknown	3	0	

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Table 1 (*continued*)

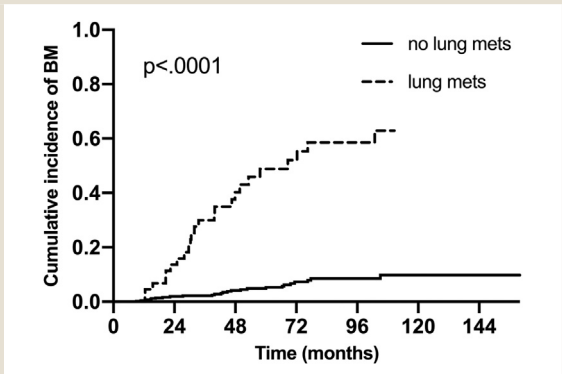
Variable	No Brain Metastases	Brain Metastases	*P*-value
Local recurrence (LR)			.001
Yes (n = 0, %)	30 (75.0)	10 (25.0)	
No (n = 445, %)	406 (91.2)	39 (8.8)	
Regional recurrence (RR)			<.001
Yes (n = 53, %)	38 (71.7)	15 (28.3)	
No (n = 432, %)	398 (92.1)	34 (7.9)	

Table 2 Cumulative Incidence of Brain Metastases (BM) by Different Clinicopathologic Variables for all Patients (n = 485)

Variable	5-y Cumulative Incidence	*P*-value
Age at diagnosis		**.01**
<40 y	17.5%	
≥40 y	7.4%	
NAC response		**.05**
pCR	3.6%	
ypT+ypN0	10.5%	
ypT+ypN+	13.9%	
HER2 status		.24
Positive	8.8%	
Negative	11%	
ER status		.13
Positive	6.1%	
Negative	13%	
LVSI		**.02**
Yes	17.7%	
No	7.1%	
Lung metastaes		**<.0001**
Yes	48.8%	
No	4.8%	

Abbreviations: NAC = neoadjuvant chemotherapy; pCR = pathologic complete response; ER = estrogen receptor; LVSI = lymphovascular space invasion.

Figure 1 Patients with lung metastases had a nearly 50% cumulative incidence of brain metastases at 5 years compared to only 5% for patients without lung metastases (*P* < .0001).



There were 8 patients who developed BM as their first and only site of DM. Table 3 lists their clinical characteristics, treatment of BM, and outcomes. All presented with neurologic symptoms and most (5 of 8) had HER2+ disease. The median age was 38 years (range 23-60 years) and the median time to developing BM was 24 months (range 9-57 months). The median number of BM was 5 (range 1-11).

On multivariable analysis evaluating predictors of brain metastases in all patients, presence of lung metastases ($P < .0001$) and residual positive LNs >4 ($P = .02$) predicted for increased likelihood of BM (Table 4). For every 1 year increase in age, there was a 3.8% decreased likelihood of BM ($P = .01$). Due to the very small number of patients who presented with solitary BM, it was not possible to develop a model assessing for predictive factors in this population.

High-risk Patient Cohort

To validate the proposal of a formal screening approach for patients with breast cancer, we classified patients within our cohort as high-risk if they were under the age of 40 years old, had ypN = N2 or N3 disease, and had either HER2+ or triple negative breast cancer. These patients were found to have a higher cumulative incidence of BM ($P = .013$), as well as a worse PFS ($P = .045$) and near significant worse OS ($P = .072$). In addition, patients in this cohort had an incident rate of positive lymph nodes that was 1.78 times higher than that for the low-risk patients ($P = .040$).

Survival Outcomes

Among patients with distant metastatic disease (n = 112), there was no difference in OS between those who had BM and those who did not ($P = .90$). The median OS for patients with BM, when calculating from time of initial diagnosis, was 47 months versus 51 months for patients without. On multivariable analysis for OS, presence of lung metastases was the most significant predictor of poor outcome ($P < .0001$).

Discussion

The benefits of identifying brain metastases at a time of minimal intracranial burden include lower incidence of symptomatic BM, decreased use of emergent WBRT, decreased need for craniotomy, and decreased risk of neurologic death.[12] In our study, half of patients with BM required craniotomy and/or WBRT, both of which are associated with significant morbidity.[13,14] In addition, surgery for breast cancer BM has been associated with development of leptomeningeal disease, which has an incredibly poor prognosis,[15,16] and use of WBRT has been associated with decreased

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Table 3 Characteristics of Patients With Brain Metastases (BM) as First and Only Site of Distant Metastatic Disease

Clinical History	Treatment	Time to BM	No BM	Symptomatic	Treatment of BM	Disease Status
39F, ER/PR- HER2+	NAC, left breast lumpectomy, adjuvant RT	14 mo	10	Seizure, right sided weakness, confusion	Craniotomy and tumor resection followed by radiosurgery to resection cavity and remaining lesions	AWD
47F, ER/PR- HER2+	NAC, mastectomy, PMRT	26 mo	1	Stable headaches	Craniotomy and tumor resection, whole brain RT	DOD
60F, ER/PR- HER2+	NAC, mastectomy, no RT	9 mo	5	Sudden dizziness and vomiting, confusion	Craniotomy followed by whole brain RT and posterior fossa tumor bed boost	DOD
60F, ER/PR- HER2+	NAC, mastectomy, PMRT	43 mo	6	Imbalance	Craniotomy and tumor resection followed by radiosurgery to resection cavity and remaining lesions	AWD
36F, ER/PR- HER2+	NAC, mastectomy, PMRT	22 mo	11	Headache, vomiting	Whole brain RT	DOD
23F, ER+/PR- HER2-	NAC, mastectomy, PMRT	47 mo	1	Hallucination, altered mental status	Craniotomy and tumor resection followed by radiosurgery to resection cavity	DOD
35F, ER/PR/HER2-	NAC, mastectomy, PMRT	20 mo	6	Nonspecific headaches	Radiosurgery	AWD
38F, ER/PR/HER2-	NAC, lumpectomy, adjuvant RT	57 mo	1	Nonspecific headaches	Radiosurgery	AWD

Abbreviations: NAC = neoadjuvant chemotherapy, RT = radiation treatment; AWD = alive with disease; DOD = dead of disease; BM = brain metastases.

Table 4 Multivariable Analysis of Clinical Factors Predicting for the Development of Brain Metastases in Patients With Breast Cancer who Received Neoadjuvant Chemotherapy (NAC)

Variable	Hazard Ratio (HR)	95% Confidence Interval	*P*-value
Age >40 y*	0.96	0.934-0.991	.011
Lung metastases	18.19	8.602-38.452	<.0001
<4 positive LNs after NAC	0.39	0.172-0.885	.024

* Age was analyzed as a continuous variable. Each 1 year increase in age decreases the hazard of developing brain metastases (BM) by 3.8%

cognitive function and decreased quality of life (QOL), without an improvement in OS.[17,18] Response rates to WBRT are lower than that for stereotactic radiosurgery (SRS), with only ~60% of patients achieving meaningful improvement.[19] Conversely, SRS has a >80%-90% chance of providing durable control for BM, depending on tumor histology,[20] and with significantly lower rates of side effects and improved QOL.[21] Therefore, a proactive screening approach that identifies intracranial disease at an earlier timepoint will facilitate SRS as a viable treatment option for these patients, decrease symptoms, and ultimately improve QOL.

The risk factors for BM that we identified in our analysis are consistent with previously published reports.[4,5] We found young age (<40 years), presence of lung metastases, and significant residual nodal disease (>4 lymph nodes positive) after NAC predicted for an increased likelihood of developing BM. Presence of lung metastases was the clinical variable most predictive for development of BM in our study population. In a large series from Belgium, Maurer et al also found that development of lung metastases as a first site of relapse (HR 6.97) predicted for development of BM.[5] The mechanism of metastatic spread from the lungs to the brain is an active area of investigation.[22,23]

There are 2 ongoing prospective clinical trials evaluating the use of screening brain MRI for breast cancer patients. A study from South Korea (NCT03617341) is evaluating the incidence of brain metastases in patients with unresectable or metastatic triple negative or HER2+ breast cancer. A phase II clinical trial from Brigham and Women's Hospital (NCT04030507) is performing screening brain MRI in women with newly diagnosed triple negative or inflammatory breast cancer, and randomizing patients with metastatic breast cancer to screening brain MRI versus usual care.

Limitations of our study include its small and retrospective nature. As a single institution study, our results may not be generalizable to the breast cancer population. Significant selection bias likely confounds some results, as is inherent in retrospective analyses. Additionally, the study period spans across decades when treatment modalities may have changed. Importantly, however, all HER2+ patients received HER2-targeted therapy, which may not be the case in other published series.

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Conclusion

In conclusion, we feel that our study uniquely supports the use of screening brain MRI in patients with high-risk breast cancer with the goal of decreasing invasive and morbid treatments. After careful review, we propose a selective screening approach with a yearly brain MRI for 1) young (<40 years) patients with breast cancer receiving NAC and 2) patients who develop metastatic disease post-NAC, especially those with lung involvement. We do not recommend screening brain MRI in older women with indolent breast cancer subtypes such as luminal A, as these patients were the least likely to develop BM. Ideally, this screening approach should be validated in the form of a prospective, multi-institutional effort to identify patients that would most benefit from such an intervention.

Clinical Practice Points

Development of brain metastases is a known concern for patients with metastatic breast cancer.

Notably, patients with breast cancer who are also under age 40 ($P = .011$), have presentation of lung metastases ($P < .0001$), and present with residual nodal disease with >4 lymph nodes positive after NAC ($P = .024$) tend to have higher likelihoods of developing BM.

After creating a "high-risk cohort" within our patient population defined as breast cancer patients under age 40, with ypN = N2 or N3, and either HER2+ or triple negative disease, we found that high-risk patients have a higher cumulative incidence of developing BM ($P = .013$).

These "high-risk" patients also have higher likelihoods of having worse PFS ($P = .045$) and a trend toward worse OS ($P = .072$).

A validated screening approach may help reduce morbidity and mortality in this patient population by detecting BM earlier.

Disclosure

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript. Margaret Kozak consults for Elekta. The other authors have no relevant financial or non-financial interests to disclose.

References

1. Bailleux C, Eberst L, Bachelot T. Treatment strategies for breast cancer brain metastases. *Br J Cancer*. 2021;124:142–155. doi:10.1038/s41416-020-01175-y.
2. 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;121:991–1000. doi:10.1038/s41416-019-0619-y.
3. Evans AJ, James JJ, Cornford EJ, et al. Brain metastases from breast cancer: identification of a high-risk group. *Clin Oncol (R Coll Radiol)*. 2004;16:345–349. doi:10.1016/j.clon.2004.03.012.
4. Koniali L, Hadjisavvas A, Constantinidou A, et al. Risk factors for breast cancer brain metastases: a systematic review. *Oncotarget*. 2020;11:650–669. doi:10.18632/oncotarget.27453.
5. Maurer C, Tulpin L, Moreau M, et al. Risk factors for the development of brain metastases in patients with HER2-positive breast cancer. *ESMO Open*. 2018;3. doi:10.1136/esmoopen-2018-000440.
6. Rudat V, El-Sweilmeen H, Brune-Erber I, et al. Identification of breast cancer patients with a high risk of developing brain metastases: a single-institutional retrospective analysis. *BMC Cancer*. 2014;14:289. doi:10.1186/1471-2407-14-289.
7. Atahan IL, Ozyigit G, Yildiz F, et al. Percent positive axillary involvement predicts for the development of brain metastasis in high-risk patients with nonmetastatic breast cancer receiving post-mastectomy radiotherapy. *Breast J*. 2008;14:245–249. doi:10.1111/j.1524-4741.2008.00569.x.
8. Dawood S, Lei X, Litton JK, Buchholz TA, Hortobagyi GN, Gonzalez-Angulo AM. Incidence of brain metastases as a first site of recurrence among women with triple receptor-negative breast cancer. *Cancer*. 2012;118:4652–4659. doi:10.1002/cncr.27434.
9. Gonzalez-Angulo AM, Cristofanilli M, Strom EA, et al. Central nervous system metastases in patients with high-risk breast carcinoma after multimodality treatment. *Cancer*. 2004;101:1760–1766. doi:10.1002/cncr.20530.
10. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol*. 2010;28:3271–3277. doi:10.1200/JCO.2009.25.9820.
11. Sihto H, Lundin J, Lundin M, et al. Breast cancer biological subtypes and protein expression predict for the preferential distant metastasis sites: a nationwide cohort study. *Breast Cancer Res*. 2011;13:R87. doi:10.1186/bcr2944.
12. Cagney DN, Martin AM, Catalano PJ, et al. Implications of screening for brain metastases in patients with breast cancer and non-small cell lung cancer. *JAMA Oncol*. 2018;4:1001–1003. doi:10.1001/jamaoncol.2018.0813.
13. Steinmann D, Vordermark D, Gerstenberg W, et al. Quality of life in patients with limited (1-3) brain metastases undergoing stereotactic or whole brain radiotherapy: a prospective study of the DEGRO QoL working group. *Strahlenther Onkol*. 2020;196:48–57. doi:10.1007/s00066-019-01506-w.
14. Barker 2nd FG. Craniotomy for the resection of metastatic brain tumors in the U.S., 1988-2000: decreasing mortality and the effect of provider caseload. *Cancer*. 2004;100:999–1007. doi:10.1002/cncr.20058.
15. Scott BJ, Kesari S. Leptomeningeal metastases in breast cancer. *Am J Cancer Res*. 2013;3:117–126.
16. van der Ree TC, Dippel DW, Avezaat CJ, Sillevis Smitt PA, Vecht CJ, van den Bent MJ. Leptomeningeal metastasis after surgical resection of brain metastases. *J Neurol Neurosurg Psychiatry*. 1999;66:225–227. doi:10.1136/jnnp.66.2.225.
17. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18:1049–1060. doi:10.1016/S1470-2045(17)30441-2.
18. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*. 1998;280:1485–1489. doi:10.1001/jama.280.17.1485.
19. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363:1665–1672. doi:10.1016/S0140-6736(04)16250-8.
20. Firlik KS, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brain metastases from breast cancer. *Ann Surg Oncol*. 2000;7:333–338. doi:10.1007/s10434-000-0333-1.
21. 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;316:401–409. doi:10.1001/jama.2016.9839.
22. Ebben JD, You M. Brain metastasis in lung cancer: building a molecular and systems-level understanding to improve outcomes. *Int J Biochem Cell Biol*. 2016;78:288–296. doi:10.1016/j.biocel.2016.07.025.
23. Ni W, Chen W, Lu Y. Emerging findings into molecular mechanism of brain metastasis. *Cancer Med*. 2018;7:3820–3833. doi:10.1002/cam4.1667.

Please cite this article as: Margaret M Kozak et al, Incidence of Brain Metastases in Women Treated With Neoadjuvant Chemotherapy for Breast Cancer: Implications for Screening, Clinical Breast Cancer, https://doi.org/10.1016/j.clbc.2022.08.002