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RESEARCH

Clinical–pathological patterns and prognosis of young women with breast cancer brain metastases: a single-center retrospective study

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Abstract

Purpose Breast cancer (BC) is the most frequent cancer among women and the second leading cause of central nervous system (CNS) metastases. While the epidemiology of CNS metastases from BC has been well described, little is known about the treatment patterns and outcomes of young women < 40 years of age with BC that is metastatic to the CNS.

Methods In this retrospective analysis, we identified patients with metastatic breast cancer (MBC) to the CNS who were treated at the Sunnybrook Odette Cancer Center, Toronto, Canada between 2008 and 2018. Young women were defined as those who were < 40 years of age at the time of diagnosis of CNS metastases. Descriptive statistics were completed, and survival analyses performed.

Results Similar clinical and pathological characteristics were observed among young and older women with CNS metastases. However, young women were significantly more likely to develop leptomeningeal metastatic disease (LMD) than older women (39.6% vs. 22.3%, $p = 0.004$). Additionally, young women were significantly more likely to be re-treated for CNS metastases (43.4% vs. 24.5%, $p = 0.003$). There was no significant difference in median brain-specific progression-free survival (bs-PFS) (log-rank $p = 0.35$) or overall survival (OS) (log-rank p value = 0.52) between young and older women.

Conclusions Women < 40 years of age were more likely to develop LMD than women ≥ 40 years of age. Although young women were also more likely to be re-treated for progression of CNS metastases, their bs-PFS and OS were not inferior to those ≥ 40 years of age.

Keywords Breast cancer · Brain metastases · Prognostic factors · Age · Young women · Leptomeningeal disease

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Introduction

Breast cancer is the most commonly diagnosed malignancy amongst women worldwide and the 2nd most common origin of central nervous system (CNS) metastases [1, 2]. Unfortunately, while most women present with early-stage disease, a high proportion ultimately develop metastatic recurrences both outside and, less commonly, within the CNS [3–7]. Further, the incidence of CNS metastases among women with MBC is increasing due to improvements in diagnostic imaging and prolonged patient survival as a result of more effective systemic treatments [8–12].

Despite advances in both systemic treatments and radiotherapy, the prognosis of patients with MBC and CNS metastases remains poor [10–14]. Several factors have been shown to portend a poor prognosis among women with MBC and CNS metastases [8, 12]. Although patients with leptomeningeal metastatic disease (LMD) are not well

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represented in the so-called Graded Prognostic Assessment (GPA) Index, factors associated with poor prognosis among patients with MBC and CNS metastases include the presence of multiple brain metastases (as opposed to a solitary metastasis), the presence of extra-cranial metastases, a Karnofsky performance score ≤ 60, as well as a basal disease subtype [8, 12].

Likely, because BC in women aged less than 40 is relatively rare, accounting for an estimated 5–7% of cases, whether there is a prognostic association between young age and outcomes of patients with CNS metastases has not been definitively determined [15–17]. Some studies have suggested that in women with MBC and CNS metastases, young age is associated with a more aggressive disease biology, as well as a higher likelihood of relapse and/or death [18–22]. However, other groups have identified young age as a favorable prognostic factor [13, 23], while another study reported no difference in survival [24].

Given limited and conflicting results regarding the impact of young age on outcomes of women with MBC and CNS metastases, our study sought to compare the clinical-pathological characteristics, treatment patterns and outcomes of women aged less than 40 and those age ≥ 40 with CNS metastases in a single-center retrospective cohort study.

Materials and methods

Study design and population

In this single-center retrospective study, we identified 689 female patients (age 18+) with MBC and CNS metastases with either parenchymal brain metastases (BrM) or LMD who were treated with surgery, whole-brain radiotherapy (WBRT), and/or stereotactic radiosurgery (SRS) at Sunnybrook Odette Cancer Center, Toronto, Canada between 2008 and 2018. This study period was chosen to permit a 2-year follow-up for all participants at the time of original data analysis. The diagnosis of BrM and/or LMD were made based on CSF pathology, radiological findings and clinical judgement, as per standard of care evaluation by the treating oncology team. Data pertaining to clinical and pathological characteristics as well as treatment patterns were collected from the electronic patient record.

We compared clinical-pathologic characteristics, treatment patterns, and outcomes of young women with MBC who were < 40 years-of-age to patients who were ≥ 40 years-of-age at the time of CNS metastases. "Young" was defined as age < 40 to align with convention in the literature [23, 25–31]. BC subtypes were combined due to lack of power for a more detailed analysis. The research protocol was approved by our institution's ethics review board.

Study outcomes

The two main clinical outcomes of interest in this study were brain-specific progression-free survival (bs-PFS) and overall survival (OS). bs-PFS was calculated as the time from diagnosis of CNS metastases to disease progression in the brain based on radiographic imaging or death, with times censored at last follow-up if neither of these events occurred. For cases where the date of progression was not reported, the date of second-line treatment to the brain was used as a substitute. OS was defined as time elapsing from initial diagnosis of CNS metastases to the date of death from any cause, with times censored at last follow-up if no death was recorded.

Statistical analysis

Patient characteristics and treatment patterns were described with medians and interquartile ranges for continuous variables and percentages for categorical variables. Categorical variables were compared between young and older patients using Chi-square tests and continuous variables using Wilcoxon rank-sum tests. In younger women, the association of LMD with BC subtype, histology and first line treatment was explored using similar methods. Kaplan–Meier survival plots for age group were presented for bs-PFS and OS. Univariable and multivariable Cox proportional hazards models were completed for bs-PFS and OS with the following pre-specified variables: age group, BC subtype, first line local treatment and LMD status. Analyses by BC subtype were not pursued due to the small sample size of the younger group and resultant lack of power. A p value less than 0.05 was considered to be statistically significant.

Results

Clinical and pathological characteristics

A total of 689 patients with MBC and CNS metastases were included in this study, among whom 53 (7.7%) were classified as "young" (< 40 years of age). The median time between MBC diagnosis and CNS metastases was 8 months for both younger and older patients ($p = 0.38$) (Table 1). 75.5% of younger women had ductal carcinoma as tumor histology versus 66.4% of older women ($p = 0.36$). Among 163 patients in our cohort with LMD, 19 patients had LMD only, whereas the remaining 144 also had BrM. No significant differences in BC subtype were observed among women < 40 years vs. ≥ 40 years of age ($p = 0.30$). The majority of patients in each age group had neurological symptoms at the time of initial presentation with CNS metastases (< 40 years: 67.9% vs. ≥

Table 1 Clinical-pathologic characteristics and local treatment patterns for patients with breast cancer brain metastases

	All 689	Age < 40 *N* = 53	Age ≥ 40 *N* = 636	*P*[a]
Time from MBC Dx to BCBM Dx (months), median (IQR)	8 (0.23.8)	8 (0.15)	8 (0.25)	0.38
BC subtype, n (%)				0.30
HR + HER2−	232 (33.7%)	15 (28.3%)	217 (34.1%)	
HER2+	195 (28.3%)	20 (37.7%)	175 (27.5%)	
TNBC	157 (22.8%)	13 (24.5%)	144 (22.6%)	
Unknown	105 (15.2%)	5 (9.4%)	100 (15.7%)	
Histology, n (%)				0.36
Lobular	41 (6%)	3 (5.7%)	38 (6%)	
Ductal	462 (67.1%)	40 (75.5%)	422 (66.4%)	
Unknown	186 (27%)	10 (18.9%)	176 (27.7%)	
Neurological symptoms, n (%)				0.24
Yes	531 (77.1%)	36 (67.9%)	495 (77.8%)	
No	117 (17%)	12 (22.6%)	105 (16.5%)	
Unknown	41 (6%)	5 (9.4%)	36 (5.7%)	
Leptomeningeal disease, n (%)				0.004
Yes	163 (23.7%)	21 (39.6%)	142 (22.3%)	
No	526 (76.3%)	32 (60.4%)	494 (77.7%)	
Lymph node metastasis, n (%)				0.17
Yes	424 (61.5%)	37 (69.8%)	387 (60.8%)	
No	232 (33.7%)	16 (30.2%)	216 (34%)	
Unknown	33 (4.8%)	0 (0%)	33 (5.2%)	
Lung metastasis, n (%)				0.31
Yes	387 (56.2%)	27 (50.9%)	360 (56.6%)	
No	268 (38.9%)	25 (47.2%)	243 (38.2%)	
Unknown	34 (4.9%)	1 (1.9%)	33 (5.2%)	
Liver metastasis, n (%)				0.17
Yes	373 (54.1%)	28 (52.8%)	345 (54.2%)	
No	281 (40.8%)	25 (47.2%)	256 (40.3%)	
Unknown	35 (5.1%)	0 (0%)	35 (5.5%)	
Bone metastasis, n (%)				0.75
Yes	470 (68.2%)	37 (69.8%)	433 (68.1%)	
No	193 (28%)	15 (28.3%)	178 (28%)	
Unknown	26 (3.8%)	1 (1.9%)	25 (3.9%)	
First line local therapy, n (%)				0.59
Radiotherapy based: SRS only	124 (18%)	13 (24.5%)	111 (17.5%)	
WBRT only	459 (66.6%)	31 (58.5%)	428 (67.3%)	
SRS + WBRT	1 (0.1%)	0 (0%)	1 (0.2%)	
Surgery based: surgery only	40 (5.8%)	2 (3.8%)	38 (6%)	
Surgery + WBRT	40 (5.8%)	5 (9.4%)	35 (5.5%)	
No treatment	25 (3.6%)	2 (3.8%)	23 (3.6%)	
Re-treatment for BrM progression				
Retreated, n (%)	179 (26%)	23 (43.4%)	156 (24.5%)	0.003
Time from treatment for 1st BrM to retreatment (months), median (IQR)	8 (4,13)	6 (3,9)	8.5 (5,14)	0.08

MBC metastatic breast cancer, *BCBM* breast cancer brain metastasis, *Dx* diagnosis, *HR+* hormone receptor positive, *TNBC* triple negative breast cancer, *BrM* brain metastasis, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiotherapy, *IQR* inter-quartile range

[a]P values from Wilcoxon rank sum tests for continuous variables and Chi-square tests for categorical variables

40 years: 77.8%, $p = 0.24$), with no significant differences in the incidence of lymph node, lung, liver, or bone metastases. However, there was a significant difference in the incidence of LMD among women < 40 years compared to women ≥ 40 years of age (39.6% vs. 22.3%, $p = 0.004$).

Leptomeningeal disease

We explored whether the presence or absence of LMD in young women is associated with differences in tumour histology, BC subtype, or treatment characteristics (Table 2). Ductal carcinoma made up 85.7% of younger women with LMD versus 68.8% of those without LMD ($p = 0.08$). The

Table 2 Association of BC subtype, histology and first line treatment with leptomeningeal disease in young women < 40 years

	LMD present $N=21$	LMD absent $N=32$	P^a
BC subtype, n (%)			0.18
HR + HER2−	7 (33.3%)	8 (25%)	
HER2+	7 (33.3%)	13 (40.6%)	
TNBC	7 (33.3%)	6 (18.8%)	
Unknown	0 (0%)	5 (15.6%)	
Histology, n (%)			0.08
Lobular	2 (9.5%)	1 (3.1%)	
Ductal	18 (85.7%)	22 (68.8%)	
Unknown	1 (4.8%)	9 (28.1%)	
First line local therapy, n (%)			0.32
SRS only	4 (19%)	9 (28.1%)	
WBRT only	12 (57.1%)	19 (59.4%)	
Surgery-based	3 (14.3%)	4 (12.5%)	
No treatment	2 (9.5%)	0 (0%)	
Re-treated for BCBM progression, n (%)			0.95
Yes	9 (42.9%)	14 (43.8%)	
No	12 (57.1%)	18 (56.2%)	

LMD leptomeningeal metastatic disease, *BC* breast cancer, *HR+* hormone receptor positive, *TNBC* triple negative breast cancer, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiotherapy

[a]P values from Chi-square to test the hypothesis of no association

distribution of BC subtype, first line treatment and numbers undergoing retreatment did not differ significantly; however the sample size is small.

Treatment patterns

The first line treatment modalities were similar between young and older women (24.5% vs. 17.5% SRS only, 58.5% vs. 67.3% WBRT only, 3.8% vs. 6.0% surgery only, $p=0.59$), (Table 1). However, young women < 40 years were significantly more likely to be re-treated for CNS metastases progression than those ≥ 40 years of age (43.4% vs. 24.5%, $p=0.003$). Among those patients who were re-treated, the median time from first treatment of CNS metastases to re-treatment was shorter among young women compared to those ≥ 40 years (6.0 months vs. 8.5 months, $p=0.075$).

Brain-specific progression-free survival

Overall median bs-PFS for the population was 13 months (95% CI 10, 15 months) with median follow-up 11 months (95% CI 10, 15 months). There was no significant difference in median bs-PFS between women < 40 years and women ≥ 40 years (log-rank $p=0.35$, Fig. 1) and in a Cox model for bs-PFS, the hazard ratio for the younger versus the older age group was 1.19 (95% CI 0.83, 1.72), $p=0.34$ (Table 3). In further univariable analyses, women with human epidermal growth factor receptor 2 (HER2) positive disease had significantly longer bs-PFS compared to patients with hormone receptor (HR) positive/HER2 negative disease (HR 0.63, 95% CI 0.48, 0.83, $p=0.001$). Patients treated with WBRT alone had a significantly shorter bs-PFS than those treated with SRS alone (HR 2.09, 95% CI 1.55, 2.81, $p<0.001$) as did those with LMD relative to those with

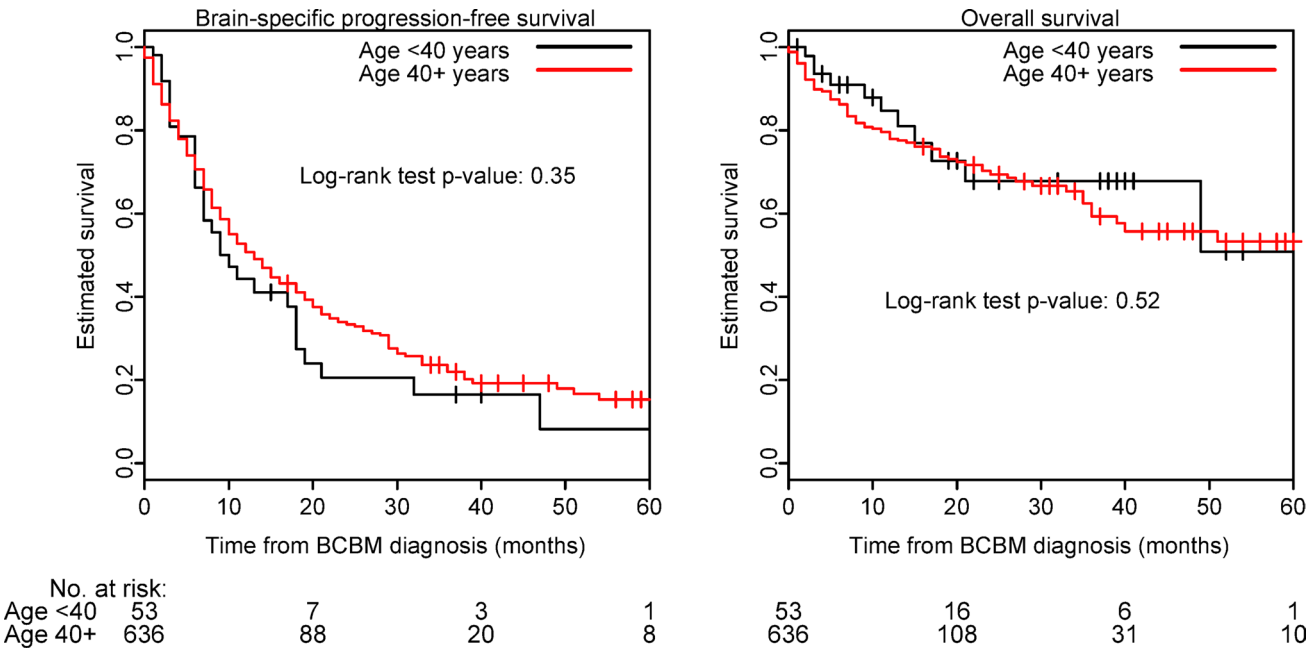

Fig. 1 Brain-specific progression-free survival and overall survival for women with breast cancer brain metastasis ($N=689$) according to age

Table 3 Factors affecting brain-specific progression free survival (bs-PFS) in patients with breast cancer brain metastases: univariable and multivariable analyses

	Univariable models $N=689$ HR (95% CI), P^a	P^a	Multivariable model $N=689$ HR (95% CI), P^b	P^b
Age group				
≥ 40 years	1		1	
< 40 years	1.19 (0.83, 1.72)	0.34	1.11 (0.77, 1.61)	0.57
BC subtype				
HR + HER2−	1		1	
HER2+	0.63 (0.48, 0.83)	0.001	0.7 (0.53, 0.92)	0.01
TNBC	1.33 (1, 1.79)	0.05	1.46 (1.09, 1.96)	0.01
Unknown	0.43 (0.26, 0.71)	0.001	0.48 (0.29, 0.81)	0.006
First line local therapy				
SRS only[c]	1		1	
WBRT only	2.09 (1.55, 2.81)	<0.001	1.81 (1.34, 2.45) 4	<0.001
Surgery based	1.04 (0.7, 1.56)	0.84	0.89 (0.59, 1.34)	0.59
No treatment	1.58 (0.78, 3.19)	0.20	1.52 (0.75, 3.08)	0.24
LMD status				
Absent	1		1	
Present	1.58 (1.24, 2.01)	<0.001	1.42 (1.11,1.82)	0.006

HR hazard ratio, *CI* confidence interval, *BC* breast cancer, *ref* reference, *HR+* hormone receptor positive, *TNBC* triple negative breast cancer, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiotherapy, *LMD* leptomeningeal metastatic disease

[a]P values from separate univariable Cox regression models

[b]P values from a multivariable Cox regression model

[c]Includes the one patient who was treated with SRS + WBRT

Table 4 Factors affecting overall survival in patients with breast cancer brain metastases: univariable and multivariable analyses

	Univariable models $N=689$ HR, (95% CI), P^a	P^a	Multivariable model $N=689$ HR, (95% CI), P^b	P^b
Age group				
≥ 40 years	1		1	
< 40 years	0.82 (0.44, 1.52)	0.52	0.81 (0.43, 1.51)	0.51
BC subtype				
HR + HER2−	1		1	
HER2+	0.41 (0.26, 0.64)	<0.001	0.49 (0.31, 0.77)	0.002
TNBC	1.06 (0.68, 1.63)	0.81	1.27 (0.82, 1.98)	0.29
Unknown	0.2 (0.07, 0.56)	0.002	0.24 (0.09, 0.67)	0.006
First line local therapy				
SRS only[c]	1		1	
WBRT only	3.42 (2.01, 5.85)	<0.001	2.79 (1.62, 4.8)	<0.001
Surgery based	0.9 (0.4, 2.05)	0.81	0.72 (0.32, 1.65)	0.44
No treatment	2.86 (1.05, 7.83)	0.04	2.66 (0.97, 7.3)	0.057
LMD status				
Absent	1		1	
Present	1.73 (1.19, 2.51)	0.004	1.43 (0.98, 2.09)	0.065

HR, hazard ratio, *CI* confidence interval, *BC* breast cancer, *ref* reference, *HR+* hormone receptor positive, *TNBC* triple negative breast cancer, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiotherapy, *LMD* leptomeningeal metastatic disease

[a]P values from separate univariable Cox regression models

[b]P values from a multivariable Cox regression model

[c]Includes the one patient who was treated with SRS + WBRT

no LMD (HR 1.58, 95% CI 1.24, 2.01, $p<0.001$). These patterns were maintained in the multivariable model.

Overall survival

Median OS in the overall population was not reached; median follow-up for OS was 7 months (95% CI: 6–9 months). Overall survival did not differ significantly by patient age (log-rank p value = 0.52, Fig. 1). In a Cox model for OS, the hazard ratio for age < 40 years as compared to ≥ 40 years was 0.82 (95% CI 0.44, 1.52), $p=0.52$ (Table 4). In further univariable analyses, women with HER2 + disease had significantly longer OS compared to patients with HR + HER2- disease (HR 0.41, 95% CI 0.26, 0.64, $p<0.001$). Patients treated with WBRT alone had a significantly shorter OS than those treated with SRS alone (HR 3.42, 95% CI 2.01, 5.86, $p<0.001$). Patients with LMD had significantly shorter OS relative to patients with no LMD (HR 1.73, 95% CI 1.19, 2.51, $p=0.004$). These patterns were also seen in the multivariable model.

Discussion

In our retrospective cohort study of 689 patients treated for MBC and CNS metastases at the Sunnybrook Odette Cancer Centre, young women (< 40 years) had similar clinical-pathologic characteristics as older women, including a

similar distribution of BC subtypes, tumour histology, and sites of extra-cranial metastatic disease. Incidence of symptomatic CNS metastases and median time between MBC diagnosis and CNS metastases was also similar between the two groups. The fact that young women with MBC and CNS metastases were significantly more likely to develop LMD and were more likely to be re-treated for CNS progression than women ≥ 40 years of age suggests a more aggressive biology of CNS metastases, but this did not translate into inferior bs-PFS or OS in our study.

In our study, women < 40 years and women ≥ 40 years with MBC and CNS metastases shared similar clinical-pathologic features. Mustillo et al. (2020) similarly found no difference in the distribution of BC subtype nor the site of extra-cranial disease between young and older women within a cohort of 121 patients with MBC and CNS metastases [23]. In that study, younger women were significantly more likely to receive local treatment to the brain, which was defined as surgery with or without radiotherapy or radiotherapy alone [23]. In our study, the overall treatment patterns of younger versus older women were similar, but younger women were more likely to be re-treated for progression of CNS metastases. It is possible that a more aggressive approach to re-treatment in a younger population of patients may explain their similar bs-PFS and OS despite a higher likelihood of LMD and a shorter time period to re-treatment.

LMD, which is often a late-stage complication of breast cancer with a dismal prognosis [32–38] was reported in 23.7% of our study cohort ($n = 163$ patients) and was significantly more common among young women (< 40 years) than older women (≥ 40 years). These findings are supported by other small cohort studies [23, 39]. In the study by Mustillo et al. (2020), LMD occurred in 21% of the overall cohort ($n = 25$ patients) and twice as frequently in women < 40 years of age compared to older women (35% vs. 18%, $p < 0.001$) [23]. Jung et al. (2012) also identified young age (< 40 years) as an independent risk factor for developing LMD, although only 14% ($n = 27$) of patients in their cohort had LMD [39]. Although each of these studies, including ours, is limited by small sample sizes the increased risk of LMD among young women with MBC and CNS metastases appears to be consistent.

Beyond young age, other clinical factors have been shown to increase the likelihood of developing LMD. Breast cancers of lobular histology [33, 40, 41] and TNBC subtype [33, 40] have a predilection to metastasize to the meninges. In addition, several studies have shown that BrM resection followed by postoperative stereotactic radiosurgery increases the likelihood of LMD compared to treatment with SRS alone [33, 42–44]. The proposed pathogenesis for this finding involves intraoperative disruption and seeding of cancer cells into the meninges [39, 43]. Given that only a small proportion of patients in our cohort were treated with surgical resection, we were not able to comment on surgery as a mechanism of leptomeningeal seeding in this study.

Several studies have suggested that breast cancer in young women is more aggressive [20, 21, 45]. A prior study found that young women with an initial diagnosis of non-metastatic BC had a threefold-greater risk of distant recurrence at 5 years with a significantly higher propensity to develop CNS metastases compared to older women [31]. Young women are also more likely to be diagnosed with advanced-stage BC than older women [45–47]. In addition, a large body of literature suggests that more aggressive disease among young women with BC may be attributed to differences in their disease biology [15, 18, 20–22, 45, 46, 48–50]. Distinct oncogenic signalling pathways, markers of immature mammary epithelial cells, diminished hormone sensitivity (ER-negative, PR negative) as well as a greater extent of HER2 and EGFR expression have been observed in young women [18, 19, 21, 30, 45, 49]. Young women are also more likely than older women to have hereditary BC. Whether somatic and/or germline genomic differences in CNS metastases among younger women with MBC result in a higher risk of LMD remains unknown.

In addition to a higher likelihood of LMD, we found that young women with MBC and CNS metastases are more likely to be re-treated with radiotherapy. The existing data from literature specific to young women with MBC and CNS metastases is scarce. Although meta-analyses have demonstrated that younger women with BC have worse outcomes than older women [15, 17, 19, 48], some groups have shown a particularly good prognosis among young women with MBC and CNS metastases [13, 23]. For example, in a single-center retrospective study of 121 patients diagnosed with MBC and CNS metastases, younger women (< 40 years), compared to older women (≥ 40 years), had a significantly longer median OS (21 months vs. 6 months, $p = 0.014$). Similar findings were reported in a study of 42 patients with MBC who underwent craniotomy for CNS metastases [13]. However in contrast, our analysis of 683 patients with MBC and CNS metastases found no significant difference in median bs-PFS nor OS between young and older women. Xiao et al. 2020 similarly found that age does not affect survival in patients with MBC and CNS metastases [24].

We subsequently evaluated factors that influence bs-PFS and OS in women with MBC and CNS metastases. While age was not a significant factor, we found that relative to patients with HR+/HER2- disease, the TNBC subtype was independently prognostic for shorter bs-PFS in both the univariate and multivariate analyses, which is in accordance with findings previously published by Sperduto et al. [12].

Last, we acknowledge several limitations to our study, which was conducted retrospectively at a single institution. In addition, the sample of patients < 40 years of age was small ($n = 53$, 7.7% of the study cohort) and even fewer developed LMD. Due to a limited sample size, we were not able to study whether the effect of age group differed by BC subtype, which remains an open question for further research. Lack of tissue-based analyses is another limitation of our study. We also acknowledge incomplete data pertaining to histology, breast cancer subtype, and/or other clinical information for patients whose medical records resided primarily at outside institutions, as their treatment at our tertiary centre was solely focused on local therapy for BrM.

Conclusion

In our single-center retrospective cohort study, we identified that young women (< 40 years) with MBC and CNS metastases were significantly more likely to develop LMD than older women. Younger women were also more likely to be re-treated for progression of CNS metastases. However, there was no significant difference in median bs-PFS and/or OS between young and older women.

Author contributions K.J., J.F., I.K., E.W., H.S., B.I., and S.V. contributing to manuscript writing, data analysis, and data interpretation. M.E was responsible for statistical analysis and generating tables/figures.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests K.J.J has been a consultant, speaker, or advisory board member for Amgen, AstraZeneca, Apo Biologix, Daiichi Sankyo, Eli Lilly, Esai, Genomic Health, Gilead Sciences, Knight Therapeutics, Merck, Myriad Genetics, Novartis, Organon, Pfizer, Roche, and Viatris; has received research funding from AstraZeneca, Eli Lilly, and Pfizer; and has received drug supply from Pfizer and Viatris for an investigator initiated clinical trial.

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