European Journal of Cancer 74 (2017) 17–25

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Prognostic factors and survival according to tumour subtype in women presenting with breast cancer brain metastases at initial diagnosis

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Received 2 August 2016; received in revised form 29 October 2016; accepted 16 December 2016
Available online 6 February 2017

KEYWORDS
Breast cancer;
Brain metastases;
Prognostic factors;
Tumour subtypes;
Oestrogen receptor;
Progesterone receptor;
HER2

Abstract ***Background:*** The presence of brain metastases at the time of initial breast cancer diagnosis (BMIBCD) is uncommon. Hence, the prognostic assessment and management of these patients is very challenging. The aim of this study was to analyse the influence of tumour subtype compared with other prognostic factors in the survival of patients with BMIBCD.
Methods: We evaluated women with BMIBCD, reported to Surveillance, Epidemiology and End Results program from 2010 to 2013. Patients with other primary malignancy were excluded. Univariate and multivariate analyses were performed to determine the effects of each variable on overall survival (OS).
Results: We included 740 patients. Median OS for the whole population was 10 months, and 20.7% of patients were alive at 36 months. Tumour subtype distribution was: 46.6% hormone receptor (HR)+/HER2−, 17% HR+/HER2+, 14.1% HR−/HER2+ and 22.3% triple-negative. Univariate analysis showed that the presence of liver metastases, lung metastases and triple-negative patients (median OS 6 months) had worse prognosis. The HR+/HER2+ subtype had the longest OS with a median of 22 months. In multivariate analysis, older age (hazard ratio 1.8), lobular histology (hazard ratio 2.08), triple-negative subtype (hazard ratio 2.25), liver metastases (hazard ratio 1.6) and unmarried patients (hazard ratio 1.39) had significantly shorter OS.

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http://dx.doi.org/10.1016/j.ejca.2016.12.015

Conclusions: Although the prognosis of patients with BMIBCD is generally poor, 20.7% were still alive 3 years after the diagnosis. There were substantial differences in OS according to tumour subtype. In addition to tumour subtype, other independent predictors of OS are age at diagnosis, marital status, histology and liver metastases.

1. Introduction

Breast cancer represents the second most frequent cause of brain metastases after lung cancer, with metastases occurring in 10–16% of the patients [1]. The incidence of brain metastases seem to have increased in recent years, this is likely due to prolonged survival of patients receiving more efficient treatments and the availability of better imaging techniques that lead to increased detection of this event [2].

Brain metastases in breast cancer patients represent a catastrophic event that portends a poor prognosis, with a median survival that ranges from 2 months to 25.3 months despite the treatment [3–6]. In addition, brain metastases are a major cause of morbidity, associated with progressive neurologic deficits that result in a reduced quality of life [7].

Previous studies have identified the subgroups of patients with triple-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer as having an increased risk for the development of brain metastases [8–11], with up to half of patients with HER2-positive metastatic breast cancer experiencing brain metastases over time [12]. Tumour subtypes are also an important factor for the median time interval from primary diagnosis to the development of brain metastases; a recent large study showed shorter intervals for triple-negative and HER2-positive patients, and longer periods for oestrogen receptor positive tumours [13].

Brain metastases generally occur as a late event in the natural course of breast cancer. Most of them will be detected after a median of 32 months from the initial cancer diagnosis [3]. Therefore, the analysis of prognostic factors and survival of this patient population can be confounded by the potential changes that cancer cells might develop at the time of distant relapse, as well as potential changes related to treatment exposure. The presence of brain metastases at initial diagnosis of breast cancer is less common. There is a lack of data about patient characteristics and prognostic factors in this unique group of patients, which makes the prognostic assessment and management very challenging.

The aim of this study was to analyse the influence of tumour subtype compared with other prognostic factors in the survival of patients who present with brain metastases at the time of initial diagnosis of stage IV breast cancer.

2. Materials and methods

2.1. Data source and study design

We obtained data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, using the 18 registry (1973–2013) database [14]. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28% of the US population. The SEER Program registries routinely collect data on patient demographics, primary tumour site, tumour morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. More recently, SEER started collecting sites of metastasis at initial diagnosis since 2010, because of this, we used that year as the starting point for our study.

We extracted all cases of women with brain metastases at the time of initial diagnosis of microscopically confirmed stage IV breast cancer, diagnosed between 2010 and 2013. We selected women with only one primary malignancy in their lifetime.

Study variables included age at diagnosis, race, year of diagnosis, histology, tumour grade, tumour subtype, type of breast surgery, radiation therapy, laterality, marital status, site of metastases, survival months and vital status. Four tumour grades were collapsed into 3 grades, with grade 4 merged with grade 3 tumours. Histology codes were grouped according to frequency into five categories using the WHO classification (ductal, lobular, mixed ductal and lobular, mucinous and other carcinoma). Tumour stage was registered according to the American Joint Committee on Cancer Staging System seventh edition. Tumour subtypes were classified according to the breast subtype variable as: hormone receptor (HR)-positive/HER2-negative, HR-positive/HER2-positive, HR-negative/HER2-positive and triple-negative. The variables metastasis at diagnosis to bone, liver and lung were used to define other sites of metastases.

The University of Iowa Institutional Review Board exempted this study from review because patients cannot be identified. This study was approved by Scientific and Ethical Committee of GOCS.

2.2. Statistical analysis

Descriptive statistics, including frequencies, medians and proportions, were used to evaluate characteristics of

Table 1
Patient characteristics according to tumour subtypes.

Patient characteristics		Tumour subtype:												*P*
		HR-positive/ HER2-negative		HR-positive/ HER2-positive		HR-negative/ HER2-positive		Triple negative		Unknown[a]		Total		
		N	%	N	%	N	%	N	%	N	%	N	%	
All patients		293	39.6%	107	14.5%	89	12.0%	140	18.9%	111	15.0%	740	100.0%	
Age at diagnosis, y	<50	54	18.4%	25	23.4%	26	29.2%	35	25.0%	9	8.1%	149	20.1%	0.005
	50–64	125	42.7%	59	55.1%	44	49.4%	62	44.3%	54	48.6%	344	46.5%	
	>64	114	38.9%	23	21.5%	19	21.3%	43	30.7%	48	43.2%	247	33.4%	
Race	White	231	78.8%	78	72.9%	62	69.7%	105	75.0%	73	65.8%	549	74.2%	0.19
	Black	46	15.7%	16	15.0%	19	21.3%	28	20.0%	33	29.7%	142	19.2%	
	Other (American Indian/AK Native, Asian/Pacific Islander)	15	5.1%	12	11.2%	8	9.0%	7	5.0%	5	4.5%	47	6.4%	
	Unknown[a]	1	0.3%	1	0.9%	0	0.0%	0	0.0%	0	0.0%	2	0.3%	
Year of diagnosis	2010	64	21.8%	24	22.4%	18	20.2%	39	27.9%	33	29.7%	178	24.1%	0.424
	2011	78	26.6%	33	30.8%	28	31.5%	29	20.7%	33	29.7%	201	27.2%	
	2012	61	20.8%	27	25.2%	20	22.5%	28	20.0%	23	20.7%	159	21.5%	
	2013	90	30.7%	23	21.5%	23	25.8%	44	31.4%	22	19.8%	202	27.3%	
Grade	I	20	6.8%	1	0.9%	0	0.0%	3	2.1%	2	1.8%	26	3.5%	<0.0001
	II	112	38.2%	34	31.8%	20	22.5%	20	14.3%	22	19.8%	208	28.1%	
	III/IV	89	30.4%	49	45.8%	48	53.9%	89	63.6%	29	26.1%	304	41.1%	
	Unknown[a]	72	24.6%	23	21.5%	21	23.6%	28	20.0%	58	52.3%	202	27.3%	
Histology	Ductal	213	72.7%	92	86.0%	68	76.4%	113	80.7%	76	68.5%	562	75.9%	0.002
	Lobular	29	9.9%	3	2.8%	1	1.1%	3	2.1%	2	1.8%	38	5.1%	
	Mixed ductal and lobular	6	2.0%	5	4.7%	2	2.2%	3	2.1%	1	0.9%	17	2.3%	
	Mucinous	5	1.7%	1	0.9%	0	0.0%	1	0.7%	0	0.0%	7	0.9%	
	Carcinoma	40	13.7%	6	5.6%	18	20.2%	20	14.3%	32	28.8%	116	15.7%	
Surgery	No surgery	248	84.6%	89	83.2%	73	82.0%	104	74.3%	103	92.8%	617	83.4%	0.116
	Partial mastectomy	22	7.5%	5	4.7%	9	10.1%	13	9.3%	4	3.6%	53	7.2%	
	Mastectomy	23	7.8%	10	9.3%	6	6.7%	22	15.7%	3	2.7%	64	8.6%	
	Unknown[a]	0	0.0%	3	2.8%	1	1.1%	1	0.7%	1	0.9%	6	0.8%	
Laterality	Left	140	47.8%	51	47.7%	51	57.3%	67	47.9%	48	43.2%	357	48.2%	0.347
	Right	142	48.5%	53	49.5%	34	38.2%	67	47.9%	44	39.6%	340	45.9%	
	Bilateral, single primary	2	0.7%	0	0.0%	2	2.2%	2	1.4%	3	2.7%	9	1.2%	
	Unknown[a]	9	3.1%	3	2.8%	2	2.2%	4	2.9%	16	14.4%	34	4.6%	
Bone metastases	No	65	22.2%	25	23.4%	32	36.0%	76	54.3%	48	43.2%	246	33.2%	<0.0001
	Yes	224	76.5%	82	76.6%	55	61.8%	62	44.3%	60	54.1%	483	65.3%	
	Unknown[a]	4	1.4%	0	0.0%	2	2.2%	2	1.4%	3	2.7%	11	1.5%	
Liver metastases	No	198	67.6%	68	63.6%	44	49.4%	94	67.1%	68	61.3%	472	63.8%	0.012
	Yes	82	28.0%	34	31.8%	41	46.1%	42	30.0%	36	32.4%	235	31.8%	
	Unknown[a]	13	4.4%	5	4.7%	4	4.5%	4	2.9%	7	6.3%	33	4.5%	
Lung metastases	No	162	55.3%	65	60.7%	39	43.8%	66	47.1%	53	47.7%	385	52.0%	0.037
	Yes	115	39.2%	35	32.7%	40	44.9%	70	50.0%	52	46.8%	312	42.2%	
	Unknown[a]	16	5.5%	7	6.5%	10	11.2%	4	2.9%	6	5.4%	43	5.8%	

(*continued on next page*)

Table 1 (*continued*)

Patient characteristics		Tumour subtype:										*P*
		HR-positive/ HER2-negative		HR-positive/ HER2-positive		HR-negative/ HER2-positive		Triple negative		Unknown[a]		Total		
		N	%	N	%	N	%	N	%	N	%	N	%	
Brain metastases only	No	249	85.0%	93	86.9%	72	80.9%	98	70.0%	89	80.2%	601	81.2%	0.001
	Yes	38	13.0%	14	13.1%	14	15.7%	40	28.6%	19	17.1%	125	16.9%	
	Unknown[a]	6	2.0%	0	0.0%	3	3.4%	2	1.4%	3	2.7%	14	1.9%	
Marital status at diagnosis	Single	71	24.2%	28	26.2%	18	20.2%	23	16.4%	29	26.1%	169	22.8%	0.12
	Married	118	40.3%	53	49.5%	37	41.6%	62	44.3%	35	31.5%	305	41.2%	
	Other (separated/ divorced/widowed)	81	27.6%	23	21.5%	28	31.5%	52	37.1%	41	36.9%	225	30.4%	
	Unknown[a]	23	7.8%	3	2.8%	6	6.7%	3	2.1%	6	5.4%	41	5.5%	
Status	Alive	121	41.3%	57	53.3%	32	36.0%	29	20.7%	30	27.0%	269	36.4%	<0.0001
	Dead	172	58.7%	50	46.7%	57	64.0%	111	79.3%	81	73.0%	471	63.6%	
Cause of death	Alive	121	41.3%	57	53.3%	32	36.0%	29	20.7%	30	27.0%	269	36.4%	<0.0001
	Breast cancer	161	54.9%	49	45.8%	54	60.7%	106	75.7%	77	69.4%	447	60.4%	
	Other	11	3.8%	1	0.9%	3	3.4%	5	3.6%	4	3.6%	24	3.2%	

Abbreviations: AK, Alaska; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; y, years.
[a] Unknown patients are excluded from the comparative analysis.

the patient population. Patient characteristics were compared between tumour subtypes using chi-square or Fisher's exact tests, as appropriate.

Within each variable, patients with unknown data were excluded from the comparative analysis. Overall survival (OS) was the primary endpoint chosen to assess prognosis and was defined as the interval from diagnosis of breast cancer until death from any cause or last follow-up for patients that were censored. Survival probabilities were estimated using the Kaplan–Meier method. Patient and tumour characteristics were individually analysed using log-rank test to determine the effect of each variable on OS. A Cox proportional hazards regression was used to assess the independent association of several variables with OS. Hazard ratios and their 95% confidence intervals (95% CIs) were estimated using the Cox model. All P values reported were two sided and P values $< .05$ were considered statistically significant. All statistical analyses were performed using STATA 12.0 (Stata Corporation, College Station, TX) and SPSS 20.0 (IBM Corporation, Armonk, NY).

3. Results

3.1. Patient characteristics

A total of 740 women were diagnosed with brain metastases from breast cancer at initial presentation between 2010 and 2013 and were included in this study. Median age was 60 years (range, 26–93 years). At diagnosis, brain was the only site of metastasis in 125 patients (16.9%), whereas 483 out of 740 patients (65.3%) had additional metastases in bone, 235 out of 740 patients (31.8%) had metastases in liver and 312 out of 740 patients (42.2%) had metastases in lung. Most patients had grade III/IV tumours (41.1%; n = 304). Among patients with known breast cancer tumour subtype, 293 patients (46.6%; 95% CI, 42.7–50.5%) had HR-positive/HER2-negative tumours, 107 patients (17%; 95% CI, 14.1–19.9%) had HR-positive/HER2-positive tumours, 89 patients (14.1%; 95% CI, 11.4–16.9%) had HR-negative/HER2-positive tumours and 140 patients (22.3%; 95% CI, 19–25.5%) had triple-negative tumours.

Table 1 shows the distribution of patient characteristics according to tumour subtype. There were significant differences among patients. Patients with brain metastases from triple-negative breast cancer had higher tumour grade ($P < .0001$), higher rates of brain only ($P = .001$) and lung metastases ($P = .037$), lower rate of bone metastases ($P < .0001$) and were more likely to die from breast cancer ($P < .0001$). In contrast, patients with HR-positive/HER2-negative breast cancer were older ($P = .005$), had lower tumour grade, higher rate of lobular histology ($P = .002$), higher rate of bone metastases, lower rates of brain only and liver metastases ($P = .012$).

3.2. Survival analysis

After a median follow-up of 6 months (range, 1–48 months), 471 deaths were reported (172 in the HR-positive/HER2-negative group, 50 in the HR-positive/HER2-positive group, 57 in the HR-negative/HER2-positive group and 111 in the triple-negative group).

Median OS for the entire cohort was 10 months (95% CI, 9–12 months), and 20.7% of the patients (95% CI, 16.8–24.9%) were alive at 36 months (Fig. 1). Analysis of OS according to tumour subtype showed significant differences with patients with brain metastases from triple-negative breast cancer experiencing the shortest survival (median OS: 6 months; 95% CI: 5–9 months), whereas patients with HR-positive/HER2-positive breast cancer had a median OS of 22 months (95% CI, 16 months to not estimable; $P < .0001$; Fig. 2). The impact of the presence of metastases at each individual visceral site on OS is shown in Fig. 3. Patients with liver metastases had significantly shorter survival (median OS: 7 months; 95% CI: 4–9 months) as compared with patients without liver metastases (median OS: 12 months; 95% CI: 10–15 months; $P < .0001$; Fig. 3A). A similar finding was seen for patients with lung metastases (median OS: 7 months; 95% CI: 5–9 months) versus no lung metastases (median OS: 13 months; 95% CI: 10–15 months; $P = .002$; Fig. 3B). However, there was no significant difference in OS between patients with metastases to the brain only (median OS: 12 months; 95% CI: 9–15 months) and those with metastases to the brain and other sites (median OS: 10 months; 95% CI: 8–12 months; $P = .16$; Fig. 3C).

Unadjusted models for the overall patient population were consistent with log-rank analysis and revealed a general decrease in OS in those patients who were older, black race, unmarried, lobular histology, triple-negative subtype, and those who did not receive surgery to the primary tumour (Table 2). Patients who had liver metastases, as well as those with lung metastases also had shorter OS. In contrast, univariate analysis did not show significant differences for tumour grade, bone metastases or brain metastases only. Multivariate Cox analyses confirmed the independent prognostic significance of age at diagnosis, marital status, histology, tumour subtype and liver metastases. Race, tumour grade and the other sites of metastases did not reach significance with this test. The final Cox model is shown in Table 3.

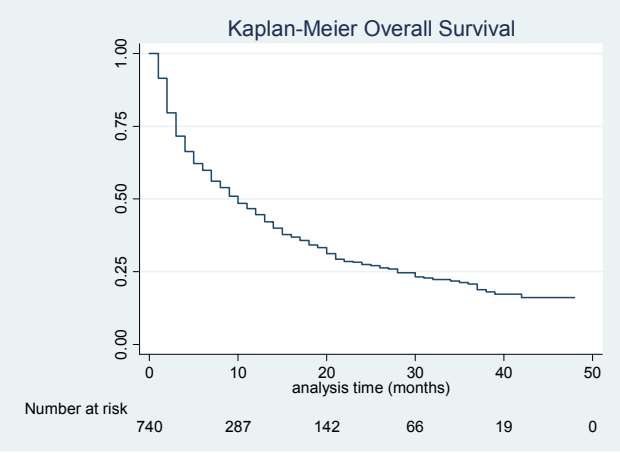

Fig. 1. Kaplan–Meier curve for overall survival for the whole population.

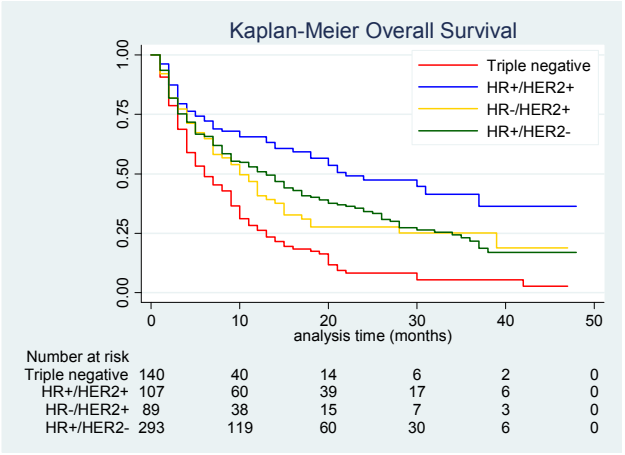

Fig. 2. Kaplan–Meier curve for overall survival according to tumour subtype. Log-rank $P < .0001$. HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

4. Discussion

Brain metastases are the fourth most common distant metastatic site in breast cancer [15]. Although they are less common than bone or other visceral metastases, they represent an important clinical problem due to their considerably poorer prognosis and lower sensitivity to systemic therapies. Most data on prognostic factors and outcomes come from studies in which brain metastases occurred after the diagnosis of early-stage breast cancer or during palliative therapy for metastatic disease. Few studies with small number of patients have evaluated the specific group of women who present with brain metastases at the time of initial breast cancer diagnosis. Given that prior lines of systemic treatment, length of disease-free interval and brain-directed therapies could modify the natural course of brain metastases in recurrent breast cancer, it is important to evaluate in a large, independent, treatment naïve cohort, the prognostic factors and outcomes of women who present with *de novo* brain metastases.

The median OS of 10 months seen in the overall patient population in our study is similar to the survival reported by previous authors in recent years [12,16–18]. Despite the poor prognosis that patients with brain metastases have, it is noteworthy that up to 20.7% of patients were alive 3 years after the diagnosis. The

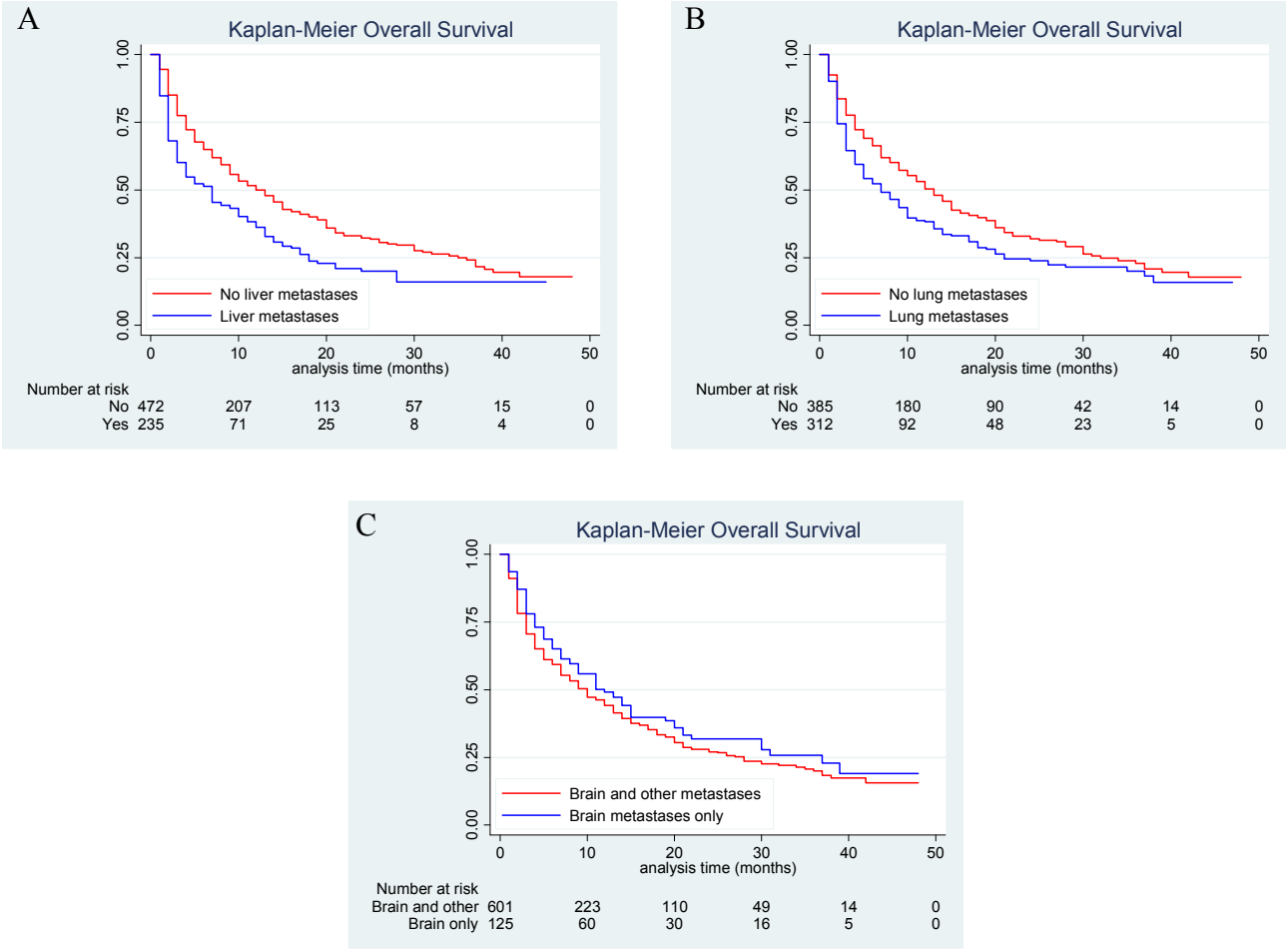

Fig. 3. A): Kaplan–Meier curves for overall survival according to individual visceral metastases. A: Liver. Log-rank $P < .0001$. (B): Kaplan–Meier curves for overall survival according to individual visceral metastases. B: Lung. Log-rank $P = .002$. (C): Kaplan–Meier curves for overall survival according to individual visceral metastases. C: Brain. Log-rank $P = .16$.

results of all these recent studies, including our own, suggest that the survival of breast cancer patients with brain metastases has improved over time, with previous reports describing median OS of 4–6 months which appear to have doubled according to our results [19,20].

Our study showed important differences in OS according to tumour subtype. Patients with HR-positive/HER2-positive breast cancer had the longest OS, and when compared with HR-positive/HER2-negative patients, they experienced a 36.1% reduction in the hazards of death. In contrast, patients with triple-negative tumours had the worst prognosis. Our findings are similar to previous reports analysing the impact of tumour subtype on OS [12,21,22]. The large difference in prognosis observed across all tumour subtypes confirms that breast cancer is a heterogeneous disease, even in the specific group of patients with brain metastases. The improvements in OS seen in HER2-positive patients could be explained in part by the efficacy of HER2-targeted agents [23,24]. In support of this, one of the largest studies evaluating patients with HER2-positive brain metastases—including both *de novo* and recurrent metastases-reported that the treatment with trastuzumab after the diagnosis of brain metastases reduced the hazards of death by 75%, and this was independent of the benefit of other therapies including chemotherapy, surgery and radiation therapy as shown in their multivariate model [25]. According to our results, the co-expression of HR in patients who are HER2-positive is an important prognostic factor that should not be ignored, in fact, the group of patients with HR-negative/HER2-positive subtype do not experience the same survival advantage as the HR-positive/HER2-positive group. Given that most patients with brain metastases will not be treated with endocrine therapy but rather with chemotherapy, our findings suggest that HER2-positive tumours are biologically different according to HR status with distinct prognosis. We observed significant differences in patient characteristics according to tumour subtype. Triple-negative patients, in addition to having worse survival, also had high-risk features, such as higher tumour grade and higher rate of visceral metastases. Despite the known increased risk of triple-negative and HER2-positive subtypes to develop

Table 2
Unadjusted overall survival.

Variable	Median OS (months)	Log-rank *P*	Hazard ratio	95.0% CI for hazard ratio	
				Lower	Upper
Age at diagnosis, y					
<50	13	0.0002	Reference		
50–64	11		1.154	0.894	1.491
>64	7		1.604	1.232	2.089
Race					
White	11	0.0041	Reference		
Black	7		1.420	1.141	1.766
Other (American Indian/AK Native, Asian/Pacific Islander)	11		1.009	0.698	1.459
Grade					
I	18	0.0696	Reference		
II	11		1.459	0.839	2.536
III/IV	9		1.704	0.991	2.933
Histology					
Ductal	10	0.0145	Reference		
Lobular	7		1.175	0.789	1.750
Mixed ductal and lobular	34		0.433	0.205	0.915
Mucinous	NR		0.179	0.025	1.277
Carcinoma	7		1.169	0.918	1.489
Surgery					
No surgery	9	<0.0001	Reference		
Partial mastectomy	13		0.686	0.481	0.979
Mastectomy	24		0.456	0.314	0.661
Tumour subtype					
HR-positive/HER2-negative	13	<0.0001	Reference		
HR-positive/HER2-positive	22		0.639	0.466	0.876
HR-negative/HER2-positive	10		1.105	0.819	1.491
Triple negative	6		1.760	1.384	2.239
Bone metastases					
No	9	0.1823	Reference		
Yes	12		0.883	0.730	1.068
Liver metastases					
No	12	<0.0001	Reference		
Yes	7		1.512	1.244	1.839
Lung metastases					
No	13	0.002	Reference		
Yes	7		1.330	1.102	1.606
Brain metastases only					
No	10	0.1597	Reference		
Yes	12		0.846	0.664	1.078
Marital status					
Single	9	0.0165	Reference		
Married	13		0.879	0.691	1.119
Other (separated/divorced/widowed)	7		1.189	0.929	1.520

Abbreviations: AK, Alaska; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NR, not reached; OS, overall survival; y, years.

brain metastases, it is noteworthy that in the present study, HR-positive/HER2-negative tumours represented the largest group of patients (46.6% of cases with known subtype). Therefore, this group should still be considered at risk for brain metastases at any point in the natural course of their disease.

The impact of the presence of extracranial disease in patients with brain metastases is controversial. A recent validation and refinement of the breast cancer-specific graded prognostic assessment did not include extracranial disease as a prognostic indicator in the final model [26]. Other studies have failed to show an association between extracranial metastases and OS [18,21]. In our cohort, patients with metastases to the brain only had no significant difference in OS when compared with patients with extracranial metastases. However, when we analysed specific extracranial metastatic sites, we identified that the presence of metastasis at other visceral locations such as the liver or lung had a significant negative impact on OS by univariate analysis, yet only metastases to the liver were found to be independently associated with shorter OS in the adjusted model. Taken together, our findings underscore the importance of individualising specific sites of extracranial disease in

Table 3
Multivariate analysis for overall survival.

Variable	*P*	Hazard ratio	95.0% CI for hazard ratio	
			Lower	Upper
Age at diagnosis, y				
<50 years		Reference		
50–64 years	0.850	1.033	0.741	1.439
>64 years	0.001	1.840	1.276	2.653
Race				
White		Reference		
Black	0.051	1.397	0.999	1.953
Other (American Indian/ AK Native, Asian/ Pacific Islander)	0.937	1.020	0.631	1.649
Grade				
I		Reference		
II	0.131	1.626	0.865	3.057
III/IV	0.081	1.765	0.932	3.342
Histology				
Ductal		Reference		
Lobular	0.006	2.081	1.238	3.496
Mixed ductal and lobular	0.199	0.552	0.223	1.366
Mucinous	0.359	0.394	0.054	2.881
Carcinoma	0.435	1.181	0.777	1.795
Tumour subtype				
HR-positive/HER2-negative		Reference		
Triple negative	0.010	1.541	1.108	2.143
HR-positive/HER2-positive	0.059	0.685	0.462	1.014
HR-negative/HER2-positive	0.325	1.222	0.820	1.821
Sites of metastases				
Bone (yes versus no)	0.780	1.054	0.730	1.521
Liver (yes versus no)	0.001	1.645	1.236	2.190
Lung (yes versus no)	0.288	1.170	0.876	1.563
Brain only (yes versus no)	0.696	1.102	0.678	1.789
Marital status				
Single		Reference		
Married	0.047	0.715	0.513	0.996
Other (separated/ divorced/widowed)	0.546	0.898	0.633	1.273

Abbreviations: AK, Alaska; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; y, years.

the prognostic assessment of patients with breast cancer brain metastases.

We acknowledge that our study has some limitations. The population-based design could include errors in data reporting, in addition, data on HR and HER2 status could not be centrally reviewed and was collected from different local pathology laboratories. We do not have information with regards to brain-directed surgery, radiotherapy or systemic treatments of this cohort, which may contribute to some of the differences observed in survival according to prognostic variables. SEER currently does not collect information on other sites of metastases such as lymph nodes, pleura, peritoneum or skin, among others, which could assist in more specific prognostic assessment of the extracranial metastases group. Finally, we do not have information about the number of brain metastases or performance status, which would allow to classify patients according to graded prognostic assessment. However, the predictive value of this and other similar models remain unclear and their use in routine clinical practice has been questioned [27]. Despite these limitations, our study has several important strengths. To our knowledge, this is the largest analysis of patients with *de novo* brain metastases at the time of initial breast cancer diagnosis conducted to date. In addition, the population-based source of our cohort confers strong external validity to our results, which is very relevant given the paucity of data about this specific group of patients. Our study, unlike others reporting outcomes after breast cancer relapse or progression, does not suffer from the confounding effects that prior local and systemic therapies might have on the timing of development and potential treatment resistance of brain metastases, therefore providing important clinical information for prognostic assessment and risk stratification of treatment naïve brain metastases from breast cancer. The prognostic information about tumour subtypes and specific sites of extracranial metastases from our study could be used for risk stratification in the design of prospective studies of brain metastases in breast cancer.

Funding

None.

Conflict of interest statement

None declared.

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