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Prognostic significance of molecular subtype, metastatic site and primary tumor surgery for survival in primary metastatic breast cancer

A SEER-based study

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Abstract

The incidence of primary metastatic breast cancer (PMBC) has not decreased despite the increasing popularity of mammography screening and data on the survival among these patients are limited. Therefore, we conducted an extensive population-based study to investigate the factors influencing the survival of patients with PMBC.

We identified 14,306 patients with de novo stage-IV breast cancer using the Surveillance, Epidemiology, and End Results data from 2010 to 2015. The overall survival (OS) time and breast cancer-specific survival (BCSS) time were compared by the Kaplan-Meier method. Univariate and multivariate analyses were performed to determine the effect of different prognostic factors.

Patients with hormone receptor positive/human epidermal growth factor receptor 2 positive showed the longest median survival time in OS (39 months) and BCSS (43 months), and those with triple negative exhibited the shortest in OS (11 months) and BCSS (12 months). We concluded that patients who had undergone primary tumor surgery had better survival than those who did not. The incidence of distant visceral metastasis in the whole cohort was as follows: bone, lung, liver, and brain. This study also substantiated that patients with only brain metastasis had poorer survival than patients with metastasis at multiple sites metastasis, not including brain metastasis ($P < .0001$).

This study confirmed that molecular subtypes, metastatic site and primary tumor surgery were associated with the survival of PMBC patients.

Abbreviations: BCSS = breast cancer-specific survival, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, OS = overall survival, PMBC = primary metastatic breast cancer, SEER = surveillance, epidemiology, and end results.

Keywords: metastatic site, molecular subtype, Primary metastatic breast cancer, surgery, survival

1. Introduction

There will be an estimation of 268,600 women in the United States being diagnosed with breast cancer in 2019 and it alone accounts for 30% of all new cancer diagnoses in women.[1] Approximately 6% of patients presented with Metastatic breast cancer (MBC) at initial diagnosis (de novo stage-IV breast cancer).[2,3] MBC is considered incurable; it is the underlying reason to cause death for the majority of patients.[2,4] The prognosis for primary metastatic breast cancer (PMBC) patients is very poor and the median survival time with brain metastases is reported to 13.8 months[5]; therefore, we should pay more attention to prolong the survival time, improve the quality of life of the patients with de novo stage-IV breast cancer. Like early-stage breast cancer, MBC is a highly complex and heterogeneous disease, the therapeutic goals are to develop appropriate regimens, ameliorate symptom, improve quality of life, and extend survival time for patients.[3,4,6,7] Actually, there existed many risk factors affecting the prognosis of MBC, among which molecular subtype was one of the most important high risk factors.[8,9] Breast cancer can be categorized into four distinct molecular subtypes according to presence of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2).[10] It has been reported that the prognosis of triple negative breast cancer is the worst for both early and advanced breast cancer.[11–13] Several studies have also suggested a range of other relative factors of outcomes with MBC including

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YL, SW, and WY contributed equally to this article.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets generated during and/or analyzed during the current study are publicly available.

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factors such as race, age at diagnosis, and distant metastatic sites.[9,14,15] The role of excision of primary tumor has been controversial due to inconsistent reports. A few retrospective studies suggested the longer OS of local treatment of primary stage IV breast cancer.[6,8,16,17] In addition, patients with different molecular types tended to have their preferential sites of distant metastases. Those with hormone receptor positive (HR+)/HER2− subtype have a higher probability of bone metastases. HER2-riched cancers have a propensity to give rise to liver and triple negative subtype to lung and brain. In general, the sites of metastases with all subtypes were most prone to bone, followed by lung, liver, and brain.[8,14,15,18–20]

Although there are many studies on MBC, mostly aiming at secondary metastatic breast cancer, the data on the primary MBC are limited. It has been reported that de novo MBC has longer disease-specific survival time than recurrent MBC[21]; in addition, it is not clear the effect of operation on the prognosis.

The purpose of this study was to illuminate factors influencing survival of patients presenting with PMBC using data from the Surveillance, Epidemiology, and End Results (SEER).

2. Methods

2.1. Patient information

We abstracted data from the SEER 18 registries research database (National Cancer Institute, Bethesda, MD) and searched patients for primary metastatic female breast cancer diagnosed from 2010 to 2015 (https://seer.cancer.gov/). A total of 19,913 cases were included who had to be microscopically confirmed as malignant including histology, exfoliative, and thus we excluded 788 women. We selected patients with only one primary malignancy and excluded 4806 patients who had >1 primary cancer. We precluded 13 patients who diagnosed with only autopsy and death certification, the remaining 14,306 patients eligible for survival analyses. We collected information as follows: age at diagnosis, race, year of diagnosis, tumor grade, laterality, lymph nodes, HR, and HER2 status, breast subtypes, marital status, insurance, surgery, distant metastatic site, and survival. And the cancer was classified into 4 molecular subtypes according to HR and HER2 status: HR+/HER2+, HR–/HER2+, HR+/HER2−, and HR−/HER2−. We use overall survival (OS) and breast cancer-specific survival (BCSS) to evaluate the prognosis of the primary metastatic breast cancer.

2.2. Ethics statement

This study was mainly based on the SEER database and was conducted in compliance with the Helsinki Declaration. We obtained permission to access the SEER program research data files. The need for informed patient consent was waived because of the retrospective nature of the study. This study was approved by the ethics committee of Tianjin Medical University Cancer Institution and Hospital.

2.3. Statistical analysis

Descriptive statistics were performed to examine the baseline characteristics. We divided the age into 3 groups: <40 years, 40–70 years, and ≥70 years. Race included American Indian/Alaska Native/Pacific Islander. These variables were stratified by molecular subtypes: HR+/HER2+, HR–/HER2+, HR+/HER2−, and HR−/HER2−. The χ^2 test for categorical variables (age, race, grade, lymph node, among others) was adopted to compare the differences among different groups.

We defined OS as the time from diagnosis to death from any cause or last follow-up. BCSS was calculated as the time from the date of diagnosis to the date of death from breast cancer or last follow-up. The OS and BCSS were summarized by Kaplan-Meier survival curves. The log-rank analyses were used to assess the differences among the four groups. We performed univariate and multivariate Cox proportional hazard model to examine the influence of different variables on OS and BCSS. Hazard ratios and their associated 95% confidence intervals (95% CIs) were obtained from the Cox regression analysis. The Kaplan-Meier method was conducted to study the OS and BCSS of primary surgery and different distant metastatic sites. All statistical tests were 2-sided and P values <.05 were considered statistically significant. Analyses were conducted using SPSS 22.0 (IBM SPSS, New York).

3. Results

3.1. Patients characteristics

A total of 14,306 patients with de novo stage IV breast cancer were enrolled in this study from 2010 to 2015. The clinical characteristics were summarized in Table 1. Among the population, 51.6%, 15.0%, 8.2%, and 11.8% of patients had HR+/Her2−, HR+/HER2+, HR−/HER2+ and HR−/HER2− subtypes, respectively, the fewest cases had HR–/HER2+ (8.2%) tumors. Patients age < 70 years accounted for 80.6% of all the HR-/Her2+ subtype. As for race, more black patients (n=436, 25.8%) within HR-/HER2- tumors than the others were observed. In addition, more patients were to be married (n=6039, 42.2%), insured (n=11138, 77.9%) and usually had 1 to 3 metastases in axillary lymph nodes (n=4831, 33.8%). Patients with HR+/HER2– subtype had a lower tumor grade ($P<.001$), a predilection to metastasize to bone ($P<.001$), and were less likely to undergo surgery ($P<.001$). In contrast, triple negative breast cancer patients had a higher tumor grade ($P<.001$), more possibilities for surgical treatment ($P < .001$), and were more frequently observed in lung metastases ($P<.001$).

3.2. Metastasis pattern

Figure 1 showed that the incidence of bone metastasis was the highest, accounting for 68.9% and brain was the least common metastatic site, reflecting 7.8% of the entire cohort. The percentage with metastasis to bone, lung, liver and brain in HR+/HER2– subtype was 77.6%, 28.5%, 20.6%, and 5.8%. In the triple negative patients, the percentage was 48.3%, 44.7%, 31.3%, and 12.5%. However, patients with HR+/HER2+ and HR–/HER2+ tumors, the probability of liver metastases was higher than lung metastases.

3.3. Survival analysis

The median OS and BCSS among the whole cohort was 25 and 30 months, respectively. As shown in Figure 2, significant statistical difference in survival outcomes was observed among different tumor subtypes ($P<.001$). Patients with HR+/HER2+ subtype experienced the longest median OS (39 months, 95% CI: 36.1–41.9) and BCSS (43 months, 95% CI: 39.6–46.4), whereas

Table 1

Demographic characteristics of patients in the SEER database according to molecular subtypes.

Patients characteristics according to molecular subtypes	Patients characteristics						Molecular subtypes						
	HR+/HER2−		HR+/HER2+		HR−/HER2+		Triple negative		Unknown		Total		
	N	%	N	%	N	%	N	%	N	%	N	%	*P*
All patients	7381	51.6	2146	15.0	1166	8.2	1690	11.8	1923	13.4	14306	100	
Age, y													<.001
<40	422	5.7	237	11.0	132	11.3	141	8.3	64	3.3	996	7.0	
40–70	4740	64.2	1481	69.0	808	69.3	1121	66.3	1078	56.1	9228	64.5	
≥70	2219	30.1	428	19.9	226	19.4	428	25.3	781	40.6	4082	28.5	
Race													<.001
White	5671	76.8	1583	73.8	838	71.9	1138	67.3	1482	77.1	10712	74.9	
Black	1103	14.9	381	17.8	206	17.7	436	25.8	311	16.2	2437	17.0	
Others	575	7.8	178	8.3	116	9.9	113	6.7	115	6.0	1097	7.7	
Unknown	32	0.4	4	0.2	6	0.5	3	0.2	15	0.8	60	0.4	
Year of diagnosis													<.001
2010	1104	15.0	291	13.6	163	14.0	282	16.7	393	20.4	2233	15.6	
2011	1244	16.9	334	15.6	183	15.7	281	16.6	338	17.6	2380	16.6	
2012	1186	16.1	370	17.2	180	15.4	265	15.7	308	16.0	2309	16.1	
2013	1311	17.8	358	16.7	198	17.0	302	17.9	325	16.9	2494	17.4	
2014	1272	17.2	376	17.5	221	19.0	286	16.9	290	15.1	2445	17.1	
2015	1264	17.1	417	19.4	221	19.0	274	16.2	269	14.0	2445	17.1	
Grade													<.001
I	671	9.1	48	2.2	4	0.3	23	1.4	70	3.6	816	5.7	
II	3011	40.8	697	32.5	257	22.0	240	14.2	321	16.7	4526	31.6	
III/IV	2135	28.9	1061	49.4	710	60.9	1166	69.0	408	21.2	5480	38.3	
Unknown	1564	21.2	340	15.8	195	16.7	261	15.4	1124	58.5	3483	24.4	
Laterality													<.001
Right	3527	47.8	994	46.3	550	47.2	803	47.5	708	36.8	6582	46.0	
Left	3552	48.1	1103	51.4	590	50.6	836	49.5	826	43.0	6907	48.3	
Bilateral	37	0.5	10	0.5	12	1.0	6	0.4	23	1.2	88	0.6	
Unknown	265	3.6	39	1.8	14	1.2	45	2.7	366	19.0	729	5.1	
Lymph node													<.001
N0	1568	21.2	401	18.7	155	13.3	308	18.2	482	25.1	2914	20.4	
N1	2600	35.2	782	36.4	434	37.2	564	33.4	451	23.5	4831	33.8	
N2	678	9.2	191	8.9	112	9.6	145	8.6	86	4.5	1212	8.5	
N3	1859	25.2	612	28.5	388	33.3	563	33.3	365	19.0	3787	26.5	
Nx	676	9.2	160	7.5	77	6.6	110	6.5	539	28.0	1562	10.9	
Marital status													<.001
Single	1609	21.8	511	23.8	241	20.7	374	22.1	449	23.3	3184	22.3	
Married	3154	42.7	957	44.6	515	44.2	708	41.9	705	36.7	6039	42.2	
Others	2191	29.7	557	26.0	336	28.8	522	30.9	633	32.9	4239	29.6	
Unknown	427	5.8	121	5.6	74	6.3	86	5.1	136	7.1	844	5.9	
Insurance													<.001
Uninsured	288	3.9	111	5.2	42	3.6	83	4.9	106	5.5	630	4.4	
Insured	5829	79.0	1660	77.4	941	80.7	1336	79.1	1372	71.3	11138	77.9	
Unknown	1264	17.1	375	17.5	183	15.7	271	16.0	445	23.1	2538	17.7	
Surgery													<.001
Surgery	1938	26.3	631	29.4	376	32.2	611	36.2	269	14.0	3825	26.7	
No-surgery	5290	71.7	1476	68.8	752	64.5	1047	62.0	1627	84.6	10192	71.2	
Unknown	153	2.1	39	1.8	38	3.3	32	1.9	27	1.4	289	2.0	
Bone metastases													<.001
No	1526	20.7	642	29.9	536	46.0	841	49.8	558	29.0	4103	28.7	
Yes	5729	77.6	1459	68.0	597	51.2	816	48.3	1257	65.4	9858	68.9	
Unknown	126	1.7	45	2.1	33	2.8	33	2.0	108	5.6	345	2.4	
Lung metastases													<.001
No	4995	67.7	1381	64.4	674	57.8	893	52.8	1153	60.0	9096	63.6	
Yes	2102	28.5	684	31.9	445	38.2	756	44.7	610	31.7	4597	32.1	
Unknown	284	3.8	81	3.8	47	4.0	41	2.4	160	8.3	613	4.3	
Liver metastases													<.001
No	5622	76.2	1268	59.1	552	47.3	1119	66.2	1263	65.7	9824	68.7	
Yes	1521	20.6	817	38.1	582	49.9	529	31.3	520	27.0	3969	27.7	
Unknown	238	3.2	61	2.8	32	2.7	42	2.5	140	7.3	513	3.6	

(*continued*)

Table 1

(continued).

Patients characteristics according to molecular subtypes

	Patients characteristics						Molecular subtypes						
	HR+/HER2−		HR+/HER2+		HR−/HER2+		Triple negative		Unknown		Total		
	N	%	N	%	N	%	N	%	N	%	N	%	*P*
Brian metastases													<.001
No	6654	90.2	1889	88.0	977	83.8	1427	84.4	1599	83.2	12546	87.7	
Yes	428	5.8	174	8.1	148	12.7	212	12.5	156	8.1	1118	7.8	
Unknown	299	4.1	83	3.9	41	3.5	51	3.0	168	8.7	642	4.5	
Vital status													<.001
Alive	3725	50.5	1245	58.0	607	52.1	402	23.8	596	31.0	6575	46.0	
Death	3656	49.5	901	42.0	559	47.9	1288	76.2	1327	69.0	7731	54.0	
Cause of death													<.001
Alive	3725	50.5	1245	58.0	607	52.1	402	23.8	596	31.0	6575	46.0	
Breast cancer	3170	42.9	801	37.3	500	42.9	1138	67.3	1076	56.0	6685	46.7	
Others	486	6.6	100	4.7	59	5.1	150	8.9	251	13.1	1046	7.3	

HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, SEER = surveillance, epidemiology, and end results.

the triple negative breast cancer had the worst survival (median OS: 11 months; median BCSS: 12 months, respectively). To further study the effect of metastasis sites and surgery on survival, we adopted the following analysis which is shown in Figures 3 and 4. We found significant difference in OS and BCSS of patients with only 1 metastasis site (Log rank $P < .001$), and patients with only bone metastases had the longest median survival (median OS: 36 months, median BCSS: 42 months), whereas brain metastases had the worst OS and BCSS (median OS: 12 months, median BCSS: 13 months). Furthermore, the median OS and BCSS in patients with multiple sites of metastases were 16 and 20 months. As shown in Figure 4 which represented the prognostic impact of primary tumor surgery. Kaplan–Meier curves showed higher OS and BCSS in patients undergoing primary tumor surgery compared with those who did not ($P < .001$). In addition, a subgroup analysis was adopted to compare the OS according to various tumor subtypes. The results showed that patients undergone primary surgery had the better OS whichever subtypes it were ($P < .001$). It had to be noted that unknown patients were excluded from our statistical analyses. We used univariate and multivariate Cox proportional hazard models to determine the prognostic factors, shown in Table 2. In the univariate analysis, age, race, tumor grade, marital status, insurance status, surgery treatment, molecular subtypes, and metastasis sites significantly affected OS and BCSS ($P < .001$). Lymph node status was significantly correlated with BCSS ($P < .05$) but not with OS. The multivariate Cox model confirmed that age, race, tumor grade, marital status, insurance status, surgery, molecular subtypes, and metastasis sites were independent prognostic factors for both OS and BCSS ($P < .001$).

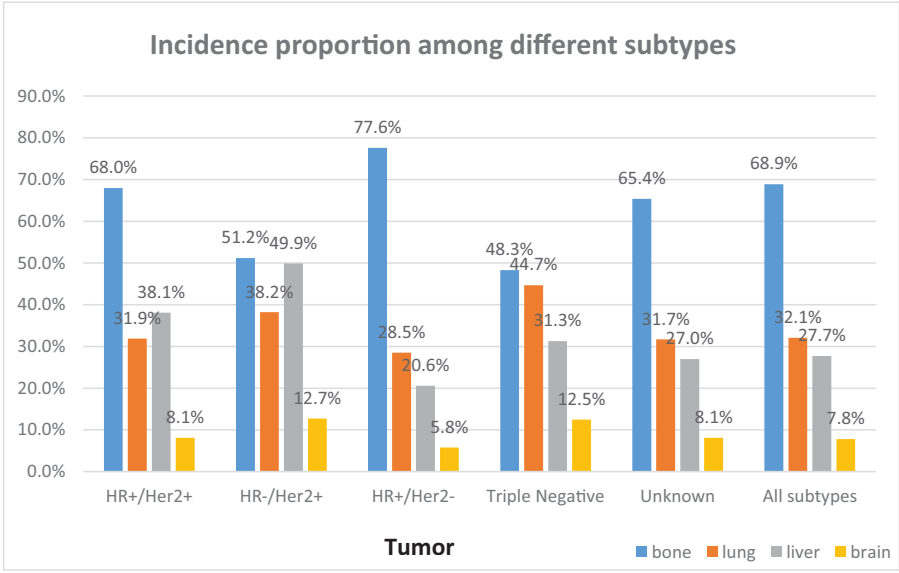

Figure 1. The incidence proportion of patients with initial different metastatic sites among breast cancer patients according to tumor subtype in the SEER cohort. SEER = surveillance, epidemiology, and end results.

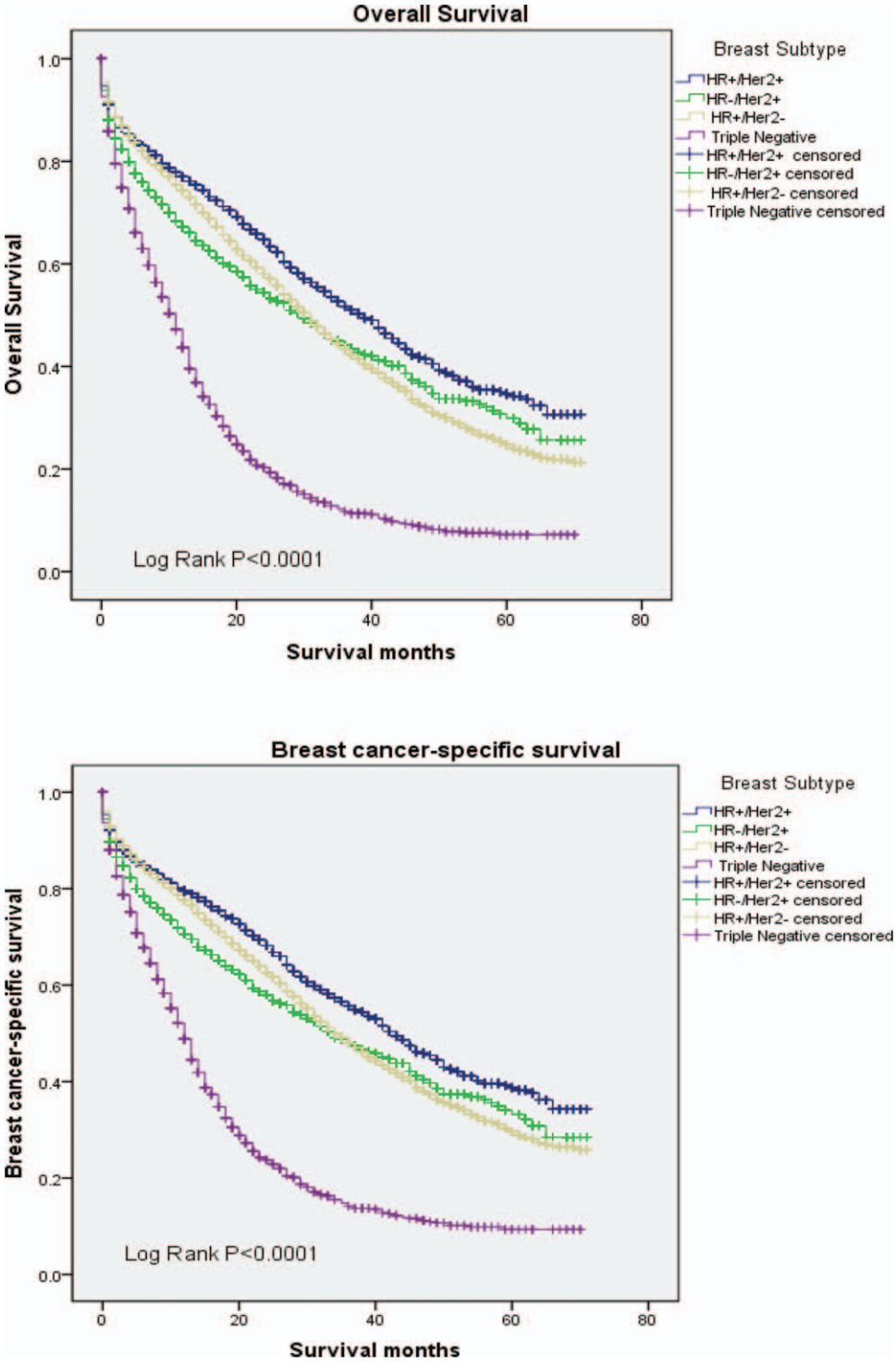

Figure 2. Overall survival and breast cancer-specific survival according to tumor subtypes.

4. Discussion

This study suggested that molecular subtypes demonstrate a strong correlation to the prognosis of patients with primary stage IV breast cancer. Patients with triple negative subtype and brain metastases had the worst outcome. Furthermore, patients undergoing primary surgery had better prognosis than those who did not.

We observed significantly differences of prognosis according to tumor subtypes. HR+/HER2+ subtype experienced the longest OS and BCSS whereas the triple negative had the worst survival. However, this result was slightly discrepant with a study

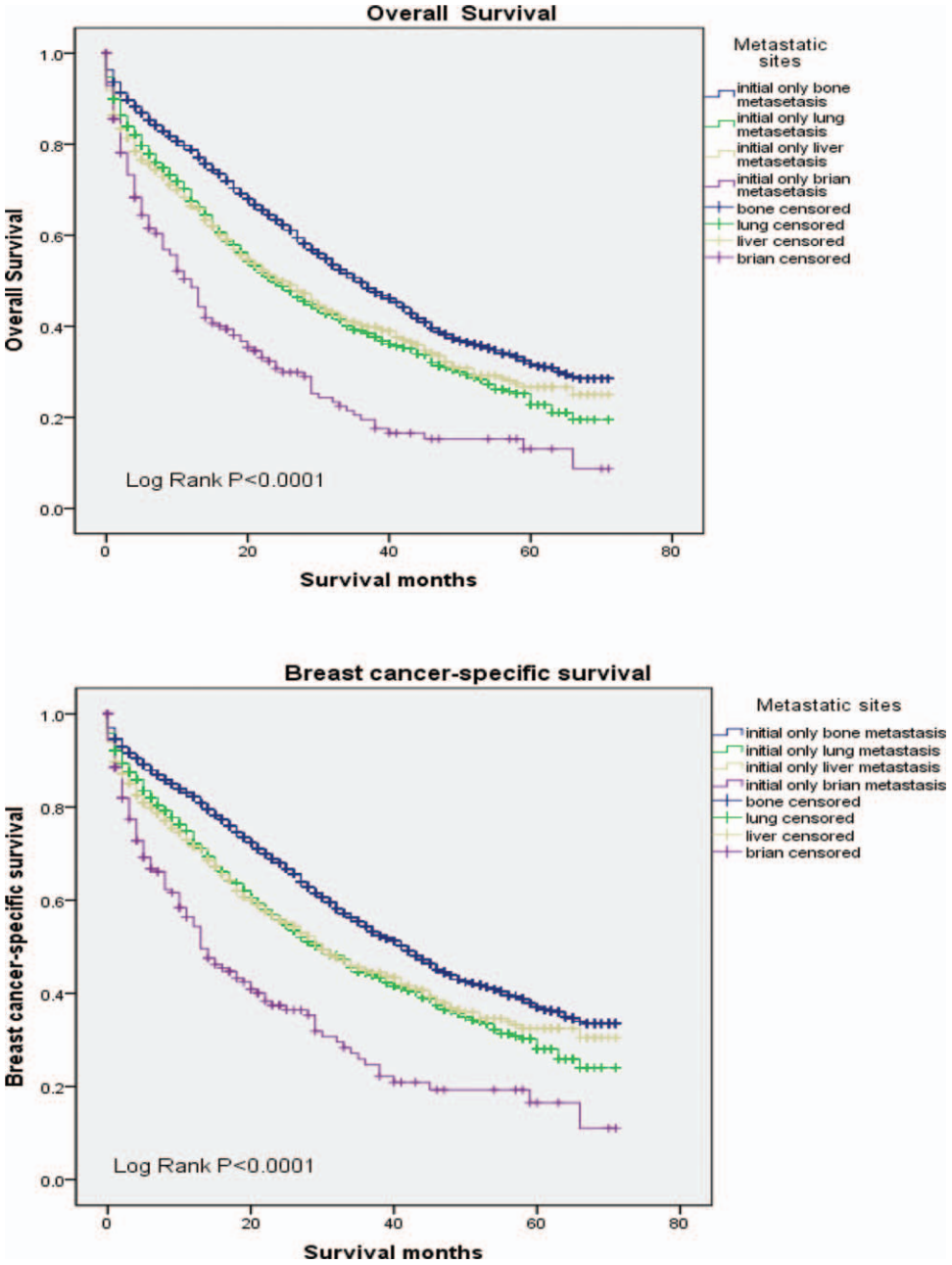

Figure 3. Kaplan-Meier curve for OS and BCSS in patients with primary metastatic breast cancer in different metastatic sites. BCSS = breast cancer-specific survival, OS = overall survival.

conducted by Kennecke et al who included 3726 patients with early-stage breast cancer from 1986 to 1992 then 1357 developed distant metastases during subsequent follow up. The median survival (MS) of luminal A (MS = 2.2 years) and luminal B (MS = 1.6 years) subtypes were longer than that of luminal/HER2 (MS = 1.3 years) subtype.[22] The survival difference may due to the fact that the latter did not undergo HER2 targeted therapy which rapidly implemented in 1998. In addition, an observational study conducted in Netherlands had drawn similar conclusion to this study that HR+/HER2+ subtype survived the longest time than the others.[23] There was light difference in the effect of molecular subtypes on the prognosis of early and advanced breast cancer. Unlike primary stage IV breast cancer patients, 10-year OS was higher for luminal A (HR+/HER2−) subtype compared with other subtypes ($P < .001$) in early-stage breast cancer patients. Triple negative subtype had the worst prognosis whether in early or metastatic ones,[24] which signified triple negative breast cancer was a heterogeneous disease and still the hotpot of future researches. Our study suggested that molecular subtypes were independent prognostic factors for PMBC and therefore it is necessity to re-biopsy the metastatic tissue to identify whether the molecular subtype has changed. In conclusion, this article confirmed that molecular subtypes are great relevance to the prognosis of the de novo stage-IV breast

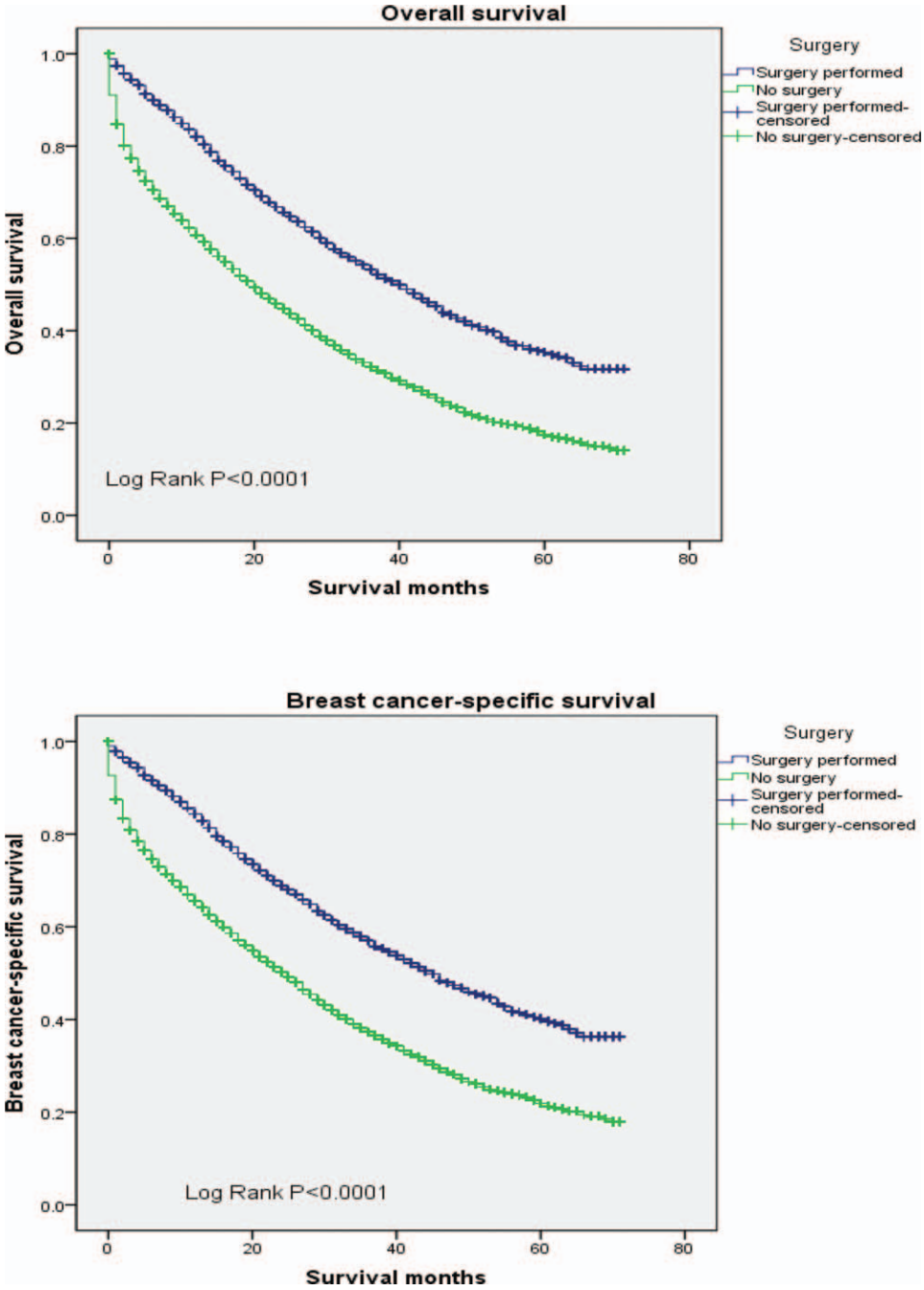

Figure 4. Surgery of survival analysis in OS and BCSS among patients in primary metastatic breast cancer patients. BCSS = breast cancer-specific survival, OS = overall survival.

cancer. This study demonstrated that breast cancer subtypes were associated with the unique site of distant metastases. We found that bone was the most common metastatic organ and the incidence of bone metastases was highest in patients with HR +/HER2− status. Several studies had indicated the similar results.[8,15,18–20] The strong association of HR–/HER2+ and triple negative subtypes with lung metastases were reported in our study. Previous research suggested the lung metastasis gene-expression was expressed in breast cancer cells and it developed a high risk of lung metastases. It was reported that this gene could both mediate and predict lung metastases.[25] Tumors with HR− status, basal-like molecular subtype were tended to lung metastases.[22,26] This study showed liver and brain metastases were more likely to occur in HR−/HER2+ tumors and furthermore, liver metastases were more frequently observed in HER2+ subtype. This could be deeply understanding by knowing the relationship between chemokine receptor CXCR4 and HER2. A research demonstrated that the expression of CXCR4 predicted for the development of liver metastases and another study showed that HER2 over-expression up-regulated the

Table 2

Cox proportional hazards regression model analysis of overall survival and breast cancer-specific survival of initial metastatic breast cancer patients.

	OS				BCSS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR	*P*	HR	*P*	HR	*P*
Age, y								
<40	**Reference**		**Reference**		**Reference**		**Reference**	
40–70	1.503 (1.354–1.668)	<.001	1.434 (1.291–1.594)	<.001	1.483 (1.328–1.656)	<.001	1.432 (1.281–1.601)	<.001
≥70	2.396 (2.151–2.668)	<.001	2.175 (1.943–2.435)	<.001	2.214 (1.975–2.482)	<.001	2.063 (1.830–2.326)	<.001
Race								
White	**Reference**		**Reference**		**Reference**		**Reference**	
Black	1.282 (1.211–1.358)	<.001	1.185 (1.117–1.257)	<.001	1.271 (1.194–1.352)	<.001	1.158 (1.086–1.234)	<.001
Others	0.880 (0.804–0.963)	.005	0.958 (0.875–1.049)	.352	0.887 (0.805–0.976)	.014	0.951 (0.863–1.047)	.306
Year of diagnosis								
2010	Reference				Reference			
2011	0.962 (0.900–1.029)	.260			0.970 (0.903–1.043)	.410		
2012	0.938 (0.874–1.007)	.075			0.974 (0.878–1.021)	.157		
2013	0.958 (0.890–1.031)	.251			0.958 (0.885–1.037)	.286		
2014	0.964 (0.888–1.046)	.378			0.944 (0.864–1.032)	.204		
2015	0.846 (0.760–0.941)	.002			0.856 (0.762–0.961)	.009		
Grade								
I	**Reference**		**Reference**		**Reference**		**Reference**	
II	1.202 (1.071–1.349)	.002	1.222 (1.089–1.372)	.001	1.297 (1.141–1.474)	<.001	1.310 (1.152–1.489)	<.001
III/IV	1.729 (1.545–1.935)	<.001	1.684 (1.499–1.892)	<.001	1.930 (1.703–2.186)	<.001	1.866 (1.641–2.122)	<.001
Laterality								
Right	**Reference**		Reference		**Reference**		Reference	
Left	1.013 (0.967–1.061)	.579	1.003 (0.958–1.050)	.902	1.019 (0.969–1.070)	.465	1.008 (0.959–1.059)	.757
Bilateral	1.520 (1.187–1.946)	.001	1.040 (0.811–1.334)	.758	1.445 (1.010–1.896)	.008	1.012 (0.770–1.330)	.933
Lymph node metastasis								
N0	**Reference**		**Reference**		**Reference**		Reference	
N1	0.863 (0.810–0.920)	<.001	0.899 (0.842–0.960)	.001	0.916 (0.855–0.981)	.013 0.930 (0.867–0.998)	0.044	
N2	0.842 (0.767–0.924)	<.001	1.026 (0.933–1.128)	.599	0.893 (0.809–0.986)	.026	1.059 (0.956–1.172)	.272
N3	1.061 (0.994–1.133)	.074	1.035 (0.968–1.107)	.315	1.115 (1.039–1.197)	.002	1.054 (0.980–1.134)	.157
Marital status								
Single	**Reference**		**Reference**		**Reference**		**Reference**	
Married	0.759 (0.716–0.805)	<.001	0.804 (0.757–0.854)	<.001	0.768 (0.721–0.818)	<.001	0.816 (0.765–0.871)	<.001
Others	1.157 (1.090–1.229)	<.001	1.010 (0.948–1.077)	.748	1.137 (1.065–1.213)	<.001	1.016 (0.949–1.088)	.644
Insurance								
Uninsured	**Reference**		**Reference**		**Reference**		**Reference**	
Insured	0.751 (0.677–0.833)	<.001	0.788 (0.709–0.875)	<.001	0.739 (0.662–0.826)	<.001	0.787 (0.704–0.881)	<.001
Surgery								
Surgery	**Reference**		**Reference**		**Reference**			**Reference**
No-surgery	1.921 (1.820–2.029)	<.001	1.784 (1.682–1.891)	<.001	1.887 (1.780–2.000)	<.001	1.798 (1.690–1.914)	<.001
Molecular subtypes								
HR+/HER2+	**Reference**		**Reference**		**Reference**		**Reference**	
HR−/HER2+	1.293 (1.163–1.436)	<.001	1.279 (1.150–1.422)	<.001	1.304 (1.166–1.458)	<.001	1.284 (1.148–1.437)	<.001
HR+/HER2−	1.223 (1.137–1.315)	<.001	1.309 (1.215–1.410)	<.001	1.194 (1.105–1.290)	<.001	1.309 (1.209–1.417)	<.001
Triple Negative	2.924 (2.683–3.186)	<.001	2.931 (2.686–3.199)	.009	2.942 (2.685–3.222)	<.001	2.977 (2.713–3.267)	<.001
Metastasis sites								
Bone	**Reference**		**Reference**		**Reference**		**Reference**	
Lung	1.383 (1.272–1.504)	<.001	1.114 (1.022–1.215)	.014	1.371 (1.252–1.502)	<.001	1.087 (0.990–1.194)	.080
Liver	1.371 (1.247–1.506)	<.001	1.423 (1.292–1.566)	<.001	1.370 (1.238–1.517)	<.001	1.386 (1.249–1.539)	<.001
Brain	2.318 (1.953–2.751)	<.001	1.904 (1.602–2.263)	<.001	2.340 (1.945–2.816)	<.001	1.904 (1.579–2.295)	<.001
≥2 Sites	1.945 (1.841–2.054)	<.001	1.742 (1.646–1.843)	<.001	2.029 (1.914–2.152)	<.001	1.792 (1.686–1.904)	<.001

BCSS = breast cancer-specific survival, CI = confidence interval, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, OS = overall survival.

expression of CXCR4.[27,28] In addition, the HER2+ had been reported having a strong relationship with brain metastases.[22,29] A phase II study revealed the HER2+ was associated with central nervous system involvement[30] and Bos et al found that 6 of the 17 genes which were associated with brain relapse were shared with lung metastasis gene-expression signature.[26,31] The univariate and multivariate analyses based on OS and BCSS demonstrated statistically significant difference in primary stage IV breast cancer diagnosed with various site-specific metastasis patterns. We only selected patients with one distant metastasis site to eliminate the hybrid bias in the study, and results showing patients with bone metastases had the best OS in all other

metastatic patterns and the shortest survival time belonged to brain metastases, which were consistent with the previous researches.[8,20] This study also found that the duration of OS in brain metastases were lower than that of multiple metastasis sites. Present international guidelines for breast cancer do not recommend the routine brain screening for patients without symptoms of brain metastasis,[29] which leads to a high degree of malignancy in patients with brain metastases. The significantly shorter OS with brain metastasis than that of multiple distant metastasis sites is, to our knowledge, a novel observation. There is a dispute over whether the patients with primary stage IV breast cancer should be treated surgically. Our study suggested tumor surgery improved the OS time of these patients. Several previous studies had reported the similar results.[6,8,16,17,32] Meanwhile, we found primary tumor excision with various molecular subtypes had the better OS. There were few studies reporting the relationship between surgery and tumor subtypes in de novo MBC patients. A study showed patients with either HR+ or HER2 + who experiencing surgery was associated with improved survival, which the authors thought this survival benefit in patients with HER2+ because of targeted therapy.[33] Recently a large, retrospective, population-based cohort study suggested patients with younger age, lower disease burden, smaller primary breast tumors, and improvement of systemic treatment could have greater benefit from surgery.[32] In contrast, some studies reported no benefit of the primary tumor removal.[34,35] Surgery-induced immunosuppression, circulating tumor cells to the target organs, surgery-induced angiogenic switch, and the post-operative inflammatory reaction could be the reason leading to the shorter duration of survival.[35] So more rigorous, large-scale clinical studies should be carried out to address this point in the future. However, this study also has some limitations. First, information relating to systemic treatment such as chemotherapy, endocrine therapy, targeted therapy and radiotherapy is not available in the seer database, which may exert an important impact on prognosis. Secondly, the SEER database only provides information on distant metastasis sites such as bone, lung, liver, and brain not on other sites. Thirdly, molecular subtypes were categorized according to HR and HER2 status without other marks such as Ki-67; thus, we could not further subdivide the molecular subtypes.

5. Conclusions

In general, in this study, we developed a deeper understanding of the relationship between primary stage IV cancer and the various molecular subtypes. The survival time of patients with brain metastases is the shortest. Surgical excision of primary tumor can improve the prognosis. Finally, we hope to develop appropriate programs for each primary metastatic breast cancer patients to prolong survival and improve quality of life.

Author contributions

Yang Li: (1) acquisition of data and analysis and interpretation of data; (2) drafting the article;
Shuaibing Wang: substantial contributions to conception and design and revising the article critically for important intellectual content;
Wenbo Yang: Contributions to statistical assistance and final revision;
Hong Liu: study design and final approval of the version to be published.

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