Int J Clin Exp Med 2017;10(2):4049-4056
www.ijcem.com /ISSN:1940-5901/IJCEM0030688

Original Article

HER2-positive Luminal B breast cancer according to the clinicopathological features: a population-based study from SEER program

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Received April 17, 2016; Accepted September 7, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: This is the population-based study to analyze the prognostic value of the clinicopathological features in HER2-positive Luminal B-subtype breast cancer. Using the 2010-2012 Surveillance, Epidemiology, and End Results Program (SEER) data, a retrospective, population-based cohort study to investigate the clinicopathological features in the overall survival (OS) and breast cancer-specific mortality (BCSM) in HER2-positive Luminal B subtype. Different characteristics, overall survival, breast cancer-specific mortality were compared. There were 16,662 patients with breast cancer (141 male; 16,521 female). Compared with females, males were more likely to be older, black (each $P < 0.01$). Male patients also showed lower grade, more advanced stages, larger tumor size and more lymph nodes metastasis (each $P < 0.05$). Males also were less likely to receive radiation compared with females ($P < 0.01$). Univariate analysis showed that a general decrease in OS in those patients who presented with age ≥ 50 years, black, male, more advanced stage and bilateral sides at diagnosis, had lower grade, larger size, more lymph nodes and distant metastasis, and those who did not receive radiation. In contrast, multivariate Cox analyses confirmed the independent prognostic significance of age at diagnosis, stage, tumor size and distant metastasis. Sex did not reach significance with this test. The similar results also performed in BCSM. We observed significant differences in patient characteristics according to age at diagnosis and race. In addition to tumor stage, tumor size and distant metastasis had clear influence on OS and BCSM in HER2-positive Luminal B.

Keywords: Breast cancer, HER2-positive Luminal B subtype, clinicopathological features, SEER program

Introduction

Breast cancer is a molecularly heterogeneous disease that appears to include at least four major tumor subtypes: basal-like breast cancer, HER2-positive breast cancer, luminal-A breast cancer and luminal-B breast cancer [1-3]. In many subsequent studies, luminal-B breast cancer has been defined as ER-positive breast cancer with increased proliferation, particularly the inclusion of ER-positive/HER2-positive breast cancer [3]. Reporting the early studies of the intrinsic molecular subtypes in breast cancer, the defining feature of Luminal-B breast cancer has been its poor outcome compared with the luminal-A subtype. And overall survival in untreated luminal-B breast cancer is similar to the basal like and HER2-positive subgroups, which are widely recognized as high risk [1, 4].

Male breast cancer (MBC) is an uncommon disease, constituting less than 1% of all breast cancers and approximately 0.2% of all male cancers [5, 6]. In contrast to the incidence of female breast cancer, the incidence of male breast cancer has been steadily increasing over the past 3 decades [7-9]. The low incidence has resulted in only a superficial knowledge of its etiology, biological behavior, and treatment. Information about prognostic factors and the behavior of breast cancer are different in males from that of women for epidemiologic and prognostic factors [7]. As more data on the tumor biology of male breast cancer emerge, it is becoming clear that male breast cancer is a

Table 1. Characteristics of male and female patients with breast cancer

	Female N=16521 (%)	Male N=141 (%)	P
Age at diagnosis, y	58.14 13.89	63.03 12.17	P < 0.01
< 40	1368 (8.3)	4 (2.8)	
40-49	3303 (20.0)	15 (10.6)	
50-64	6703 (40.6)	61 (43.3)	
≥ 65	5147 (31.2)	61 (43.3)	
Race			0.005
White	12764 (77.3)	108 (76.6)	
Black	1976 (12.0)	27 (19.1)	
Other	1655 (10.0)	6 (4.3)	
Grade			P < 0.01
Well	1128 (6.8)	5 (3.5)	
Moderately	6473 (39.2)	59 (41.8)	
Poorly	7852 (47.5)	68 (48.2)	
Undifferentiated	91 (0.6)	9 (6.4)	
Stage			P < 0.01
I	7815 (47.3)	47 (33.3)	
II	5839 (35.3)	52 (36.9)	
III	2402 (14.5)	36 (25.5)	
IV	465 (2.8)	6 (4.3)	
Tumor size, cm			
≤ 2	8409 (48.7)	48 (34.0)	0.001
2-5	5700 (34.5)	57 (40.4)	
> 5	2211 (13.4)	30 (21.3)	
Node stage			0.015
N0	9515 (57.6)	65 (46.1)	
N1	4708 (28.5)	53 (37.6)	
N2	1217 (7.4)	9 (6.4)	
N3	765 (4.6)	11 (7.8)	
Distant metastasis			0.28
M0	15235 (92.2)	123 (87.2)	
M1	1286 (7.8)	18 (12.8)	
Laterality			0.305
Left	8462 (51.2)	73 (51.8)	
Right	8017 (48.5)	67 (47.5)	
Paired	28 (0.2)	1 (0.7)	
Bilateral	10 (0.1)	-	
Radiotherapy			P < 0.01
No	8747 (52.9)	104 (73.8)	
Yes	7682 (46.5)	37 (26.2)	
Status			
Alive	15688 (95.0)	121 (85.8)	P < 0.01
Dead	833 (5.0)	20 (14.2)	
Cause of dead			0.232
Breast cancer	404 (48.5)	7 (35.0)	
Other	429 (51.5)	13 (65.0)	

y, years.

unique disease requiring its own trials and treatment guidelines.

Given that the treatment strategy and patient management depend on prognostic variables, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program data to analyze the prognostic value of the clinicopathological features in HER2-positive Luminal B-subtype breast cancer.

Patient and methods

Data source and study design

We obtained data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program between 2010 and 2012. More recently, SEER started collecting HER2 status since 2010, because of this, we used that year as the starting point for our study. We extracted all cases with invasive breast cancer diagnosed between 2010 and 2012.

Demographic variables included age at diagnosis (< 35, 35-49, 50-64, > 65 years), race (white, black, other). Cancer characteristics were classified by stage (I, II, III, IV), grade (well, moderately, poorly, undifferentiated), T stage (T0/T1, T2, T3, T4), N stage (N0, N1, N2, N3), Distant metastasis (M0, M1), laterality (right, left, Paired, bilateral). Treatment characteristics included receipt of radiation therapy (no, yes). Tumor subtypes were classified as hormone receptor (HoR)-positive/HER2-positive.

The overall survival (OS) and breast cancer-specific mortality (BCSM) were the two main outcomes in our study. Vital status was recorded as "alive" or "dead" in the SEER dataset. Survival time (in months) was calculated for each patient using the "Completed Months of Follow-up" variable in the SEER database. The overall survival (OS) was determined by them who were alive at the end of the study period or who were alive at their last follow-up. Breast cancer-specific mortality (BCSM) was determined by them whose cause of death was recorded as due to breast cancer with

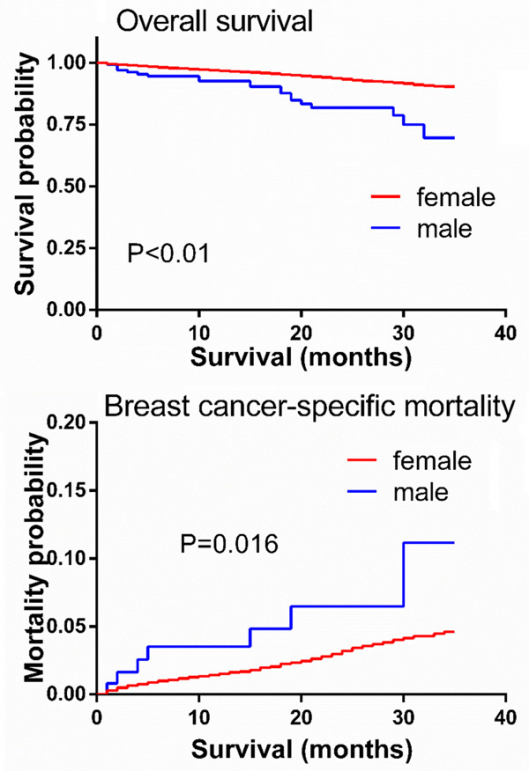

Figure 1. Survival rates with confidence bands for HER2-positive Luminal B breast cancers according to the sexes.

them who were alive at the end of the study period, had died due to other causes, or who were alive at their last follow-up. Cases with Survival time were classified as unknown and removed from the study. Inflammatory breast cancers tumors were not considered in the analysis.

Statistical analysis

Patient demographic, cancer- and treatment-related characteristics were compared between female and male using Chi square or Fisher's exact tests, as appropriate. Within each variable, patients with unknown data were excluded from the comparative analysis. Survival probabilities on OS and BCSM were estimated using the Kaplan-Meier method and variables were compared using the log-rank test. Univariate and multivariate Cox proportional hazard regressions, obtaining the hazard ratios (HRs) and their respective 95% confidence intervals (CI) to show the strength of estimated relative risk, were applied to model the relationship between potential covariates and either OS or BCSM. All statistical analyses were performed using SPSS 19.0 (IBM Corporation, Armonk, NY) and all charts of survival probabilities were performed using GraphPad Prim 6.0. A two-sided p value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 141 male and 16,521 female breast cancer patients were eligible during the 2010-2012 study period. Differences in patient demographics, cancer characteristics, treatments, and outcomes between the two groups are summarized in **Table 1**. Compared with females, age at diagnosis ≥ 65 years for males accounted for 43.3%. While males were more likely to be black and more advanced stages (each P < 0.01). Biological characteristics of the tumors also differed significantly between the sexes, MBC was more likely to be lower grade, larger size, more lymph nodes metastasis (each P < 0.01). Males also were less likely to receive radiation compared with females (P < 0.01).

Survival analysis

After a median follow-up of 15 months (range 0-35 months), the survival associated with HER2-positive Luminal B-subtype breast cancer derived from SEER data recapitulates that identified in the literature and was approximately 94.88%. This plot might be additionally stratified by including the contribution of sexes to the overall survival. Analysis of OS according to sexes showed significant differences in HER2-positive Luminal B-subtype breast cancer, 85.8% of men and 95.0% of women were alive in the overall cohort (P < 0.01). Meanwhile, analysis of BCSM according to sexes showed significant differences in HoR-positive/HER2-positive male patients experiencing the higher mortality compared with females (5.0% vs. 2.4%, P < 0.01) (**Figure 1**).

We used univariate analysis based on the Kaplan-Meier results (**Table 2**). Unadjusted models for the overall patient population were consistent with log-rank analysis and revealed a general decrease in OS in those patients who presented with age ≥ 50 years, black, male, more advanced stage and bilateral sides at

Table 2. Univariate analysis of overall survival and breast cancer-specific mortality

Variables	OS		BCSM	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age at diagnosis, y				
< 35	Reference		Reference	
35-49	1.65 (0.998, 2.727)	0.051	1.079 (0.511, 2.279)	0.841
50-64	2.744 (1.722, 4.375)	< 0.001	2.14 (1.052, 4.352)	0.036
≥ 65	7.289 (4.61, 11.523)	< 0.001	3.518 (1.735, 7.136)	< 0.001
Sex	2.763 (1.763, 4.305)	< 0.001	2.144 (1.016, 4.526)	0.016
Race				
White	Reference		Reference	
Black	1.51 (1.264, 1.804)	< 0.001	1.805 (1.413, 2.304)	< 0.001
Other	0.631 (0.477, 0.835)	0.001	0.743 (0.507, 1.087)	0.126
Grade				
Well	Reference		Reference	
Moderately	1.195 (0.867, 1.649)	0.276	2.418 (2.63, 3.526)	0.007
Poorly	1.532 (1.119, 2.097)	0.008	3.291 (1.746, 6.206)	< 0.001
Undifferentiated	2.727 (1.33, 5.594)	0.006	5.277 (1.655, 16.826)	0.005
Stage				
I	Reference		Reference	
II	1.407 (1.141, 1.737)	0.001	1.11 (0.90-1.36)	< 0.001
III	5.226 (3.804, 7.178)	< 0.001	3.77 (2.18-7.67)	< 0.001
IV	9.736 (8.169, 11.603)	< 0.001	7.19 (3.88-12.59)	< 0.001
Tumor size				
T0/T1	Reference		Reference	
T2	2.244 (1.871, 2.692)	< 0.001	4.197 (2.988, 5.895)	< 0.001
T3	5.533 (4.601, 6.654)	< 0.001	6.467 (4.388, 9.532)	< 0.001
T4	7.647 (5.969, 9.796)	< 0.001	8.793 (2.609, 18.011)	< 0.001
Node stage				
N0	Reference		Reference	
N1	1.686 (1.434, 1.982)	< 0.001	3.362 (2.644, 4.276)	< 0.001
N2	2.163 (1.71, 2.738)	< 0.001	3.19 (2.233, 4.558)	< 0.001
N3	3.799 (3.025, 4.77)	< 0.001	5.614 (3.963, 7.953)	< 0.001
Distant metastasis				
M0	Reference		Reference	
M1	10.584 (9.235, 12.131)	< 0.001	17.848 (12.729, 24.121)	< 0.001
Laterality				
Left	Reference		Reference	
Right	1.014 (0.886,1.161)	0.839	1.015 (0.836, 1.233)	0.877
Paired	5.985 (2.963, 12.006)	< 0.001	3.679 (0.914, 14.809)	0.067
Bilateral	5.981 (1.491, 23.999)	0.012	4..763 (2.291, 7.379)	0.001
Radiotherapy				
Yes	Reference		Reference	
No	1.549 (0.735, 3.264)	< 0.001	1.34 (0.272, 1.426)	< 0.001

HER2, human epidermal growth factor receptor 2.

diagnosis, had lower grade, larger size, more lymph nodes and distant metastasis, and those who did not receive radiation. The similar results also performed in BCSM. In contrast, univariate analysis did not show significant differences for race, tumor grade, node stage, lat-

Table 3. Multivariate analysis of overall survival and breast cancer-specific mortality

Variables	OS		BCSM	
	aHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Age at diagnosis, y				
< 35	Reference		Reference	
35-49	1.99 (1.203, 3.292)	0.007	1.324 (0.626, 2.80)	0.462
50-64	2.973 (1.863, 4.742)	< 0.001	2.344 (1.151, 4.774)	0.019
≥ 65	8.096 (5.112, 12.821)	< 0.001	4.246 (2.088, 8.635)	< 0.001
Sex	1.52 (0.971, 2.378)	0.067	1.488 (0.70, 3.163)	0.302
Race				
White	Reference		Reference	
Black	1.417 (1.181, 1.699)	< 0.001	1.399 (1.087, 1.80)	0.009
Other	0.794 (0.599, 1.053)	0.109	0.952 (0.648, 1.40)	0.804
Grade				
Well	Reference		Reference	
Moderately	1.139 (0.826, 1.572)	0.787	1.259 (0.657, 2.41)	0.488
Poorly	1.612 (0.78, 3.33)	0.428	1.435 (0.753, 2.736)	0.273
Undifferentiated	1.924 (0.822, 2.729)	0.354	1.676 (0.518, 5.419)	0.388
Stage				
I	Reference		Reference	
II	0.978 (0.734, 1.312)	0.884	1.11 (0.90-1.36)	0.081
III	2.648 (1.885, 3.719)	< 0.001	1.77 (1.18-2.67)	0.019
IV	2.208 (1.430, 3.411)	< 0.001	2.19 (1.88-2.59)	< 0.001
Tumor size				
T0/T1	Reference		Reference	
T2	1.742 (1.345, 2.257)	< 0.001	2.881 (2.021, 4.108)	< 0.001
T3	1.717 (1.314, 2.242)	< 0.001	2.033 (1.321, 3.127)	0.001
T4	4.653 (1.166, 7.343)	0.005	9.721 (6.519, 14.597)	< 0.001
Node stage				
N0	Reference		Reference	
N1	0.944 (0.789, 1.130)	0.531	1.229 (0.943, 1.601)	0.127
N2	1.149 (0.885, 1.493)	0.297	0.979 (0.665, 1.440)	0.914
N3	1.05 (0.799, 1.381)	0.725	1.368 (0.936, 2.001)	0.207
Distant metastasis				
M0	Reference		Reference	
M1	3.568 (2.798, 4.55)	< 0.001	12.495 (9.724, 16.056)	< 0.001
Laterality				
Left	Reference		Reference	
Right	0.735 (0.346, 1.561)	0.423	1.029 (0.846, 1.252)	0.775
Paired	1.009 (0.881, 1.156)	0.394	1.493 (1.529, 2.69)	0.15
Bilateral	1.836 (0.455, 7.415)	0.884	1.034 (0.253, 4.226)	0.962
Radiotherapy				
Yes	Reference		Reference	
No	1.198 (0.564, 2.542)	0.638	1.404 (0.438, 1.603)	0.37

aHR, adjusted hazard ratio.

erality or radiation therapy at diagnosis. Multivariate Cox analyses confirmed the independent prognostic significance of age at diagnosis, stage, tumor size and distant metastasis. Sex did not reach significance with this test. The final Cox model was shown in **Table 3**.

Discussion

Recently, a molecular classification system had been proposed to categorize breast cancers into subtypes associated with optimal therapeutic modality, which had also become widely used [3]. The prognostic value of the clinicopathological features in HER2-positive Luminal B breast cancer had been unclear.

Previous studies showed that the epidemiology and the prognosis of MBC had inconsistent results. Thus, our studies showed that there was survival disparity between males and females in HoR-positive/HER2-positive subtype unadjusting other factors, but sex did not reach significance in multivariate model. Consistent with previous studies, males in this study tended to be older than females at time of diagnosis [7, 10]. A higher prevalence of comorbidities occurred in older age, which likely resulted in the decreasing overall survival among male compared with FBC. Donegan et al. [11] reported that the high rate of post-treatment mortality from comorbid disease like heart disease or other non-breast cancers was a major contributor to the poor survival in MBC. One would expect that the male patients in this study were less likely to receive radiation compared with females, or that was likely to be of significance clinically.

Tumor stage was a pivotal prognosis factor. In this paper, tumor stage was a prognostic factor for OS and BCSM on univariate analysis, also an independent factor on multivariate analysis. The stage of tumor size and lymph nodes were particularly related to the prognosis and treatment of breast cancer [12-14]. In our study, MBC was more likely to be diagnosed at more advanced stages (stages II-IV) compared with FBC. Also MBC was more likely to be lower grade, larger size, more lymph nodes metastasis and distant metastasis. However, multivariate Cox analyses confirmed that the stage of lymph nodes had not independent prognostic significance, that was likely to be of significance clinically.

With respect to treatment, we did not have information regarding the systemic treatments of this cohort, such as surgery, chemotherapy, and hormonotherapy, which might contribute to some of the differences observed in survival. Although it had been proven that treatment of breast cancer could benefit from radiotherapy [15, 16], our results indicated that radiotherapy do not affect the prognosis. Regarding the endocrine therapies in ER+ breast cancer, the benefits of treating HoR+/HER2+ Luminal B breast cancer with the same endocrine therapies would be different. There were studies reporting that HoR+/HER2+ Luminal B breast cancer was relatively insensitive to endocrine therapy compared with luminal-A breast cancer [17]. Several studies had suggested the pathological complete response (pCR) rate was consistently lower in Luminal-B breast cancer when compared with HER2 and basal-like subtypes [18-20]. Thus, despite the expression of similar biomarkers, treatment of breast cancer might be different substantially in other unmeasured ways.

In summary, there were several limitations to our study, which were inherent to any retrospective cohort study. One limitation of retrospective cohort studies was the inability to control for selection bias. Finally, we identifeid that the significant differences in patient and tumor characteristics according to age at diagnosis, race, tumor stage, tumor size and distant metastasis. While additional work was needed to characterize the drivers of aggressive biology, future translational studies required prospective validation, and focused on the tumor biology and treatment efficacy of HER2+ Luminal B breast cancer, our study laid the foundation for the prognostic value of the clinicopathological features upon clinical trials of personalized therapies in in HER2-positive Luminal B-subtype breast cancer.

Acknowledgements

This work was partially supported by a NSFC grant to Dr. Shengrong Sun (Grant NO: 8147-1781). This work was also supported by a NSFC grant to Dr. Juanjuan Li (Grant NO: 81302314/H1622) the Fundamental Research Funds of Hubei Province Health and Family Planning Commission to Wen Wei (Grant NO: JS-2011-0118) and the Fundamental Research Funds for the Central Universities of China to Shan Zhu (Grant NO: 2042014kf0189).

Disclosure of conflict of interest

None.

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