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Gender-related differences in survival in locally advanced luminal A breast cancer patients

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Ethics Committee Approval
As this study utilized de-identified data from the SEER database, which is publicly available and maintains patient anonymity, ethical approval and informed consent were not required.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Breast cancer is known to exhibit variations in clinical outcomes based on several factors, including molecular subtypes and patient demographics, yet the influence of gender on survival outcomes in patients with locally advanced stage luminal A breast cancer remains underexplored. This study aimed to determine how gender affects the survival of patients with locally advanced stage breast cancer.

Methods: Data were obtained from the Surveillance Epidemiology and End Results (SEER) database. Patients with luminal A molecular subtype and locally advanced stage breast cancer who had been diagnosed between 2010 and 2019 were included in the study. Age, gender, marital status, race, and year of diagnosis were classified as clinical data, and tumor localization, laterality, grade, stage, surgical status, radiotherapy and chemotherapy status, cause of death, and survival time were classified as oncological data. Data were compared based on gender.

Results: The study included a total of 46,730 patients. A very small percentage of the patients were male (1.2%), while 98.8% were female. Male patients were significantly older and had a higher marriage rate. Racial distribution differed slightly with more black patients among the males. Grade 2 tumors were most prevalent in both genders, but males had higher grade 3 tumors. Stage 3B and 3C tumors were more common in males, but no significant difference for Stage 3C based on gender was detected. Surgical rates were similar between genders, while females had higher rates of treatment with radiotherapy and chemotherapy. Females exhibited significantly higher overall survival rates (64.4% versus 52.2%). Cancer-specific survival did not differ significantly (76.3% versus 72.1%). Males had a 1.6 times higher overall mortality risk, which was reduced to 1.3 times after adjusting for other prognostic factors.

Conclusion: No difference in cancer-specific survival between men and women with locally progressed luminal A breast cancer was found. These results highlight the significance of considering gender-specific characteristics while managing patients and predicting their prognosis. To fully understand the underlying mechanisms behind the survival differences between male and female patients, further studies are required.

Keywords: breast cancer, luminal A, hormone positive, survival

Introduction

One of the most common cancers in the world and the leading cause of cancer-related deaths in women is breast cancer. Breast cancer prognosis and treatment outcomes might vary depending on several variables, such as molecular subtypes and patient characteristics. A molecular subtype of breast cancer, luminal A, has a better prognosis than other subtypes and is characterized by the presence of hormone receptors. Nevertheless, it is crucial to investigate potential variations in survival outcomes within this subtype, especially when considering gender-related differences [1,2].

Gender-related characteristics may have an impact on how breast cancer patients respond to treatment and how their clinical course develops as described in previous research studies. According to several studies, male and female breast cancer patients have different survival rates; females usually have better outcomes [3,4]. The effect of gender, specifically in individuals with locally advanced luminal A breast cancer, on survival outcomes is still unknown. To determine whether a gender-related survival difference in patients with locally advanced luminal A breast cancer exists, this study investigated this possible gender-related difference.

Materials and methods

Study population

In this retrospective study, data were obtained from the Surveillance Epidemiology and End Results (SEER) database, specifically the SEER Research Plus 17 Registries. Locally advanced breast cancer patients diagnosed with a molecular subtype classified as luminal A between 2010 and 2019 were included in the study. Patients with stage 2B, 3A, 3B, or 3C breast cancer were considered eligible for the analysis.

Data collection and variables

Clinical data, including age, gender, marital status, race, year of diagnosis, tumor localization (central localization, upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant, overlapping), laterality (right/left), grade, stage, surgical status, radiotherapy and chemotherapy status, cause of death, and survival time were collected from the SEER database. Patients with early-stage or metastatic disease or missing data were excluded from the study to ensure the homogeneity of the locally advanced luminal A breast cancer cohort.

Efforts to address potential sources of bias

In this study, several steps were taken to minimize potential sources of bias and ensure the validity of the findings. First, data were obtained from the SEER database, which includes a comprehensive and standardized collection of patient information thus reducing selection bias. We included patients diagnosed with luminal A breast cancer between 2010 and 2019 to ensure a consistent timeframe and limit variations in treatment protocols over time. Patients with early stage, metastatic disease, and/or missing data were excluded to maintain the homogeneity of the study cohort. To control for confounding variables, we performed multivariate analyses adjusting for demographic factors (age, gender, marital status, race), clinical characteristics (tumor grade and stage), and treatment modalities (surgery, radiotherapy, and/or chemotherapy). By adjusting for these variables, we aimed to isolate the effect of gender on survival outcomes. Additionally, we used established statistical methods, such as the Cox regression analysis, to assess the impact of these variables on overall and cancer-specific survival. Despite these efforts, we acknowledge that inherent limitations of retrospective studies, such as unmeasured confounding factors and reliance on the accuracy of recorded data, still may have introduced some bias.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 22.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test and box plot graphs were used to assess the study data's conformity to the normal distribution of the variables together with descriptive statistical methods (mean, standard deviation). An independent t-test was used to compare groups of normally distributed variables. To compare qualitative data, the Pearson's chi-squared test was applied. Overall survival (OS) was calculated based on who was still alive at the end of the study or at the last follow-up. Breast cancer-specific survival was calculated for individuals who were alive at the end of the study period, died due to another cause, or were still living at their last follow-up and whose cause of death was breast cancer. Kaplan–Meier analysis and the log-rank test were used to assess the results of survival analyses. Cox regression analysis was used for univariate and multivariate analyses. Results were considered significant at the *P*-value <0.05 level.

Results

The study included 46,730 patients in total. The percentage of male patients was 1.2% (n=578), while 98.8% were female (n=46,152). The mean age of males was significantly higher (male: 64.9 [12.17] years; Female: 58.5 [14.21] years; $P<0.001$). The rate of being married was significantly higher in males compared to females (Male=65.2%; Female=55.9%; $P<0.001$).

Grade 2 tumors were most common in both groups with grade 1 tumors accounting for 12.3% in females and 7.3% in males, grade 2 tumors accounting for 50.8% in females and 46.7% in males, and grade 3 tumors accounting for 36.9% in females and 46% in males. Both groups had the largest percentage of Stage 2B cancers with 52% of females and 45.8% of males having these tumors. Females were more likely to be in Stage 3A than men. 29.2% of females and 23.7% of males were in stage 3B. Males had a larger percentage of Stages 3B and 3C cancer. Stage 3C was found in 9.8% in females and 11.42% in males, while Stage 3B affected females at a rate of 9.1% and males at a rate of 19%. Regarding the proportions of Stage 3C based on gender, no significant difference was found (Table 1).

No significant difference in the surgical rate between males and females (95.3% versus 94.8%; $P=0.547$) was found. Radiotherapy was used more frequently for women (59% versus 49.5%; $P=0.001$) than in men. Chemotherapy was used for 69.5% of female patients compared to 62.1% of male patients ($P<0.001$) as shown in Table 1. The median survival time was 54.06 (31.77) months and ranged from 0 to 119 months.

Females had a considerably greater overall survival rate ($P<0.001$). Females had a 5-year survival rate of 80.7%, while males had a rate of 71.2%. Males had an overall survival rate of

52.2% and females of 64.4% (Figure 1). No significant difference in terms of cancer-specific survival was found. Most females (86.9%) and 83.3% of males had cancer-specific survival at five years, whereas 76.3% of females and 72.1% of males had cancer-specific survival overall (P=0.221) as shown in Figure 2.

Table 1: Clinical, pathological and oncological results of the patients

		Female n (%)	Male n (%)	P-value
Age, mean (SD)		58.5 (14.21)	64.9 (12.17)	<0.001[a]
Marital status	Married	25787 (55.9)	377 (65.2)	<0.001[b]
	Others	20365 (44.1)	201 (34.8)	
Race	White	35778 (77.5)	443 (76.6)	<0.001[b]
	Black	5336 (11.6)	94 (16.3)	
	Others	5038 (10.9)	41 (7.1)	
Tumor localization	Upper outer quadrant	15924 (34.5)	54 (9.3)	<0.001[b]
	Upper inner quadrant	3954 (8.6)	17 (2.9)	
	Lower outer quadrant	3345(7.2)	24 (4.2)	
	Lower inner quadrant	1805 (3.9)	7 (1.2)	
	Central	3340 (7.2)	318 (55)	
	Overlapping	10598 (23)	80 (13.8)	
	Unknown	7186 (15.6)	78 (13.5)	
Laterality	Right	22944 (49.7)	271 (46.9)	0.568[b]
	Left	23194 (50.3)	307 (53.1)	
	Bilateral	8 (<0.1)	0	
	Unknown	6 (<0.1)	0	
Grade	1	5682 (12.3)	42 (7.3)	<0.001[b]
	2	23432 (50.8)	270 (46.7)	
	3	17038 (36.9)	266 (46)	
Stage	2B	24009 (52)	265 (45.8)	<0.001[b]
	3A	13455 (29.2)	137 (23.7)	
	3B	4178 (9.1)	110 (19)	
	3C	4510 (9.8)	66 (11.4)	
Surgery	Performed	43737 (94.8)	551 (95.3)	0.547[b]
	Not performed	2415 (5.2)	27 (4.7)	
Radiotherapy	Yes	27252 (59)	286 (49.5)	<0.001[b]
	No	18900 (41)	292 (50.5)	
Chemotherapy	Yes	32089 (69.5)	359 (62.1)	<0.001[b]
	No	14063 (30.5)	219(37.9)	
Vital Status	Alive	37373 (81)	414 (71.6)	<0.001[b]
	Breast	5660 (12.3)	76 (13.1)	
	Other reason	3119 (6.8)	88 (15.2)	
Survival time, mean (SD) (min -max)		54.06 (31.77) (0-119) month		

a: Independent samples t-test, b: Pearson Chi-Square Test, SD: standard deviation

Figure 1: Overall survival graphic

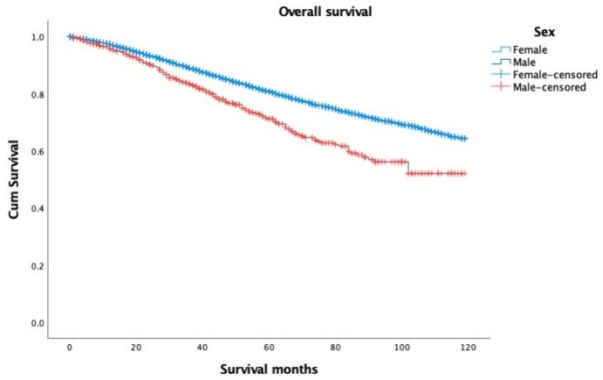
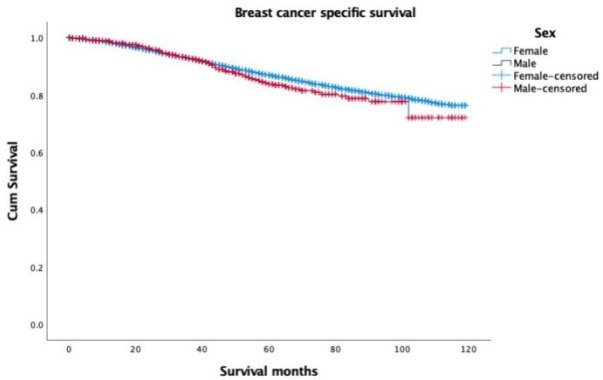


Figure 2: Cancer specific survival graphic



Males had a 1.6-fold higher overall death risk than females (P<0.001, hazard ratio [HR]: 1.604; 95% confidence interval [CI]: 1.375–1.872]). The risk of death was 1.3 times higher in males than in females after the multivariate analysis adjusted for marital status, race, grade, stage, and surgery, chemotherapy, and/or radiotherapy status (P<0.001, HR: 1.315; 95% CI: 1.126–1.535). No significant difference for cancer-specific death risk (P=0.221) as shown in Table 2. Tables 3–6 provide specific outcomes regarding prognostic factors for OS and cancer-specific survival for both males and females.

Discussion

The purpose of this study was to determine if gender-related differences in survival among patients with locally advanced stage luminal A breast cancer exist. We observed that several important distinctions between the clinical features and survival rates of males and females in this patient population were present.

Males with locally advanced luminal A breast cancer were found to be substantially older than females according to the examination of patient demographics. This age difference may have been caused by a delay in diagnosis or by gender-specific changes in tumor biology [5,6]. Male patients additionally showed a larger proportion of these patients were married, indicating possible social and support system components that could have affected survival results [7,8].

Males and females showed different tumor features, including tumor location, grade, and stage. The most frequent tumor localization varied between genders with a more prevalent upper outer quadrant in females versus a central localization in males. This variation could have been caused by differences in tumor biology or anatomical elements [6,9].

Males were more likely than females to have higher-grade tumors (grade 3), which are typically linked to worse prognoses. Similarly, the more advanced stages (3B and 3C) were more prevalent in men, indicating a more aggressive disease in this cohort. The differences in survival between genders may have been caused by these variations in tumor features [7,10].

Regarding treatment options, no significant differences in the rates of surgical treatment between males and females were found, indicating equal access to and use of surgical treatments. In contrast to males, females received radiotherapy and chemotherapy at higher rates. Depending on the features of the tumor and the response rates, several treatment techniques may be advised. Females were more likely to receive radiotherapy and chemotherapy than males, which may explain why they have better survival rates [5,11–13].

These results are supported by previous research reporting better outcomes in female breast cancer patients [3,5,7]. However, no significant difference in cancer-specific survival between genders was detected, suggesting that factors other than cancer progression may influence the observed survival differences. The survival analysis demonstrated that females presented significantly higher overall survival rates compared to males and that a significant difference in the 5-year survival rates was present.

Males had a considerably higher overall risk of mortality than females according to the multivariate analysis that adjusted for several confounding variables. Males still presented a greater risk of death after adjusting for marital status, race, grade, stage, surgery, chemotherapy, and radiotherapy. This finding indicates

Table 2: Cox regression analysis based on gender

	Overall survival				Cancer-specific survival			
	Univariate				Univariate			
			95% CI for HR				95% CI for HR	
	P-value	HR	Lower	Upper	*P*-value	HR	Lower	Upper
Female	Reference				Reference			
Male	<0.001	1.604	1.375	1.872	0.221	1.152	0.918	1.444
	Multivariate							
			95% CI for HR					
	P-value	HR	Lower	Upper				
Female	Reference							
Male	<0.001	1.315	1.126	1.535				

CI: confidence interval, HR: hazard ratio

Table 3: Cox regression analysis of female patients overall survival

		Univariate				Multivariate			
		P-value	HR	95% CI for HR		*P*-value		95% CI for HR	
				Lower	Upper		HR	Lower	Upper
Marital status	Married		Reference				Reference		
	Others	<0.001	1.919	1.840	2.003	<0.001	1.587	1.506	1.672
Surgery	Yes		Reference				Reference		
	No	<0.001	4.860	4.565	5.174	<0.001	4.733	4.375	5.120
Radiotherapy	Yes		Reference						
	No	<0.001	1.909	1.830	1.991	<0.001	1.579	1.498	1.663
Chemotherapy	Yes		Reference						
	No	<0.001	2.248	2.156	2.345	<0.001	1.398	1.324	1.477
Grade	I		Reference				Reference		
	II	<0.001	1.259	1.167	1.358	<0.001	1.616	1.447	1.805
	II	<0.001	2.033	1.884	2.193	<0.001	3.371	3.023	3.759
Stage	2B		Reference				Reference		
	3A	<0.001	1.301	1.236	1.370	<0.001	1.638	1.535	1.748
	3B	<0.001	3.367	3.158	3.589	<0.001	3.857	3.553	4.187
	3C	<0.001	2.481	2.336	2.635	<0.001	3.506	3.226	3.768

Table 4: Cox regression analysis of female patients cancer-specific survival

		Univariate				Multivariate			
		P-value	HR	95% CI for HR		*P*-value		95% CI for HR	
				Lower	Upper		HR	Lower	Upper
Marital status	Married		Reference				Reference		
	Others	<0.001	1.565	1.499	1.634	<0.001	1.353	1.283	1.427
Surgery	Yes		Reference				Reference		
	No	<0.001	2.632	2.455	2.821	<0.001	3.054	2.796	3.335
Radiotherapy	Yes		Reference						
	No	<0.001	1.381	1.318	1.447	<0.001	0.880	0.854	0.906
Chemotherapy	Yes		Reference						
	No	<0.001	2.182	2.083	2.285	<0.001	1.486	1.399	1.579
Grade	I		Reference				Reference		
	II	<0.001	1.332	1.235	1.437	<0.001	1.630	1.459	1.821
	II	<0.001	2.210	2.047	2.386	<0.001	3.324	2.979	3.710
Stage	2B		Reference				Reference		
	3A	<0.001	1.581	1.500	1.666	<0.001	1.828	1.712	1.953
	3B	<0.001	2.590	2.422	2.769	<0.001	2.884	2.648	3.141
	3C	<0.001	2.970	2.794	3.157	<0.001	3.754	3.490	4.040

Table 5: Cox regression analysis of male patients overall survival

		Univariate				Multivariate			
		P-value	HR	95% CI for HR		*P*-value		95% CI for HR	
				Lower	Upper		HR	Lower	Upper
Marital status	Married		Reference				Reference		
	Others	0.002	1.632	1.198	2.223	0.017	1.446	1.070	2.008
Surgery	Yes		Reference				Reference		
	No	<0.001	5.186	3.165	8.497	<0.001	3.924	2.333	6.598
Radiotherapy	Yes		Reference						
	No	<0.001	1.684	1.231	2.303	0.319	1.188	0.847	1.667
Chemotherapy	Yes		Reference						
	No	<0.001	2.269	1.668	3.086	<0.001	2.062	1.493	2.847
Grade	I		Reference						
	II	0.372	1.370	0.686	2.735				
	II	0.132	1.699	0.852	3.387				
Stage	2B		Reference						
	3A	0.792	1.053	0.715	1.552				
	3B	0.123	1.389	0.915	2.110				
	3C	0.652	1.119	0.687	1.821				

Table 6: Cox regression analysis of male patients cancer-specific survival

		Univariate				Multivariate			
		P-value	HR	95% CI for HR		*P*-value		95% CI for HR	
				Lower	Upper		HR	Lower	Upper
Marital status	Married		Reference				Reference		
	Others	<0.001	2.417	1.540	3.793	<0.001	2.161	1.365	3.423
Surgery	Yes		Reference				Reference		
	No	<0.001	6.850	3.497	13.417	<0.001	5.169	2.617	10.212
Radiotherapy	Yes		Reference						
	No	0.450	0.917	0.732	1.148				
Chemotherapy	Yes		Reference						
	No	0.451	0.826	0.499	1.368				
Grade	I		Reference				Reference		
	II	0.132	4.627	0.630	33.974	0.117	4.931	0.670	36.285
	II	0.031	8.819	1.216	63.973	0.032	8.799	1.211	63.919
Stage	2B		Reference						
	3A	0.039	0.687	0.482	0.981				
	3B	0.799	0.951	0.644	1.403				
	3C	0.799	0.941	0.592	1.497				

that gender alone, independent of other demographic and treatment-related characteristics, may contribute to survival differences [6,14–16].

The causes of the gender-related survival difference in patients with locally advanced stage luminal A breast cancer are still unknown. These differences may be influenced by hormonal factors, variations in tumor biology, treatment outcomes, and social support systems [4,11,17]. To fully understand the specific factors and mechanisms at play, further investigations are required.

Limitations

It is critical to recognize some of the limitations of this study. First, the study design introduces inherent biases and restrictions related to secondary data analysis due to its retrospective character and reliance on data from the SEER database. Second, the database does not contain information concerning some characteristics that might have an impact on survival outcomes, such as comorbidities and treatment compliance. Additionally, most participants in the study were female, which restricted the applicability of the results to males with luminal A breast cancer.

Conclusion

In conclusion, this study showed that patients with locally advanced stage luminal A breast cancer had different survival rates according to their gender. Even after adjusting for various confounding factors, females still had higher overall survival rates than males. These findings highlight the significance of considering gender-specific characteristics while managing and predicting the prognosis of patients with luminal A breast cancer. To improve outcomes for male breast cancer patients, future research should concentrate on elucidating the underlying mechanisms causing the survival differences between male and female patients and designing targeted therapies for both groups.

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