Early breast Cancer in Elderly: A Retrospective Study

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Abstract:

Background and objectives: Breast cancer (BC) is the most prevalent cancer among women, both in terms of incidence and mortality. Breast cancer in elderly patients present unique challenges that have led to their underrepresentation in clinical research and trials. This underrepresentation raises critical concerns regarding the outcomes of the disease for this group of patients. The main goal of the current study is to determine the different factors affecting the outcome of the disease.

Methods: This is a retrospective cohort study which included elderly female patients (aged ≥65 years) with early breast cancer (stage I, II and III tumors) who received systemic therapy at Medical Oncology Department of South Egypt Cancer Institute, Assiut University in the period between 2013 to 2018. The data was gathered through patients' physical files and electronic health records

Results: A total of 156 early breast cancer cases were recorded, with a median age of 68 years. One-hundred and eleven (71.2%) patients were estrogen receptor (ER) positive BC, one hundred and five (67.3%) were progesterone receptors (PR) positive. At five years of follow-up, obesity, nodal metastasis, extracapsular extension (ECE), ER, and PR negativity affect the overall survival (OS) and disease-free survival (DFS) among the studied participants. The COX regression analysis also demonstrates that the presence of nodal metastasis, ECE, ER negativity, and PR negativity are significantly bad prognostic factors for death and recurrence of the disease.

Conclusions: Our research shows that at five years of follow-up, obesity, nodal metastasis, ECE, ER, and PR significantly affect the overall survival (OS) among the studied participants and also affect the disease-free survival (DFS) among the studied participant.

Keywords: Breast cancer, Elderly patients, South Egypt Cancer Institute.

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Introduction:

Breast cancer is the most prevalent cancer among women globally, accounting for about 24.5% of all cancer cases. In 2022, there were around 2.3 million new breast cancer diagnoses and about 670,000 deaths caused by the disease worldwide [1,2]. The global incidence rate is approximately 46.8 per 100,000 women [3]

In Egypt, breast cancer (BC) is recognized as the most common cancer among women in Egypt, with significant variations in incidence across different regions of the country; In Lower Egypt, breast cancer accounts for 33.8% of all female cancer cases. In Middle Egypt, the incidence is slightly lower at 26.8%. Upper Egypt shows the highest prevalence, with breast cancer representing 38.7% of female cancer cases [4]. Breast cancer representing 18.9% to 19% of total cancer cases among women in Egypt, it is the most prevalent cancer among Egyptian women, and its incidence is projected to increase by 1-2% every year [5,6]. In 2020, there were nearly 22,700 cases, and forecasts estimate approximately 46,000 cases by 2050 [7]. The median age is approximately 49 years. Studies show varying median ages of breast cancer diagnosis in Egypt, from 46 to 54 years [5,8]. One study at Cairo University Hospital found a mean age of 53.7 years among 509 patients [6].

Incidence rates of breast cancer [BC] show a clear correlation with age, particularly in Western regions. Notably, over 30% of breast cancer cases are diagnosed in women aged 70 years and older. This trend is consistent with findings from various studies and cancer registries, which indicate that the risk of developing breast cancer increases significantly as women age [9].

The median age at death from breast cancer is reported to be 68 years in the United States, with a

significant proportion of deaths occurring in older women. Specifically, 57% of deaths from breast cancer are among individuals aged 65 and older [10].

In general, Breast cancer death rates have shown a consistent decline since 1989, for an overall decline of 43% through 2020. The decrease in death rates is believed to be the result of finding breast cancer earlier through screening and increased awareness, as well as better treatments. As a result, more than 460,000 breast cancer deaths were prevented during that period [11]. However, aging women over 75 years have poor survival rates. Unlike in younger women, survival for elderly patients with BC has not improved significantly over recent years [12].

One of the primary issues contributing to the lack of clear treatment guidelines for older breast cancer patients is their underrepresentation in clinical trials. Studies indicate that only 4% of women over 75 are included in clinical trials for breast cancer, which skews the available data and limits the evidence base for effective treatment protocols tailored to this demographic group [13]. Consequently, many elderly patients receive substandard care, often resulting in poorer outcomes [14].

In the current study, we comprehensively described early breast cancer in elderly as regards the general demographic and tumor characteristics in addition to the survival outcomes at our tertiary academic cancer centre.

Patients and Methods:

Patients:

This is a retrospective cohort study which included all elderly female patients (aged ≥65 years) with early breast cancer (stage I, II and III tumors) who received systemic therapy including chemotherapy and/or hormonal at Medical Oncology department of South Egypt Cancer Institute, Assiut University in the period between 2013 to 2018.

Patients with double malignancy other than bilateral breast cancer, male breast cancer patients, those lost to follow-up without any assessment, and those with another active cancer were excluded from the current study.

Sample size estimation:

Total coverage was used in the current study as we enrolled all elderly female patients (aged ≥65 years) with breast cancer who received systemic therapy including chemotherapy and/or hormonal therapy at our institution during the study period.

Data collection was recorded from the patients' physical files and electronic records includes: data on diagnosis, disease stage, histology, and survival were examined.

Statistical analysis:

All statistics were performed using SPSS (statistical package for the social sciences; SPSS Inc., Chicago, IL, USA) version 22. The data were statistically described using number (%) or mean ± standard deviations (SD) and median (range). Kaplan-Meier's method with log rank test was used for calculation of disease free and overall survival analysis. Hazard ratio (HR) with 95% Confidence Interval (CI) and COX regression analysis was calculated to determine significant factors associated with disease recurrence and mortality. P-value set significant at 0.05 level

Results:

Baseline data:

This study enrolled 156 female patients with early breast cancer. The median age of studied cases was 68 years (range; 65 to 84 years). The median BMI was 26.5 kg/m^2 (range; 18.6 to 53.7 kg/m^2). Diabetes and hypertension were the most common comorbidities in these studied patients 28.2% for each one.

Breast lump was the most common clinical presentation in 96.8%, mainly in left side (56.4%) with unifocal mass in 94.2%. 73.1% have T1/T2 tumor staging with positive nodal metastasis in 54.5% of them. invasive ductal carcinoma (IDC) is the predominant pathology in 91.7% with grade 1/2 in 92.3%. The proliferating index KI67 was ≥ 14% in 63.5%.

Estrogen receptors were positive in 71.2% with strong positivity in 53.2% of them. Of the studied patients HER2neu was positive in 16 patients (10.3%). Anthracycline based protocols were the most common used lines in 43.6%. 29.5% of patients had not received chemotherapy (Table 1).

Outcome analysis:

The median follow-up duration of the 156 early breast cancer cases was 45 months (range, 3 to 196 months). During follow-up, 102/156 patients (65.4%) died as a result of tumor progression. According to Kaplan-Meier analysis, the median OS was 55 months (95% confidence interval [CI], 45 to 65 months). A total of 120/156 patients (76.9%) developed disease progression. The median progression free survival (PFS) was 33 months (range, 1 to 190 months). According to Kaplan-Meier analysis, the median DFS was 34 months (95% CI, 24 to 45), Figure 1.

Factors affecting the overall and progression free survival

At five years of follow-up, obesity, nodal metastasis, extracapsular extension (ECE), estrogen receptors, and progesterone receptors negativity were shown to affect the overall survival among the studied participants. Additionally, obesity, nodal metastasis, ECE, estrogen receptors, and progesterone receptors were shown to affect the progression free

Independent Factors affecting overall survival:

Multivariant analysis using Cox-regression analysis shows that positive nodal metastasis, the presence of ECE, negative ER and negative PR were significant predictors for death among the studied samples (Table 3).

Multivariant analysis using COX regression shows that obesity, positive nodal metastasis, the presence of ECE, negative ER and negative PR were significant predictors for recurrence among the studied patients (Table 4).

Discussion:

The optimal treatment option for the management of breast cancer in elderly is still representing a major challenge in the field of oncological therapy, breast cancer patients aged 65 and elder have been underrepresented in the research field as most of the clinical trials in literature do not involve this group of patients due to their specific personalization and tumor characteristics [15].

Additional challenge for the management of breast cancer in elderly is the presence of comorbidities and low functional status which interfere with the management of the patients and necessitate changes in the protocol of treatment and affect the survival expectancy. This was likely the reason for excluding elderly patients from clinical trials and screening programs [16].

Due to limited data available for the treatment guidelines for older breast cancer patients are less defined compared with these guidelines for younger patients resulting in difficulty in creating a therapeutic plan for elderly breast cancer patients [15].

In literature, there is a great debate on the most suitable treatment options for the management of breast cancer in elderly. Some authors indicated that less aggressive treatment for older women with early-stage breast cancer seemed to be associated with decreased survival [17,18], other series reported that less aggressive treatments for older patients may not decrease survival compared with standard treatments [19].

The median age was 68 (ranged from 65 to 84 years), the median overall survival was 55 months (95% CI, 45 to 65 months), this was consistent with other results in the literature from all over the world ranged between 15.5 months to 56 months [20–22].

Contrary to other previous reports [23,24], our 5-year survival model did not find any significant relation between older ages of the patients and the survival rate (p= 0.791), another previous study by Diab S. et al reported the same results as our results [25], one previous study showed that disease-specific death rate decreased with age and that was attributed to the better biology of breast cancer in older women [26].

In the current study, the mean BMI was 29.5 ± 6.09(SD), obesity (BMI ≥ 30) was detected in 87 patients and had a significant impact on the estimated 5-year OS compared to non-obese patients (BMI < 30), this result was in concordance with other clinical trials and metanalyses [27–30].

Previous studies revealed that concomitant health problems and other malignancies accounted for a greater proportion of deaths in old breast cancer patients [31–33]. In the current study, diabetes mellitus and hypertension were the most common concurrent comorbidities, each was detected in 44 (28%) patients, followed by cardiac diseased in 18 (11.5%) patients, unlike other reports we found that the concurrent presence of more than two comorbidities did not significantly affect the 5 years OS (p= 0.851). The same result was reported also by previous study [34]. Another previous large cohort study revealed that; although the presence and number of comorbidities were predictive for mortality in old cancer patients, the impact of concurrent comorbidities decreased in the group of patients ≥ 75 years old and the majority of specific comorbidities did not have a significant impact on all-cause mortality among this group of patients, this was explained by the effect of aging and/or age-related factors like decreased functional status, physiologic reserves and cognition. The combination of these factors makes a patient more vulnerable to complications and mortality [35].

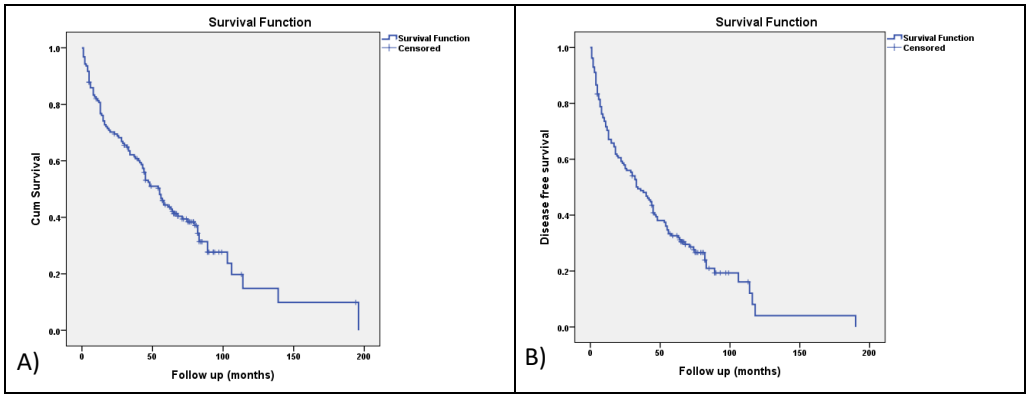

Figure 1 Kaplan Meier curve showing A) the overall survival and B) disease free survival of the whole studied early breast cancer cases.

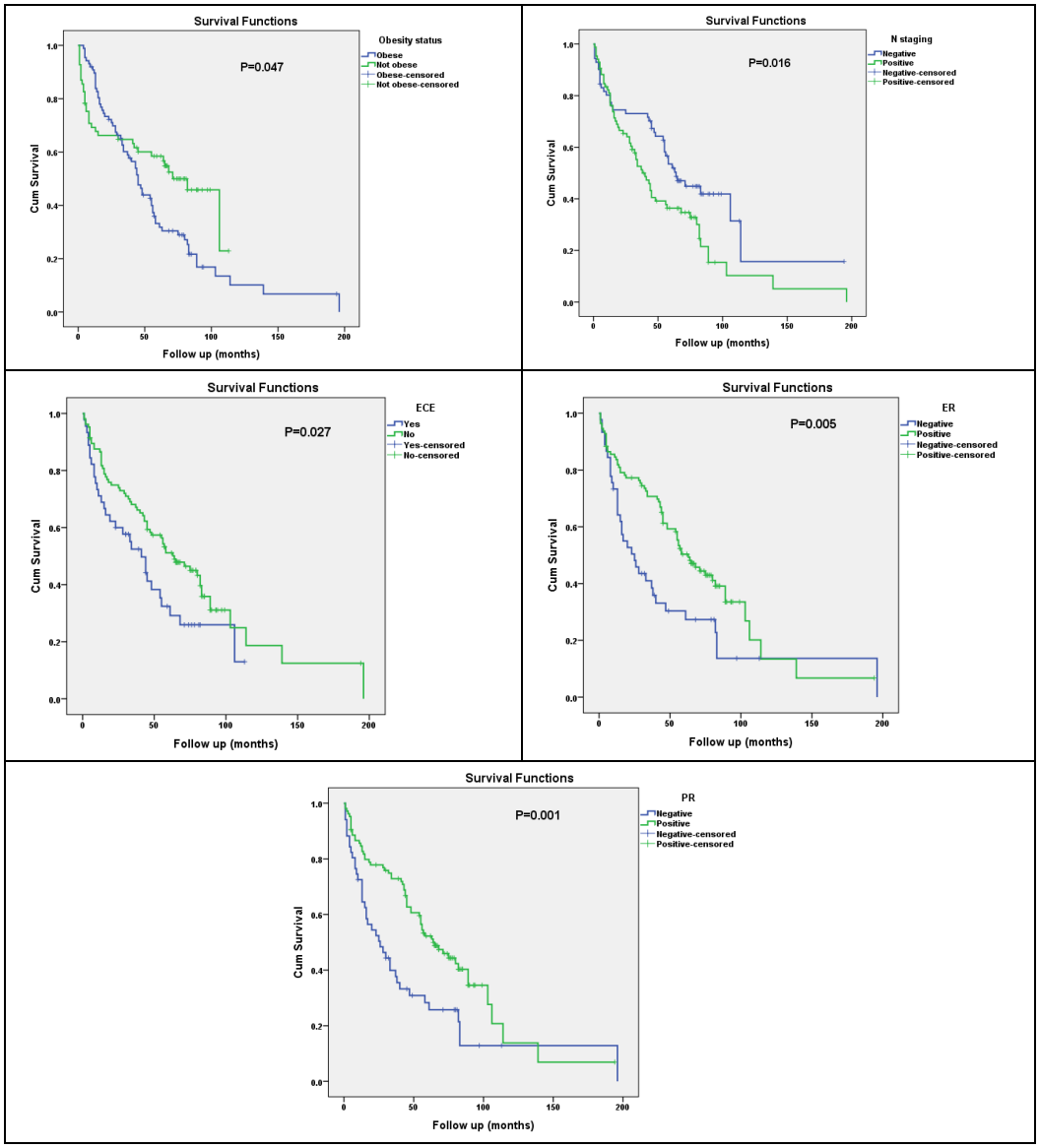

Figure 2 Kaplan Meier curve showing overall survival of the studied early breast cancer cases according to clinic-pathological details.

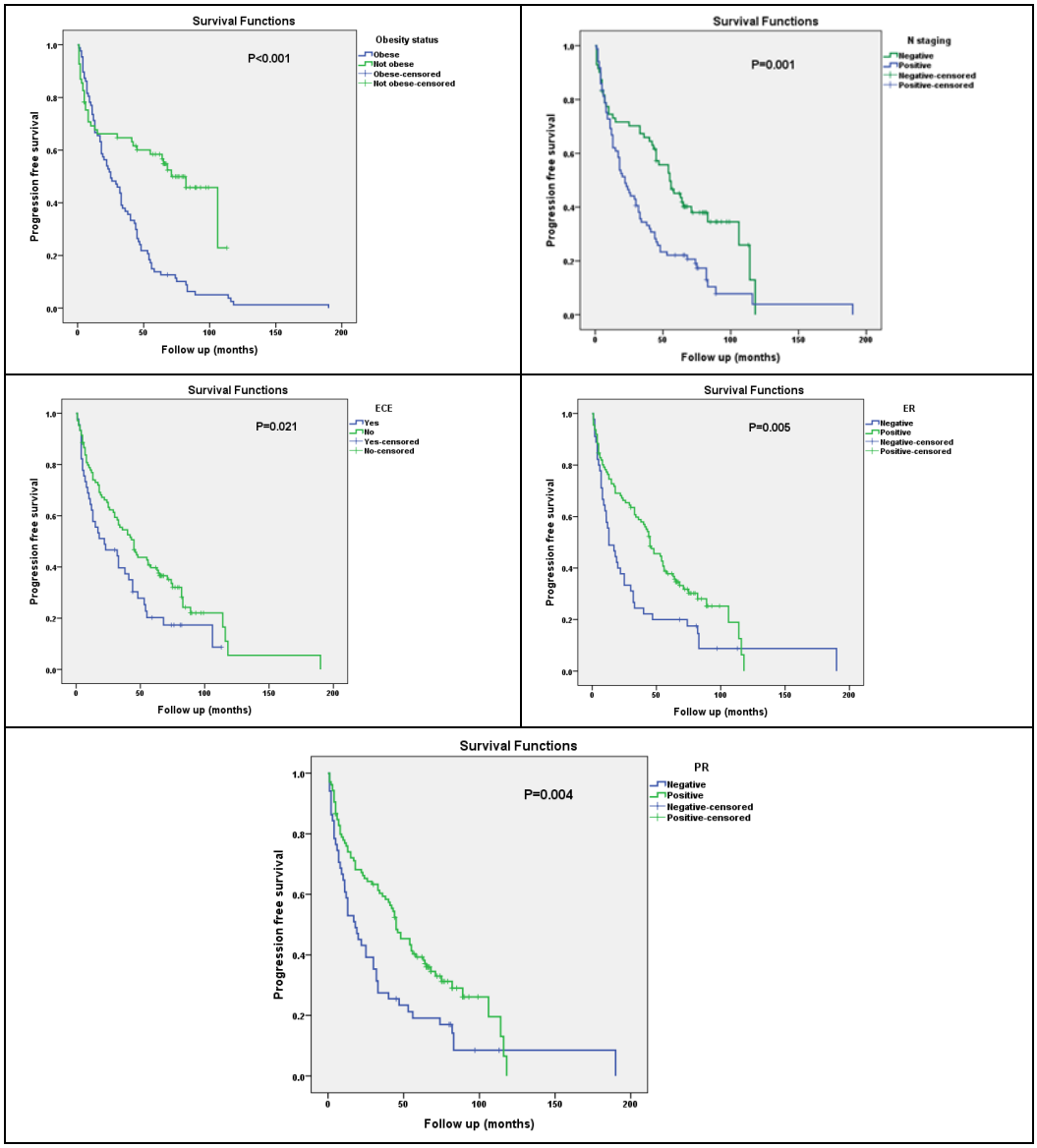

Figure 3 Kaplan Meier curve showing progression free survival of the studied early breast cancer cases according to clinic-pathological details.

Table (1): Baseline data of early breast cancer patients

Baseline data		**N=156**	
Age (years)	Median (range)	68 (65 – 84)	
BMI (kg/m^2)	Median (range)	26.5 (18.6 – 53.7)	
	Obese	87	(55.8)
	Not obese	69	(44.2)
Associated comorbidities	Diabetic	44	(28.2)
	Hypertensive	44	(28.2)
	Cardiac	18	(11.5)
	DVT	7	(4.5)
	Hepatic	3	(1.9)
	Chest	1	(0.6)
Presentation	Mass	151	(96.8)
	Pain	18	(11.5)
	Skin/nipple changes	15	(9.6)
Tumor focality	Unifocal	147	(94.2)
	Multifocal	9	(5.8)
Tumor Site	Right side	67	(42.9)
	Left side	88	(56.4)
	Bilateral	1	(0.6)
T staging	T1/T2	114	(73.1)
	T3/T4	42	(26.9)
Nodal metastasis (N)	Negative	71	(45.5)
	Positive	85	(54.5)
Histology	IDC	143	(91.7)
	ILC	6	(3.8)
	Mixed	6	(3.8)
	Intracyctic papillary carcinoma	1	(0.6)
Tumor grading	G1/G2	144	(92.3)
	G3	12	(7.7)
ER hormonal status	Negative	45	(28.8)
	Positive	111	(71.2)
Estrogen receptor strength (Allred Score)	Negative (0-1/8)	45	(28.8)
	Weak (2-3/8)	11	(7.1)
	Moderate (4-6/8)	17	(10.9)
	Strong (7-8/8)	83	(53.2)
PR hormonal status	Negative	51	(32.7)
	Positive	105	(67.3)
Progesterone receptor strength (Allred Score)	Negative (0-1/8)	51	(32.7)
	Weak (2-3/8)	24	(15.4)
	Moderate (4-6/8)	22	(14.1)
	Strong (7-8/8)	59	(37.8)
HER2neu IHC	Ultra Low	63	(40.3)
	Low	77	(49.4)
	Positive	16	(10.3)
KI67	<14	57	(36.5)
	≥14	99	(63.5)
Type of received CTH	No	46	(29.5)
	Anthracycline based protocol	68	(43.6)
	Anthracycline + Taxanes	36	(23.1)
	Taxanes based protocol	6	(3.8)

Table (2): Overall and progression free survival according to clinic-pathological details of the studied early breast cancer cases (n=156)

	OS (5 years)		PFS (5 years)	
	Estimate ± SE	**P value**	**Estimate ± SE**	**P value**
Age		0.791		0.791
• 65 – 69 years	44.4 ± 5.4%		44.4 ± 5.4%	
• ≥ 70 years	44.6 ± 6.4%		44.6 ± 6.4%	
Obesity		**0.047**		**<0.001**
• Obese	33.2 ± 5.3%		13.8 ± 3.7%	
• Not obese	58.4 ± 6.0%		58.4 ± 6.0%	
No. of associated comorbidities		0.851		0.839
• 0 - 2	44.5 ± 4.4%		34.4 ± 4.2%	
• ≥ 3	43.8 ± 10.8%		36.4 ± 10.3%	
Focality		0.818		0.070
• Unifocal	45.5 ± 4.2%		34.7 ± 4.0%	
• Multifocal	25.9 ± 15.7%		****	
TNM staging (T)		0.384		0.057
• Early (T1+T2)	48.0 ± 4.9%		36.8 ± 4.6%	
• Advanced (T3+T4)	34.9 ± 7.5%		21.4 ± 6.3%	
TNM staging (N)		**0.016**		**0.001**
• Negative	53.5 ± 6.1%		45.1 ± 6.0%	
• Positive	36.4 ± 5.5%		22.1 ± 4.6%	
DCIS		0.759		0.954
• Yes	43.5 ± 4.9%		33.9 ± 4.6%	
• No	46.5 ± 7.7%		29.5 ± 6.9%	
Tumor grade		0.476		0.719
• Grade 1 + Grade 2	45.3 ± 4.3%		32.5 ± 4.0%	
• Grade 3	33.3 ± 13.6%		33.3 ± 13.6%	
Margin		0.537		0.345
• Free	45.4 ± 4.2%		33.2 ± 4.0%	
• Positive	66.7 ± 27.2%		66.7 ± 27.2%	
LVI		0.219		0.215
• Yes	35.2 ± 6.2%		24.6 ± 5.3%	
• No	53.8 ± 5.5%		41.6 ± 5.5%	
Perineural invasion		0.201		0.501
• Yes	33.7 ± 7.2%		27.3 ± 6.7%	
• No	51.5 ± 5.0%		36.9 ± 4.8%	
Histopathology		0.404		0.637
• IDC	44.0 ± 4.3%		34.0 ± 4.1%	
• Other pathology	48.8 ± 13.8%		20.0 ± 10.3%	
ECE		**0.027**		**0.021**
• xYes	32.4 ± 7.6%		20.2 ± 6.2%	
• No	51.1 ± 5.0%		39.7 ± 4.8%	
ER		**0.005**		**0.005**
• Negative	30.3 ± 7.2%		20.0 ± 6.0%	
• Positive	50.3 ± 4.9%		37.8 ± 4.7%	
PR		**0.001**		**0.004**
• Negative	28.3 ± 6.6%		19.1 ± 5.6%	
• Positive	52.2 ± 5.0%		39.3 ± 4.9%	
Her2neu		0.457		0.602
• Negative	46.4 ± 4.6%		33.2 ± 4.2%	
• Positive	36.9 ± 9.1%		30.0 ± 8.7%	
KI67		0.891		0.703
• < 14	47.9 ± 6.8%		35.8 ± 6.5%	
• ≥ 14	42.4 ± 5.2%		30.8 ± 4.7%	

Table (3) Independent factors affecting overall survival among the studied early breast cancer cases

	Univariate analysis			Multivariate analysis		
	HR	**95% C.I. for HR**	**P value**	**HR**	**95% C.I. for HR**	**P value**
Obesity						
• Obese	1.517	0.999 – 2.304	0.051			
• Not obese	ref					
TNM staging (N)						
• Negative	ref			ref		
• Positive	1.624	1.086 – 2.429	**0.018**	1.608	1.059 – 2.441	**0.026**
ECE						
• Yes	1.620	1.048 – 2.502	**0.030**	1.518	1.132 – 3.213	**0.045**
• No	ref			ref		
ER						
• Negative	1.806	1.189 – 2.743	**0.006**	1.722	1.023 – 2.743	**0.014**
• Positive	ref			ref		
PR						
• Negative	1.924	1.283 – 2.884	**0.002**	1.861	1.225– 2.825	**0.004**
• Positive	ref			ref		

Table (4) Independent factors affecting disease recurrence among the studied early breast cancer cases

	Univariate analysis			Multivariate analysis		
	HR	**95% C.I. for HR**	**P value**	**HR**	**95% C.I. for HR**	**P value**
Obesity						
• Obese	2.531	1.683 – 3.807	**<0.001**	ref		
• Not obese	ref			2.877	1.877 – 4.410	**<0.001**
TNM staging (N)						
• Negative	ref			Ref		
• Positive	1.860	1.279 – 2.703	**0.001**	2.147	1.177 – 5.230	**0.003**
ECE						
• Yes	1.586	1.065 – 2.362	**0.023**	1.726	1.153 – 2.584	**0.008**
• No	ref			ref		
ER						
• Negative	1.717	1.168 – 2.524	**0.006**	1.049	1.007 – 3.420	**0.010**
• Positive	ref			Ref		
PR						
• Negative	1.717	1.182 – 2.495	**0.005**	2.042	1.623 – 2.310	**0.021**
• Positive	ref					

Regarding tumor characteristics, Positive nodal metastasis was observed in 85 (54.5%) of our patients and had a significant impact on the 5-year survival analysis (p= 0.016), it was considered a significant prognostic factor of death in the multivariate cox regression analysis (HR= 1.61, CI= 1.06 – 2.44, p= 0.026), This result matched the results observed in earlier studies [36,37]. In disagreement with other studies, we found that other tumor characteristics such as tumor focality and T-staging had no significant impact on the 5-year survival analysis (p=0.818 and p= 0.384 respectively [37,38], another previous study showed no significant effect of tumor focality on the survival rates [39].

Invasive ductal carcinoma (IDC) was the most histopathological type in our group of patients with early breast cancer, detected in 143 (91.7%) patients. Although it has been mentioned in literature that invasive lobular carcinoma (ILC) tends to occur more frequently [40], only 6 (3.6%) patients of our study group had ILC. our 5-year OS analysis did not show a significant difference between IDC and other histopathological types (p=0.404), this result was in consistent with a recent large cohort study that show no significant difference in the 5-year OS of early stage ductal and lobular cancer patients [41]. However, many other reports showed a significant impact of histopathology of breast cancer on survival rates [40,42], Dian et al., had performed Kaplan–Meier survival analysis of OS between IDC and ILC patients and showed a statistically significantly better OS for patients with ILC (p = 0.030) [43].

Many studies in literature indicated that the presence and extent of ECE have been associated with poorer survival outcomes [44,45], Kanyılmaz et al. had shown that ECE was a significant predictor of overall survival (OS) and disease-free survival (DFS) in a cohort of patients with pathological T1-2 and N1 breast cancer including those who were elderly. our results were similar to the previous report. ECE was found in 45 (30%) of our patients while 105 (70%) were without ECE, the 5-year overall survival analysis indicated that the presence of ECE had a significant impact on the prognosis of the patients (32.4% for the patients with ECE versus 51.1% for the patients without ECE, p= 0.027). Another previous report found a correlation between the presence of ECE and the number of additional positive lymph nodes. But found no significant impact on overall survival, and disease-free survival in a follow-up of 10 years.

As regard hormonal receptors, we found that estrogen receptor positivity (ER) was detected in 111 (71.2%) patients, progesterone receptor positivity (PR) was detected in 105 (67.3%) patients, while the Human Epidermal growth factor Receptor HER2-neu was positive in 16 (10.3%) patients.

Our results were in concordance with a previous study -with a cohort of breast cancer patients of 70 years old or older- showed that ER positivity, PR positivity and HER2-neu positivity were found in 73.5%, 63.5% and 17.9% of the study population respectively [34], another systematic review reported slightly different results with ER positivity, PR positivity and HER2 positivity in 81.1%, 59.3% and 13.4% of the cohort respectively [46], In deed, the same systematic review and other studies indicated that breast cancer tends to present with less aggressive features with age, hormonal receptor expression increases, while HER2 neu expression decreases [47].

In our survival analysis, ER and PR status showed significant impacts on the 5-year survival (p=0.005 and p=0.001 respectively). This was consistent in previous studies indicated that overall survival rates were significantly affected by receptors subtype with ER+/PR+ patients having the highest survival rates and ER−/PR− patients having the lowest rates. These differences were largely explained by the less aggressive nature of hormone receptor positive tumors as well as the effectiveness of the adjuvant hormonal therapies that only affect the hormone positive tumors [48].

Our survival analysis failed to show a significant impact of the negativity of the HER2 on survival rates (p=0.457). This was in contrast to other reports in the literature which showed that HER2-neu positive subtype remained the most aggressive phenotype in elderly breast cancer patients with the shortest overall survival [49,50]. Another study involving a study population of elderly Caucasian Women showed no significant difference in survival rates between HER2 neu +ve tumors and other subtypes (p= 0.285) [51].

Limitations:

Limitation of our study is that patients with Her2neu positive tumor did not receive anti-Her2 therapy due to either contraindications or per local protocol during the study period.

Conclusion:

Our research shows that at five years of follow-up, obesity, nodal metastasis, ECE, ER, and PR significantly affect the over-all survival (OS) among the studied participants and also affect the disease-free survival (DFS) among the studied participant.

Competing interests:

The authors declare that they have no competing interests.

Acknowledgements: (Not applicable)

Ethics approval and consent to participate:

The protocol was approved by the Institutional Review Board of Faculty of Medicine, South Egypt Cancer Institute, Assiut University (approval number: IORG0006563, date of approval 16 October 2021). Our study conformed to all requirements as governed by the declaration of Helsinki.

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