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Proportion and impact of low positive versus negative estrogen/progesterone receptor status on survival outcomes in HER2-negative breast cancer

Marwa A. Ahmed

dr_marwaabdelsattar@yahoo.com

National Cancer Institute (NCI) - Cairo University

Nancy H Amin

National Cancer Institute (NCI) - Cairo University

Mostafa A Hussein

National Cancer Institute (NCI) - Cairo University

Mohamed Yousri Ahmed

National Cancer Institute, Cairo University

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Title:

Proportion and impact of low positive versus negative estrogen/progesterone receptor status on survival outcomes in HER2-negative breast cancer

Authors:

Marwa A. Ahmed, Nancy H Amin, Mostafa A Hussein, Mohamed yousri Ahmed.

Affiliations:

Oncologic Pathology Department, National Cancer Institute (NCI) - Cairo University, Cairo, Egypt.

Corresponding author: Marwa A. Ahmed, Oncologic Pathology Department, National Cancer Institute (NCI), Cairo University, Cairo, Egypt.

E-mail address: dr_marwaabdelsattar@yahoo.com

The 16-digit ORCID of the corresponding author: 0009-0001-6614-7828

Authors' information:

First Author: Marwa A. Ahmed (corresponding author), MSc, MD, PhD

Assistant Professor of Oncologic Pathology,

Oncologic Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt.

dr_marwaabdelsattar@yahoo.com

Second Author: Nancy H Amin, MSc, MD, PhD

Assistant Professor of Oncologic Pathology,

Oncologic Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt.

Nancy.amin@nci.cu.edu.eg

Third author: Mustafa A Hussein, MSc, MD, PhD

Assistant Professor of Oncologic Pathology,

Oncologic Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt.

mostafa86hussein@gmail.com

Fourth author:

Mohamed Yousri Ahmed, MSc, MD, PhD

Assistant Professor of Oncologic Pathology,

Oncologic Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt.

mohamed.yousri@nci.cu.edu.eg

Abstract

Purpose: Estrogen receptor low-positive breast cancer (ER-low) is a new entity introduced by the updated American Society of Clinical Oncology/College of American Pathologists guideline. In such tumors ER is expressed in 1-10% of tumor cells. There is limited data available about the biological behavior of this group. This study aims to assess the proportion of ER-low positive breast cancer in a single institute and compare such group with triple negative one as regard clinicopathologic features and survival.

Methods: This is a retrospective study that included 103 patients diagnosed and treated as breast cancer at National Cancer Institute, Cairo University Cases were categorized according to their hormone receptor status into low ER-positive group (ER/PR expression ≤10%) and triple negative group. Tumor characteristics, type of treatment, OS and DFS were evaluated among both groups.

Results: Triple negative and ER-low positive cases were 79 (76.7%) and 24 (23.3%), respectively. Demographic, clinic-pathologic and treatment characteristics were comparable between both groups. Triple negative group shows higher histologic grade than ER-low positive group (p value = 0.002). According to survival status, there is no significant difference in OS and DFS between triple negative and low ER positive group. In 58 patients receiving neoadjuvant chemotherapy (13 ER-low versus 45 triple negative cases), triple negative group showed higher complete pathologic response when compared to ER-low positive group, despite this difference is not statistically significant (12.7% versus 4.2% respectively, p = 0.513).

Conclusion: ER-low positive group has the same clinical behavior as triple negative breast cancer.

Keywords

ER-low, Triple negative, Breast cancer, Pathologic features, Survival

Introduction

Breast cancer is a heterogeneous disease that has distinct molecular subtypes categorized by the expression of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2) [1]. In such tumor, estrogen receptor (ER) remains the most important biomarker regarding clinical decision making and predicting outcomes [2]. According to immunohistochemical analysis of hormone receptor, different intrinsic breast cancer subtypes were identified and they include: luminal A [estrogen receptor (ER)+ and/or progesterone receptor (PR)+, Ki67 low and human epidermal growth factor receptor 2 (HER2)−], luminal B [ER+ and/or PR+, Ki67 high and HER2−], luminal HER2+ [ER+ and/or PR+, any Ki67 and HER2+], HER2 [ER−, PR−, and HER2+], and triple negative (TN) [ER−, PR−, and HER2−] [3]. Tumors with positive hormone receptor received adjuvant endocrine therapy while triple negative one received only chemotherapy and was associated with the worst survival [4]. The exact definition of cutoff value for ER positivity is still controversial. The joint panel of ASCO Clinical Practice Guidelines Committee (CPGC) and CAP Council on Scientific Affairs (CSA) recommended that ER and PR show ≥1% nuclear expression by immunohistochemistry (IHC) is considered positive [5]. Also, these guidelines mentioned that the decision regarding hormone therapy in patients with low ER expression (1%-10%) should be made after weighing both the risks and benefits as different expressions may result in different responses and outcomes [6]. Aligned with this, the latest ASCO/CAP guideline recommends reporting tumors with 1 to 10% ER expression as “ER Low Positive” group. Most of the previously reported data stated that such tumors had limited benefits of hormone therapy and had clinical outcomes and molecular biology comparable to triple negative cancers [2]. We conduct this retrospective study to estimate the proportion of ER-low positive tumor among the studied cases. Secondary we will compare between them and triple negative one as regard clinico-pathologic characteristic and survival.

Material and methods

Study Population

This is a retrospective study that was conducted after the approval of the institutional review board of National Cancer Institute, Cairo University. An institutional search was performed to identify female patients diagnosed with invasive breast cancer between January 2018 till December 2018. The identified patients were classified as triple negative and those with ER and PR expression ranged from (1-10%). Clinicopathologic data were gathered from patient's clinical files and pathology report regard (age, sex, histologic type, histologic grade, operation, stage, ER, PR and HER2 status, date of recurrence, therapy intake), and clinical outcome. Cases diagnosed as invasive breast cancer with ER or PR expression more than 10% and those with equivocal or positive HER2 were excluded. A total of 278 were identified, of whom 175 were excluded due to unavailable blocks, missing files, incomplete clinical data or lost follow-up.

Histopathologic evaluation and immunohistochemical analysis

All pathologic specimens were reviewed by single dedicated pathologists. The histologic type of all tumors was defined according to World Health Organization's classification system (7). The histologic grade was defined according to Nottingham modification of Bloom-Richardson system, based on (a) tumor tubular formation, (b) nuclear pleomorphism and (c) number of mitotic figures in most active areas, with each given a score of 1, 2 or 3 (8). Immunostaining for ER, PR and HER2 was done using BenchMark XT (Ventana) autostainer. All markers are ready to use rabbit primary monoclonal antibodies. Testing of hormone receptors was performed using the standard procedures and following the ASCO/CAP Guideline Recommendations. ER/PR positivity was determined by IHC analysis of the number of positively stained nuclei (1-10%). For HER2 protein

overexpression, tumors exhibiting 0 or 1+ staining were considered HER2-negative, and they were included. Other immunostaining patterns were excluded.

Statistical analysis

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 27. Patients were categorized according to ER, PR and HER2 immunohistochemical expression into two groups: Triple negative (ER and PR <1%, HER2 0 or 1+) and ER-low positive (ER and PR 1%-10%). Numerical data were summarized using means and standard deviations or medians and/or ranges, as appropriate. Categorical data were summarized as numbers and percentages. Estimates of the frequency were done using the numbers and percentages. Numerical data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test.

The overall survival was estimated using the Kaplan and Meier method. Overall survival was calculated from date of diagnosis to date of death or last follow up. Disease free survival was calculated from date of surgery to date of recurrence or death. Differences between the survival curves were assessed with the log-rank test. Kaplan-Meier method was used to estimate overall survival and disease-free survival. Multivariate analysis was done by Cox regression model to test for independent prognostic effect of statistically significant variables on univariate level with calculating hazard ratio and its 95% confidence interval. All tests were two tailed & Probability (p-value) ≤ 0.05 is considered significant.

Results

1. **Study Population and Clinicopathologic Characteristics:**

   This study encompasses 103 female patients diagnosed as invasive breast cancer. The mean age was 52 years, with a range of 26 to 85 years. 20 patients (19.4%) had a positive family history of breast cancer and other cancers which include (ovary, uterus, colon and liver).

Mean tumor size was 4 cm, with a range of 1 to 12 cm. Near one third of cases (30.1%) have a tumor diameter greater than 5 cm. Half of cases have left side tumor (50.5%, 52). Approximately (58.3%, 59) of patients underwent mastectomy. 79 (76.7%) of our cases were diagnosed with invasive carcinoma, NST and most of them were intermediate grade. Most cases were stage 2&3 (63.1% & 27.2% respectively). Positive lymph nodes were detected in (42.7%, 44). Positive hormone receptors (especially ER and PR) were detected in (23.3%, 24) and all of them received endocrine therapy with or without chemotherapy. Triple negative breast cancer constituted 76.7% (79/103) of patients and they received chemotherapy either neoadjuvant, adjuvant or combined. Those who received neoadjuvant chemotherapy (56.3%, 58), a complete pathologic response was detected in 11 cases (10.7%). Chemotherapy regimens received in the Low-ER and triple negative group were the same. Furthermore, 88 (85.4%) of cases received postoperative radiotherapy and only two cases received palliative radiotherapy. Among the Low–ER group, ER expression ranged 2%–10% and PR expression ranged 5-10%. Within the Low-ER group, 50% (12/24) had both ER and PR expression 1–10%, 45.8% (11/24) had ER expression 1–10% with PR expression <1%, and 4.2 % (1/24) had PR expression 1–10% with ER expression <1% (Figures 1&2).

2. Clinicopathologic characteristics among Low-ER and Triple negative groups:

Detailed demographic data and clinicopathologic characteristics were demonstrated in table (1). No significant difference regarding age, site and size of tumor, histologic type and stage was observed among both groups. In our study, triple negative group showed higher histologic grade of tumor than ER-low group with significant P value (p value =0.002). All patients included in ER-low positive group received adjuvant endocrine therapy. In patients received neoadjuvant chemotherapy (13 within ER-low positive group and 45 within triple negative group), only 11 patients achieved complete pathologic response (1 case within ER-low and 10 cases within triple negative groups), respectively.

3. Survival outcome among both groups:

103 patients were followed up for five years with a median follow-up period of 55 months (ranging from 0.6-85 months). At the end of follow up period, 34 patients showed evidence of recurrent disease (either local recurrence, distant metastasis or both) and 28 died. The cumulative 5-year overall (OS) was 74% in the whole population, 70% for patients with ER-low positive breast cancer and 75% for patients with triple negative breast cancer respectively. Disease-free survival was calculated for (100) cases only. The cumulative 5-year disease free survival (DFS) was 61%, 49% and 64% for whole population, patients with ER-low positive and patients with triple negative breast cancer respectively. For both groups no significant difference was observed in OS and DFS (Figures 3&4). According to univariate analysis, the presence of comorbidities, tumor size greater than 5 cm, advanced stage and the presence of positive lymph nodes are all associated with lower overall survival (P value 0.029, 0.003, 0.001 & 0.003 respectively) (Table 2). Also, patients underwent mastectomy had lower OS than those underwent lumpectomy (P value 0.040). In contrast for disease free survival, patients underwent lumpectomy and those with positive lymph nodes or advanced stage have significantly lower disease-free survival (P value 0.002, 0.001 & 0.001 respectively) (Table 3).

In Multivariate analysis, advanced stage was the most important predictor for OS survival (P <0.001, HR=4.2, 95% C.I: 2-9.1). While for DFS, lymph node metastasis was the most important predictor (P <0.001, HR=4.1, 95% C.I: 2.1-8.1).

Table (1): Clinicopathologic characteristics among ER-low and triple negative groups

Clinicopathologic variable	Low positive n=24 (%)	Triple negative n=79 (%)	*P value*
Age group			
< 50 Year	12 (50)	31 (39.2)	0.479
≥ 50 Year	12 (50)	48.6 (60.8)	
Family history			
Yes	3 (12.5)	17 (21.5)	0.393
No	21 (87.5)	62 (78.5)	
Comorbidity			
Yes	8 (33.3)	23 (29.1)	0.800
No	16 (66.7)	56 (70.9)	
Maximum tumor diameter (cm)			
< 5 Cm	16 (66.7)	54 (68.4)	0.877
≥ 5 Cm	8 (33.3)	25 (31.6)	
Tumor site			
Left	13 (54.2)	39 (49.4)	0.680
Right	11 (45.8)	40 (50.6)	
Histologic type			
IDC	18 (75)	61 (77.2)	NA
ILC	1 (4.2)	2 (2.5)	
Other carcinomas	5 (20.8)	16 (20.3)	
Histologic type			
IDC	18 (75)	61 (77.2)	0.822
Non IDC	6 (25)	18 (22.8)	
Histologic grade			
Grade I	2 (8.3)	0 (0)	NA
Grade II	19 (79.2)	40 (50.6)	
Grade III	3 (12.5)	39 (49.4)	
Histologic grade			
Low grade (grade I&II)	21 (87.5)	40 (50.6)	0.002
High grade (grade III)	3 (12.5)	39 (49.4)	
Stage			
Stage I	2 (8.3)	4 (5.1)	NA
Stage II	13 (54.2)	52 (65.8)	
Stage III	8 (33.3)	20 (25.3)	
Stage IV	1 (4.2)	3 (3.8)	
Stage			
Early stage	15 (62.5)	56 (70.9)	0.437
Advanced stage	9 (37.5)	23 (29.1)	
Surgery			
Lumpectomy	6 (25)	37 (46.8)	0.057

Mastectomy	18 (75)	42 (53.2)	
Neoadjuvant chemotherapy			
Yes	13 (54.2%)	45 (57%)	0.513
No	11 (45.8%)	34 (43%)	
Pathologic response			
No response	11 (45.8)	34 (43)	0.513
Partial response	12 (50)	35 (44.3)	
Complete response	1 (4.2)	10 (12.7)	

Table (2): Overall survival in relation to pathological factors:

OS	No. of cases	No. of events	(%) 1 year	(%) 2 year	(%) 3 year	(%) 4 year	(%) 5 year	(%) 6 year	Median survival time (years	*P value*
Whole group	103	28	90	86	81	75	74	73	NR	
Age										
<50 years	43	9	95	93	88	83	80	77	NR	0.215
≥50 years	60	19	87	82	77	69	69	65		
Family history										
Positive	20	4	90	87	82	74	73	71	NR	0.550
Negative	83	24	90	85	79	79	79	79		
Co-morbidity										
Yes	31	13	81	74	71	64	60	60	NR	0.029
No	72	15	94	92	86	80	80	76	NR	
Maximum tumor diameter (cm)										
< 5 Cm	70	13	94	94	90	85	83	81	NR	0.003
≥ 5 Cm	33	15	82	70	64	55	55	55	NR	
Tumor site										
Left	52	15	92	90	83	74	72	69	NR	0.736
Right	51	13	88	82	80	76	76	76	NR	
Histologic type										
IDC	79	20	91	87	82	76	75	75	NR	0.494
Non IDC	24	8	88	83	79	70	70	65	NR	
Histologic grade										
Low grade (grade 1&2)	61	15	90	89	80	78	78	76	NR	0.555
High grade (grade 3)	42	13	91	83	83	71	68	68	NR	
Stage										
Low stage (stage I&II)	71	11	92	90	90	86	84	84	NR	<0.001

Advanced stage (stage III&IV)	32	17	88	78	62	51	51	47	5.2	
Nodal status										
Negative	59	10	92	92	90	83	83	83	NR	0.003
Positive	44	18	89	79	70	64	60	57	NR	
Hormone receptor status										
Low positive	24	7	88	88	75	70	70	70	NR	0.752
Triple negative	79	21	91	86	83	76	75	73	NR	
Surgery										
Lumpectomy	60	21	88	83	77	67	65	65	NR	0.040
Mastectomy	43	7	93	91	88	86	86	83	NR	

NR: Not reached, P value <0.05 is considered significant

Table (3): Disease free survival in relation to pathological factors

DFS	**No. of cases**	**No. of events**	**(%) 1 year**	**(%) 2 year**	**(%) 3 year**	**(%) 4 year**	**(%) 5 year**	**(%) 6 year**	**Median survival time (years)**	***P value***
Whole group	100	41	82	78	70	63	61	55	NR	
Age										
<50 years	43	16	91	84	74	69	66	53	NR	0.462
≥50 years	57	25	75	74	67	59	57	54	NR	
Family history										
Positive	20	6	85	74	74	69	69	69	NR	0.440
Negative	80	35	81	79	69	62	59	52	NR	
Co-morbidity										
Yes	29	15	72	59	59	51	51	45	5.6	0.140
No	71	26	86	80	74	68	65	58	NR	
Maximum tumor diameter										
< 5 Cm	69	24	87	84	78	70	68	60	NR	0.033
≥ 5 Cm	31	17	71	65	52	48	45	45	4	
Tumor site										
Left	50	20	86	80	68	63	63	53	NR	0.783
Right	50	21	78	76	68	63	59	56	NR	
Histologic type										
IDC	76	31	82	79	71	64	60	54	NR	0.951
Non IDC	24	10	83	75	67	63	58	58	NR	
Histologic grade										
Low grade (grade 1&2)	58	24	85	81	72	66	62	51	NR	0.940
High grade (grade 3)	42	17	79	74	66	59	59	59	NR	

Stage										
Early stage (stage I&II)	71	20	87	85	82	75	72	67	NR	<0.001
Advanced stage (stage III&IV)	29	21	69	62	41	35	35	28	2.6	
Nodal status										
Negative	56	12	88	86	80	80	78	78	NR	<0.001
Positive	44	29	75	68	56	40	38	27	3.7	
Hormone receptor status										
Low positive	23	11	83	74	65	55	49	49	4.4	0.419
Triple negative	77	30	82	78	71	66	64	57	NR	
Surgery										
Lumpectomy	60	32	73	70	58	49	47	44	3.9	0.002
Mastectomy	40	9	95	90	87	85	82	72	NR	

NR: Not reached, P value <0.05 is considered significant

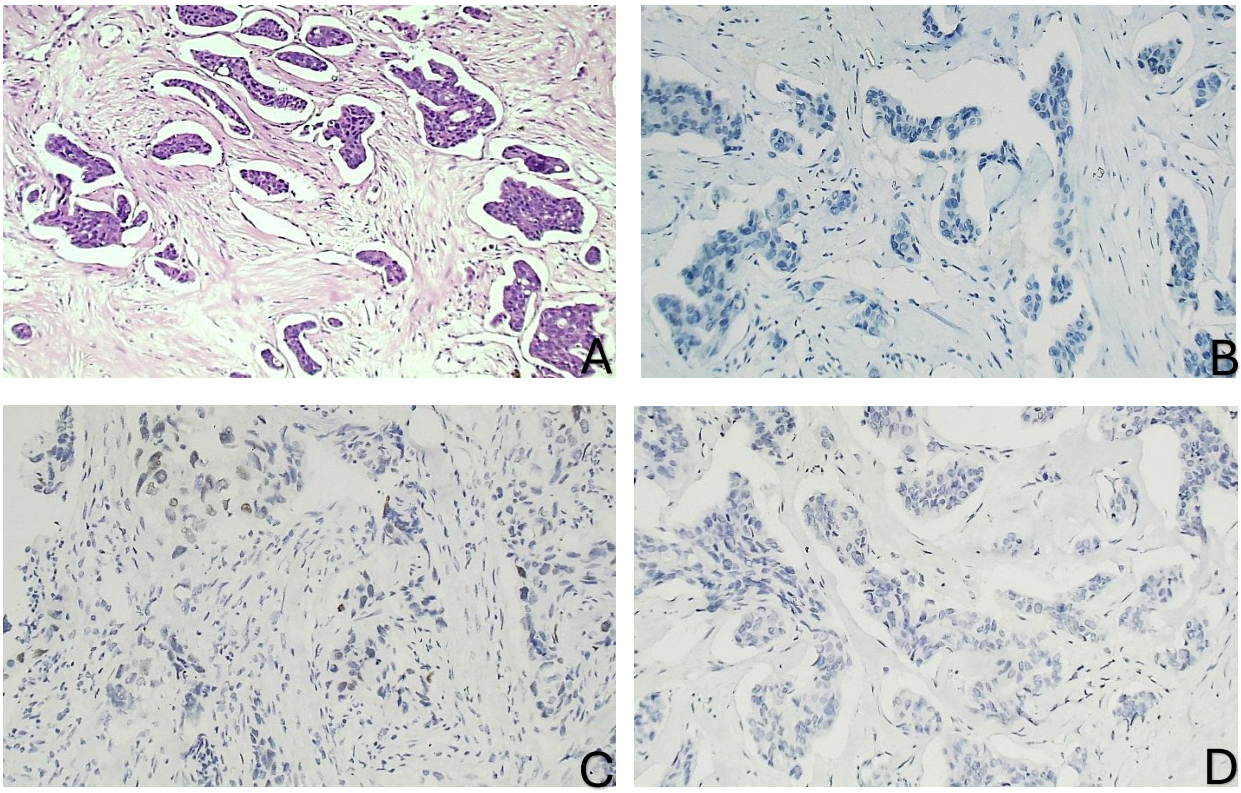


Figure (1): A case of invasive micropapillary carcinoma, grade 2 with low PR expression (X400).

(A) H & E-stained slide showing papillary clusters set within cystic spaces of retraction stromal artifact. (B) ER is negative with absence of nuclear reaction within tumor cells. (C) Weak positive nuclear reaction of PR in about 2% of tumor cells. (D) HER2 neu is negative in tumor cells (score 0).

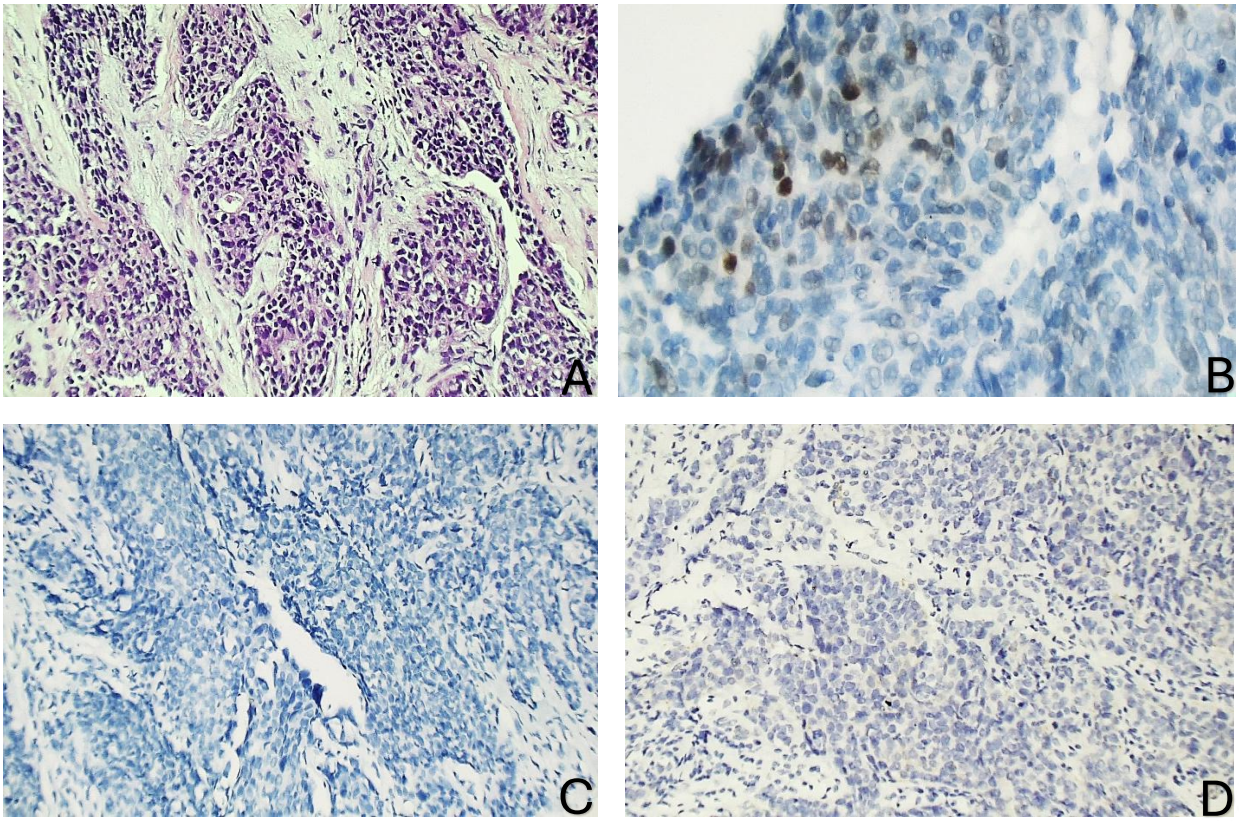


Figure (2): A case of invasive carcinoma, NST, grade 3 with low ER expression (X400).

(A) H & E-stained slide showing solid sheets of tumor cells with poor ductal differentiation. (B) Moderate positive nuclear reaction of ER in about 3% of tumor cells. (C) PR is negative with absence of nuclear reaction within tumor cells. (D) HER2 neu is negative in tumor cells (score 0).

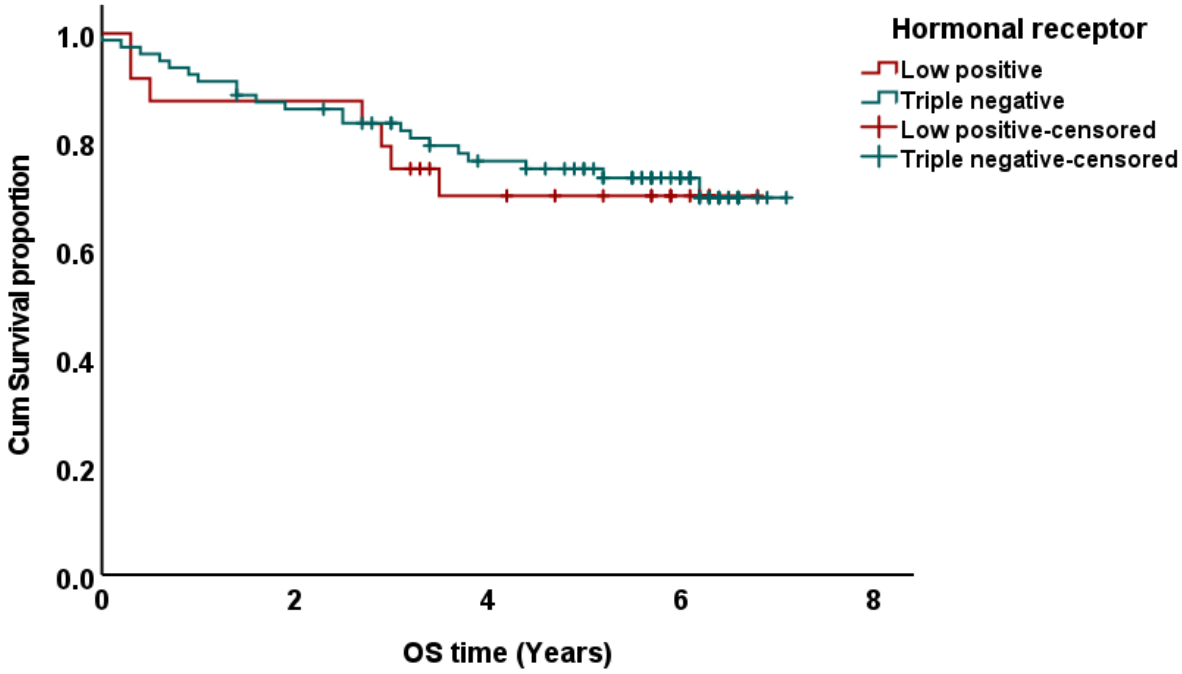


Figure (3): Kaplan and Meier curve representing OS in relation to hormonal receptors

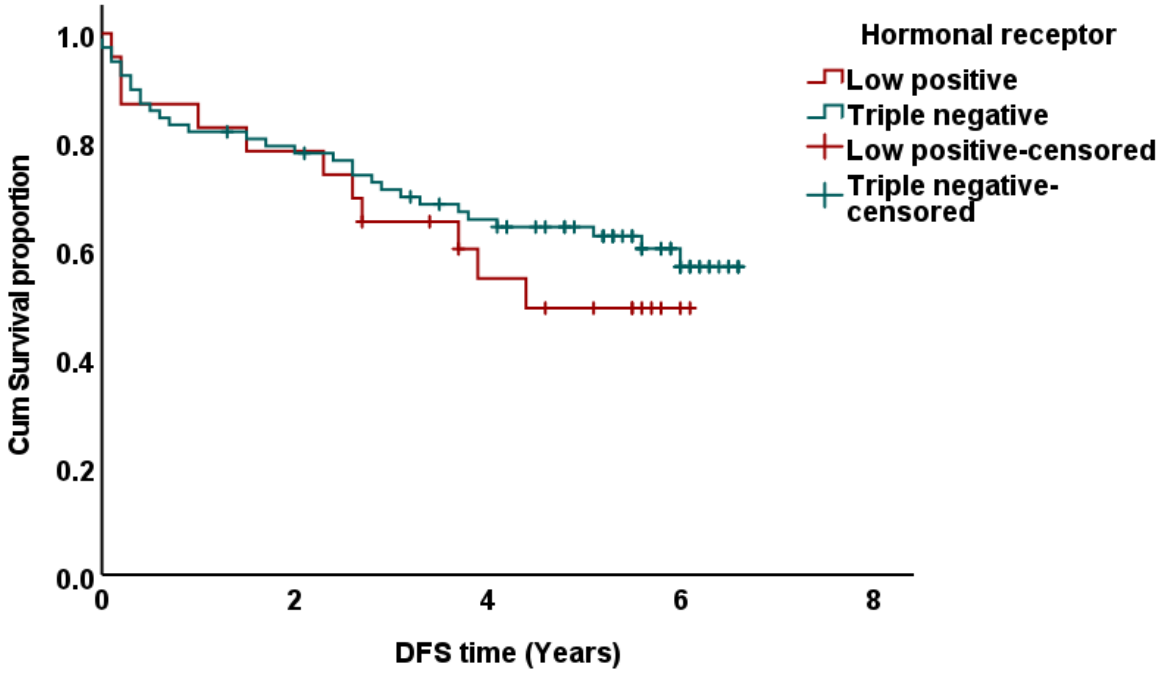


Figure (4): Kaplan and Meier curve representing DFS in relation to hormonal receptors

Discussion

Breast cancer is a heterogenous disease and the immunohistochemical assessment of hormone receptor status is one of the important prognostic and predictive factors in such tumors. Although most BCs (breast cancers) show either complete absence of ER staining (0%) or ER positivity in ≥10% of tumor cells. A small proportion of BCs presents low levels of ER expression (i.e., defined by 1–9% of ER+ stained cells). These ER-low positive tumors are a new entity introduced by 2020 ASCO/CAP update and they have biological features like triple negative tumors. This mono-institutional study describes clinicopathological characteristics, treatments, and outcomes of low ER positive BC and compares them with triple negative cases.

In previous large series, ER-low positive breast cancer is rare with a reported incidence of 2-5% of all breast cancer [13]. Although some smaller cohorts, including our one report a higher incidence rate (23% &28% and 24% respectively) [14&15]. On the other hand, we found that the

proportion of triple negative breast cancer cases was three times more than ER-low positive cases which was consistent with the results from prior studies [5&9]. In this cohort study, ER-low positive and triple negative breast cancer demonstrated similar aggressive clinicopathologic characteristics and median age at diagnosis. Both show the same results as regards tumor size, tumor site and histological type with no significant difference between subgroups. In our series, we observed that triple negative tumors were associated with higher histologic grade than ER-low positive tumors, in accordance with the previous results reported by [3&12]. Our study and another study done by **(Dieci et al., 2021)** conclude that ER-low positive BCs did not show a more favorable stage at diagnosis when compared with ER-negative BCs. On the contrary, both subgroups presented with locally advanced stage at diagnosis. Even ER-low positive BCs presented by a higher frequency of advanced stage. This might be due to the small size of the ER-low positive subgroup.

About 79 (76.7%) of our cases received either neoadjuvant, adjuvant or combined chemotherapy. The type of chemotherapy applied for both groups was the same. About half of ER- low positive group received neoadjuvant chemotherapy (13 cases) This confirms the fact that both ER-low positive and triple negative tumors were recommended for chemotherapy intake rather than ER-positive cases. It is well known that complete pathologic responses are less frequent among ER positive tumors compared to triple negative ones. Our study confirms this issue as complete pathologic response was slightly higher among triple negative cases than ER-low positive cases (12.7% versus 4.2%), despite this, no significant difference was observed. Our findings are in line with previous studies done by **Park et al., 2021 & Dieci et al., 2021 & Yoder et al., 2022 & Peng et al, 2024** all these studies showed that ER-low positive and triple negative breast cancer had a comparable pCR (pathological complete response) [9&16&17&18]. Our results demonstrate that both the ER-low positive and triple negative breast cancer show the same long-term outcome in the form of overall and disease-free survival. Various published studies compare the outcome of both ER-low positive and triple negative breast cancer reported similar results [10&11&18]. Consistent with previous study done by **Yoder et al., 2022** only nodal status and higher tumor stage are significantly associated with overall and disease-free survival [16].

In summary ER-low positive breast cancer is a small but important subset that resembles triple negative cases in the term of clinical behaviour, chemosensitivity and survival outcome.

Conclusion

ER-low positive group has the same clinical behavior as triple negative breast cancer.

Declaration

Ethical Consideration:

The study protocol was approved by the Institutional Review Board of the National Cancer Institute, Cairo University (Approval No. PA2412-506-075-194, IRB0004025).

Consent to participate:

Informed consent was waived due to the retrospective nature of the study, and all data were anonymized to ensure patient confidentiality.

Funding:

This study was conducted without any external funding or financial support.

Conflict of Interest:

The authors declare no conflicts of interest or financial relationships that could have influenced the study's findings or interpretations.

Availability of Data and Materials:

Data and materials can be accessed upon reasonable request.

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