Zagazig University Medical Journal
www.zumj.journals.ekb.eg

Volume 28, Issue 6, November 2022(303-310) Supplement Issue

Manuscript ID ZUMJ-2006-1873 (R2)
DOI **10.21608/zumj.2020.31917.1873**

ORIGINAL ARTICLE

Correlation between Strength of Estrogen Receptor Positivity and Outcome of Adjuvant Tamoxifen Therapy in Breast Cancer Patients

Mohamed Ragab [1*], ***Nasr Mohamed Ali Allahloubi*** [2], ***Salem Eid Salem*** [2], ***Mohamed Ghareeb*** [2], ***Abdelrahman Nabawy Zekri*** [3]

[1] *Department of Medical Oncology, Faculty of Medicine, Zagazig University, Egypt*
[2] *Department of Medical Oncology, National Cancer Institute, Cairo University, Egypt*
[3] *Department of cancer biology, National Cancer Institute, Cairo University, Egypt*

***Corresponding author:**
Mohamed Ragab
Department of Medical Oncology, Faculty of Medicine, Zagazig University, Egypt

Email: dr.ragab22@yahoo.com

Submit Date 2020-06-06
Revise Date 2020-06-13
Accept Date 2020-06-23

ABSTRACT

Background: Estrogen receptor (ER) positive breast cancer patients showed benefit from endocrine therapy and had better survival compared to women with ER-negative tumors. Despite this benefit, up to 30 % of patients subsequently develop a recurrence or distant metastases may be due to heterogeneity in tumor biology among the ER-positive tumor. Therefore, it is clinically important to identify predictive and prognostic factors associated with variable outcomes in tamoxifen treated patients. The aim of this work was to assess the impact of the percentage of ER staining on the outcome of breast cancer cases that received adjuvant tamoxifen.

Method: This retrospective study included 100 ER-positive breast cancer patients who received adjuvant tamoxifen and were followed up in the period from June 2009 until December 2018. Levels of ER staining intensity were measured as the percentage of cells staining positive for ER by immunohistochemistry and graded as mild (1-10%), moderate (11-50%) and high (> 50%). The degree of intensity was correlated with disease free survival (DFS) and overall survival (OS).

Results: The mean age was 49.4 years and stage II and III represented 33% and 62% of cases, respectively. Progesterone receptors were positive in 96% of cases. Only one patient had weak ER positivity, 49% was moderate; and 50% of cases had strong positivity. Patients with strong ER positive disease had significantly prolonged OS (p=0.018) and superior DFS but of borderline significance (p=0.064) when compared with moderate or weak positivity.

Conclusions: The degree of estrogen receptor positivity is associated with the outcome of adjuvant hormonal treatment and breast cancer survival. These findings should be taken into consideration when deciding on adjuvant hormonal treatment.

Keywords: Estrogen Receptor; Breast Cancer; Retrospective study; Tamoxifen; Hormonal Treatment

INTRODUCTION

Breast cancer (BC) is the second most frequent cancer in the world and, the most common cancer among women [1]. Worldwide, Breast cancer comprises 22.9% of invasive cancers in women and 16% of all female cancers [2]. In Egypt; breast cancer is the most common malignancy in females. It accounts for 32 % of cancer in women [3].Several prognostic factors (stage, axillary nodal status, grade, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) status had been identified in breast cancer patients. They correlated with disease free and or overall survival in the absence of adjuvant therapy [4].Estrogens are essential regulators of growth, development and progression of breast carcinoma. Estrogens regulate gene expression through estrogen receptors (ER) [5]. Based on the ER status, breast tumors can be classified as ER-positive and ER-negative. About 75% of breast cancer cases are estrogen receptor positive at diagnosis [6].While ER-positive cases benefit from endocrine therapy and have better survival compared to women with ER-negative tumors, there is evidence for heterogeneity in tumor biology among the ER-positive cases [7]. Weak ER-positive tumors have lower overall survival rates compared to strongly ER-positive tumors [8].Tamoxifen is an anti estrogenic drug, used for the treatment of ER-positive breast cancer patients. Adjuvant tamoxifen treatment significantly

reduces breast cancer relapse and mortality rates [9].The aim of the current study was to determine the impact of estrogen receptor grade of positivity on the prognostic outcome of ER-positive breast cancer patients receiving adjuvant tamoxifen, as regards DFS and OS.

METHODS

This is a retrospective study that was conducted at the National Cancer Institute, Cairo University, in the period from June 2009 until December 2018. The study included 100 patients with hormone receptor positive breast cancer who received adjuvant hormonal treatment in the form of tamoxifen. Eligible patients were female ≥18 years with pathologically proved ER- positive breast cancer without evidence of metastatic disease who received tamoxifen in the adjuvant setting. Patient excluded from the study were those with the following characteristics: age above 80 years old, history of GIT disorders that might affect tamoxifen absorption and patients with a history of thromboembolism or suffering from any other malignancies. The research protocol was approved by the Institutional Review Board (IRB) of the National Cancer Institute, Cairo University. The work was carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Data of eligible patients was anonymously extracted from patients' medical files from department of Biostatistics and Epidemiology. Data retrieved include age, BMI, menopausal status, stage, grade, pathological subtypes, ER, PR, HER2 status, type of surgery, types of adjuvant chemotherapy, radiation, status at last contact, cause of death, and date of last contact. Levels of ER positivity, measured as the percentage of cells staining positive for ER by immunohistochemistry according to the Allred Score for Estrogen and Progesterone Receptor Evaluation [10]. ER staining was graded as weakly ER+ (1–10%), moderately ER+ (11–50%), and strongly ER+ (> 50%).

***Statistical analysis*:**

We analyzed raw data using MedCalc Statistical Software version 20.0 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Continuous variables were checked for normal Gaussian distribution by using Kolmogorov-Smirnov test. Continuous variables were expressed as the mean ± standard deviation (SD), or median and (minimum - maximum) according to the normality of the data. Categorical data was expressed as a number (percentage). For quantitative variables, independent sample *t* test was used for comparison in the case of normally distributed data, while it's non parametric equivalent Mann–Whitney *U* (MW) test was used for non-Gaussian distribution. For comparisons of quantitative variables among the three groups, one-way ANOVA was used if data was parametric, while Kruskal-Wallis (KW) test was used if the data was non-parametric. For categorical variables, they were compared using the Chi-square ($\chi 2$). A p value < 0.05 was considered statistically significant (S).Primary end point: Disease free survival (DFS): the time elapsed between treatment initiation and tumor progression or death from any cause, with censoring of patients who are lost to follow-up [11].Secondary end point: Overall survival (OS): the time from random assignment to the date of death due to any cause, or to the date of censoring at the last time the subject was known to be alive **[12]**.

RESULT

One hundred patients were included in the current study. As shown in Table (1), the mean age was 49.4 years and 59 subjects were premenopausal. Nineteen percent of cases had diabetes mellitus, while 23% of them had hypertension and about one third had a history of oral contraceptive pills intake.Right breast cancer was the predominant side found in 55% of patients. The majority of patients had pathological stage III, followed by stage II, representing 62% and 33% respectively. ER was positive in all patients, PR was positive in 96% of cases and 8% of our study patients had overexpression of HER2-neu by IHC. Regarding the intensity of ER staining, only one patient was weakly positive (score 1), 49% of patients had moderately positive disease (score 2) and half of patients were strongly positive (score 3) as shown in Table (1).Surgery was done for 78% of patients as primary treatment and for 22% of them after they received neoadjuvant chemotherapy. Adjuvant chemotherapy was administered to 93% of patients. Furthermore, all of our study patients who received adjuvant hormonal therapy in the form of tamoxifen, 3% of them developed venous thromboembolism and 1% developed vaginal bleeding as described in (Table 1).

***Survival*:**

The median follow up of our study was 65.5 months (Range 19-114) months). Five-year disease free survival for the whole group was 52.0%. Age, history of hypertension (HTN) or diabetes mellitus, oral contraceptive pills (OCP) intake and menopausal status had no significant impact on DFS as shown in table (2). Tumor laterality, pathological type or grade did not have significant impact on DFS. Patients with early stage disease had significantly prolonged DFS compared to advanced stage as shown in table (3). Patients with strong ER positive disease had superior DFS but of borderline significance (p=0.061) when compared to moderate or weak positivity as described in

Figure (1).Five-years overall survival for all patients was 55.9%. Age, history of hypertension (HTN) or diabetes mellitus, oral contraceptive pills (OCP) intake and menopausal status had no significant impact on OS as illustrated in table (2). Patients with strong ER positive disease had significantly prolonged OS (p=0.018) when compared to moderate or weak positivity as shown in Figure (2). Laterality, type of surgery, pathological subtype and tumor grade did not significantly affect OS while higher tumor stage had significantly poor OS compared to early stage. The data are presented in table (3).

Table (1): Demographic features, Tumor characteristics and Treatment modalities of patients

Characteristics	Number	%	Mean± SD	Range
No of cases	100	100%		
Age (years)			49.4±9.0	28-68
Menopausal state				
Postmenopausal	41	41%		
Premenopausal	59	59%		
DM*				
No	81	81%		
Yes	19	19%		
HTN*				
No	87	87%		
Yes	23	23%		
OCP* **No**	64	64%		
Yes	36	36%		
Side				
RT*	55	55%		
LT*	43	43%		
Bilateral	2	2%		
Pathological Subtype				
IDC*	87	87%		
ILC*	10	10%		
Others	3	3%		
Grade				
II	95	95%		
III	5	5%		
Pathological Tumor Size				
T1	10	10%		
T2	61	61%		
T3	19	19%		
T4	10	10%		
Pathological Lymph node status				
N0	20	20%		
N1	26	26%		
N2	30	30%		
N3	24	24%		
Pathological Stage (AJCC)				
Stage I	5	5%		
Stage II	33	33%		
Stage III	62	62%		
ER status*				
1	1	1%		

Characteristics	Number	%	Mean± SD	Range
2	49	49%		
3	50	50%		
PgR status*				
0	4	4%		
1	23	23%		
2	35	35%		
3	38	38%		
HER2* Score status				
Negative	84	84%		
Equivocal	3	3%		
Positive	8	8%		
Unknown	5	5%		
Surgery (n=100)				
MRM*	86	86%		
BCT*	14	14%		
Type of chemotherapy				
Neoadjuvant chemotherapy (n= 22)	22	22%		
Adjuvant chemotherapy (n= 93)	93	93%		
Adjuvan RT*	83	83%		
No	17	17%		
Yes	83	83%		
Tamoxifen side effects	4	4%		
Thromboembolism	3	3%		
Vaginal Bleeding	1	3%		

DM: diabetes mellitus, **HTN**: hypertension, OCP: oral contraceptive pills, SD**:** standard deviation, RT: right side, LT: left side, IDC: Invasive duct carcinoma, ILC: Invasive lobular carcinoma, ER: Estrogen receptor, PgR: Progesterone receptor, Her2: Human epidermal growth factor receptor 2, 0: negative, 1: weak positive, 2: moderate positive, 3: strong positive, RT: radiotherapy, MRM: Modified Radical Mastectomy, BCS: Breast Conserving surgery

Table (2): Correlations between demographic features with DFS & OS in univariate analysis.

		OS%			DFS%		
Factors	**n**	**3 years**	**5 years**	**p value**	**3 years**	**5 years**	**p value**
All	100	92.0	55.9	NA	58.0	52.0	NA
Age							
≤50	58	91.4	58.6	0.958	60.3	50.0	0.809
>50	42	92.9	59.9		59.6	54.8	
Menopausal Status							
Post menopausal	42	90.5	59.5	0.896	61.9	57.1	0.524
Premenopausal	58	93.1	58.6		55.2	48.3	
DM							
No	81	91.4	58.0	0.968	59.3	51.9	0.968
Yes	19	94.4	63.2		63.2	47.4	
HTN							
No	77	90.9	54.4	0.284	55.8	48.1	0.151
Yes	23	95.7	73.9		73.9	65.2	

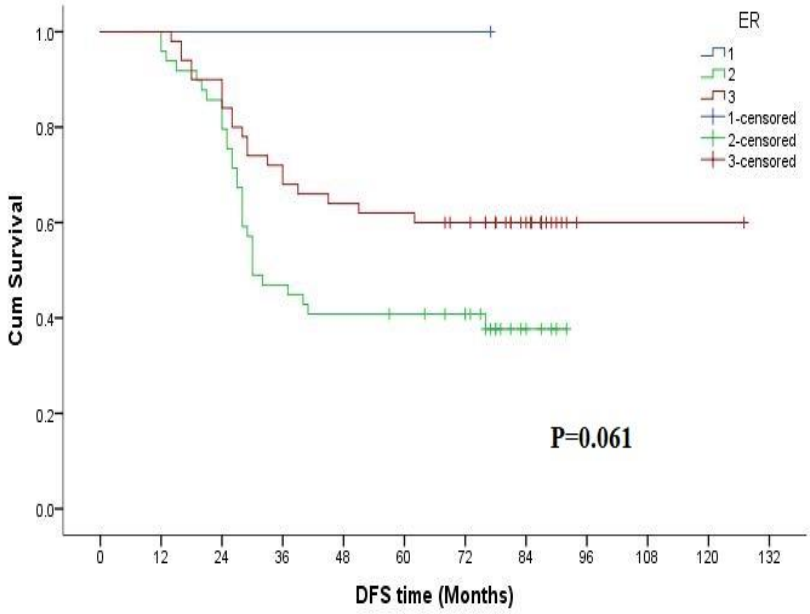
		OS%			DFS%		
OCP							
No	64	93.8	62.5	0.539	57.8	54.7	0.761
Yes	36	94.4	58.3		58.3	47.2	

DFS: disease free survival, OS: overall survival, DM; diabetes mellitus, HTN: hypertension, OCP: oral contraceptive pills, NA=not applicable.

Table (3): Correlations between clinicopathologic factors with DFS & OS in univariate analysis.

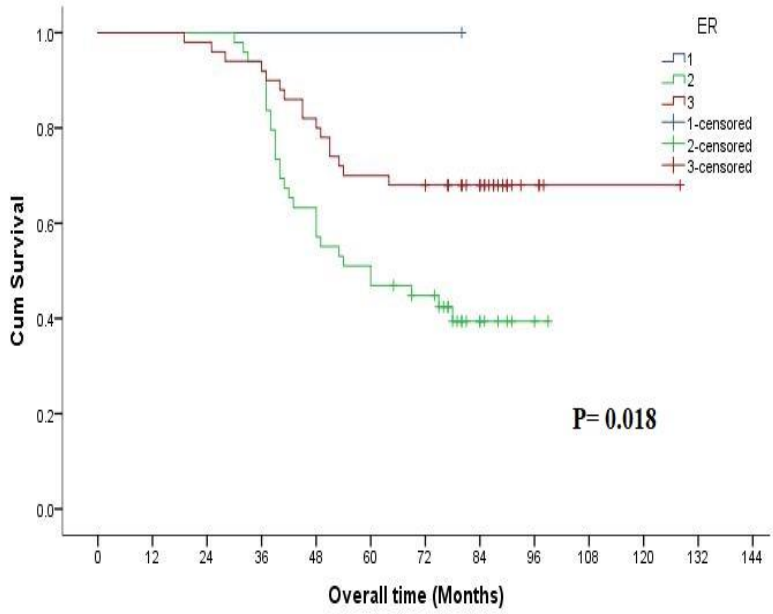
		OS%			DFS%		
Factors	**n**	**3 years**	**5 years**	**p value**	**3 years**	**5 years**	**p value**
All	100	92.0	55.9	NA	58.0	52.0	NA
laterality							
Bilateral	2	100	50.0	0.992	100	50.0	0.719
LT	42	92.9	57.1		61.9	54.8	
RT	56	91.1	58.9		53.6	50.0	
Pathology Type							
IDC	87	93.1	56.3	0.251	54.0	47.1	0.065
ILC	10	80.0	70.0		80.0	70.0	
Others	3	100	100		100	100	
Grade							
II	95	92.6	61.1	0.983	57.9	51.6	0.625
III	5	80.0	60.0		60.0	60.0	
PT							
T1-2	71	93.0	64.8	0.100	66.2	56.3	**0.032**
T3-4	29	96.6	44.8		37.9	37.9	
PN							
N0-1	46	93.5	71.7	**0.004**	71.7	65.2	**0.008**
N2-3	54	90.7	46.3		46.3	40.7	
Stage							
I-II	38	92.1	73.7	**0.010**	76.3	68.4	**0.006**
III	62	91.9	50.0		46.8	41.9	
ER							
1	1	100	100	**0.018**	100	100	0.061
2	49	91.8	51.0		46.9	40.8	
3	50	92.0	70.0		68.0	62.0	
PR							
0	4	75.0	75.0	0.287	50.0	50.0	0.264
1	23	91.3	52.2		60.9	47.8	
2	35	94.3	51.4		48.6	40.0	
3	38	92.1	68.4		65.8	63.2	

RT: right side, **LT**: left side, **IDC:** Invasive duct carcinoma**, ILC:** Invasive lobular carcinoma**, ER:** Estrogen receptor**, PgR:** Progesterone receptor**,** 0: negative, 1: weak positive, 2: moderate positive, 3: strong positive**,** NA=not applicable, **DFS:** Disease free survival, **OS**: Overall survival, **PT**: Pathological tumor size, **PN**: Pathological lymph node



1:weak positive, 2: modearate positive, 3: strong positive

Figure (1): Correlation between degree of ER positivity and DFS



1:weak positive, 2: modearate positive, 3: strong positive

Figure (2): Correlation between degree of ER positivity and OS.

DISCUSSION

Estrogen receptors (ER)-positive breast cancer represents about 70% of breast cancer patients, making hormonal treatment a cornerstone in their management [13]. Tamoxifen is used as an adjuvant endocrine therapy for ER-positive breast cancer patients [14]. Tamoxifen efficiency is mostly affected by the ER status and scoring; therefore, a more comprehensive characterization of the ER scoring is required to predict endocrine outcomes and possible resistance in hormone receptor positive breast cancer patients.Despite the proven benefits associated with adjuvant 5 years of tamoxifen treatment, up to 30 % of patients subsequently develop a recurrent disease or distant metastases [15]. Therefore, it is clinically important to identify predictive and prognostic factors associated with variable outcomes in tamoxifen treated patients [16]. In the current study, we tried to assess one of these factors, which is the degree of ER-positivity, as measured immune-histochemically, in predicting survival in patients with ER-positive breast cancer. Patients with strong ER positivity had significantly superior OS while the DFS was of borderline significance relative to moderate or weak positivity.There are

many scoring systems used to grade ER positivity, such as McCarthy's "H"score and Remmele score [17], but we used the Allred score as it was the only clinically validated scoring system and most widely used hormone receptor scoring [18]. Similar to our work, two other studies used a similar method but with different cutoffs in determining grades of ER positivity and its relation to outcome in patients receiving adjuvant hormonal treatment. Morgan and colleagues [19] in a retrospective study included 563 post-menopausal patients with early breast cancer (stage I and II) receiving adjuvant tamoxifen and no chemotherapy following surgical resection of pathologically proven ER-positive breast cancer assessed the impact of the degree of ER-positivity, as measured immune-histochemically on OS and /or DFS. Using different cutoffs, they classified patients into 3 groups: the first with staining of up to 33% of cells, the second staining between 34% and 67%, and the third group with staining above 67%. Three percent of the patients were in the first group while 7% and 90% of patients were in the second and third group respectively.Despite including patients with different characteristics; all were postmenopausal, had early stage disease and no adjuvant chemotherapy, they reach to a conclusion that degree of ER staining significantly affect DFS but not OS. The significant difference in OS may be diluted or lost due to imbalance between the groups, as most of the patients were found in the third group, another recent study with similar design using the same cutoffs in grading ER positivity had addressed this issue. Purrington and colleagues [20], evaluated the impact of ER staining levels on survival in 1652 patients with ER+/ HER2− breast cancer who were treated with surgery, adjuvant chemotherapy and hormonal treatment from 2010 to 2017 at the Karmanos Cancer Institute (KCI) in Detroit, MI. In this cohort, strongly positive (< 50%) staining level accounted for 94.1% of patients compared to 50% in or study. Having a weakly ER+ tumor, however, was itself significantly associated with breast cancer specific (BCS) mortality and marginally significantly associated with OS (overall HR 1.57, P= 0.083; BCS HR 2.11, P= 0.017) in comparison with patients with strongly positive ER. These results are in the concordance with the findings identified by our study.The results of this study should be interpreted after taking into consideration various limitations, mainly inherent to its retrospective design. We included only the patients with sufficient data in the medical records and available archived tumor paraffin blocks. Another limitation for this study was relatively small sample size. This small sample size did not provide a Cox regression analysis to estimate independent prognostic factors influencing DFS and OS in the patient groups.

To conclude, the present study confirmed that the degree of estrogen receptor intensity is associated with the outcome of adjuvant hormonal treatment and breast cancer survival. These findings may have an impact on decisions about adjuvant systemic therapy.

Conflict of interest: The authors declare no conflict of interest.

Funding sources: The authors have no funding to report.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86.
2. Siegel, R.L., Miller, K.D. and Jemal, A. (2019), Cancer statistics, 2019. CA A Cancer J Clin, 69: 7-34.
3. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in egypt: results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971.
4. Bleicher RJ, Ruth K, Sigurdson ER, Beck JR, Ross E, Wong Y-N, et al. Time to surgery and breast cancer survival in the United States. JAMA oncology 2016, 2(3), 330-339.
5. Wolmark N, Mamounas EP, Baehner FL, Butler SM, Tang G, Jamshidian F, Sing AP, Shak S, Paik S. Prognostic impact of the combination of recurrence score and quantitative estrogen receptor expression (ESR1) on predicting late distant recurrence risk in estrogen receptor-positive breast cancer after 5 years of tamoxifen: results from NRG Oncology/National Surgical Adjuvant Breast and Bowel Project B-28 and B-14. J Clin Oncol. 2016 Jul 10;34(20):2350-8.
6. Allred DC, Brown P, Medina D. The origins of estrogen receptor alpha-positive and estrogen receptor alpha-negative human breast cancer. Breast Cancer Res. 2004;6(6):240-5.
7. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ; Panel members. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol. 2009 Aug;20(8):1319-29.
8. Iwamoto T, Booser D, Valero V, Murray JL, Koenig K, Esteva FJ, et al. Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. J Clin Oncol 30(7) 2012:729–734. https ://doi.org/10.1200/JCO.2011.36.2574.
9. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 May 14-20;365(9472):1687-717.

10. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010, 28(16):2784–95.

11. Soria JC, Massard C, Le Chevalier T. Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy? Ann Oncol. 2010 Dec;21(12):2324-32.

12. Cheema PK, Burkes RL. Overall survival should be the primary endpoint in clinical trials for advanced non-small-cell lung cancer. Curr Oncol. 2013;20(2):e150-60.

13. American Cancer Society. Breast Cancer Facts & Figures 2017-2018. Atlanta, GA: American Cancer Society; 2017.

14. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer. Ann Oncol. 2013;24(9):2206–23.

15. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med. 2011;62:233–47.

16. Chang J, Fan W. Endocrine therapy resistance: current status, possible mechanisms and overcoming strategies. Anticancer Agents Med. Chem. 2013;13(3):464–75.

17. Allred DC. Issues and updates: evaluating estrogen receptor-alpha, progesterone receptor, and HER2 in breast cancer. Mod Pathol. 2010;23(Suppl 2):S52–9.

18. Cheang MC, Treaba DO, Speers CH, Olivotto IA, Bajdik CD, Chia SK, et al. Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival. J Clin Oncol. 2006;24(36):5637–4.

19. Morgan DA, Refalo NA, Cheung KL. Strength of ER positivity in relation to survival in ER-positive breast cancer treated by adjuvant tamoxifen as sole systemic therapy. Breast 20(3) 2011:215–9.

20. Purrintgon KS, Gorski D, Simon MS, Hastert TA, Kim S, Rosati R, et al. Racial differences in estrogen receptor staining levels and implications for treatment and survival among estrogen receptor positive, HER2-negative invasive breast cancers. Breast Cancers Res. Treat.2020, 181, 145-54.

To Cite:

Ragab, M., Allahloubi, N., Salem, S., Ghareeb, M., Zekri, A. Correlation between Strength of Estrogen Receptor Positivity and Outcome of Adjuvant Tamoxifen Therapy in Breast Cancer Patients. *Zagazig University Medical Journal*, 2022; (303-310): -. 10.21608/zumj.2020.31917.1873.