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Breast cancer prognosis with relation to the human epidermal growth factor receptor-2 & hormonal status among women Mosul city – 2018

ABSTRACT

Background: Breast cancer is the leading cause of death of women around the world. Rates differ by around fivefold across the globe, but they are rising in areas where the disease was previously uncommon.

Aim of the study: the aim was to discover whether the molecular classification of breast cancer offers more knowledge about survival relative to traditional histopathological prognostic factors.

Methodology:

In this study, the prognostic influence of ER, PR, and HER2 expression was analyzed independently in breast cancer patients using an immunohistochemical study (n = 297) at Mosul Oncology Hospital in 2018 on women diagnosed with primary breast cancer, and, in combination, survival analysis was performed using age-adjusted Kaplan-Meier and Cox relative risk models. Patient, Breast Cancer Stage.

Result: The results showed that patients (n=297) with different ER, PR, and HER2 expressions had different clinical outcomes with different treatment responses. Breast cancer's molecular classification was based on the pattern of expression of ER, PR, and HER2. The breast cancer subtype ER + / PR + / HER2 + was found in 36.3% of cases, ER + / PR + / HER2- observed in 23.9% of cases, ER - / PR- / HER2 + was observed in 23.5% of cases, and finally, a triple-negative subtype was found in 16.16% of cases.ER+/PR+/HER2- tumor patients have a positive prognosis, while triple-negative adenoma patients have the worst prognosis. We also suggest that this molecular classification be used to select the best treatment form in all breast cancer patients.

***Keywords*:**

Estrogen receptor, human epidermal growth factor receptor-2 , ER, HER2, Breast cancer, Mosul

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Introduction:

In the world, including the Eastern Mediterranean region of EMR, the cancer burden is rising. [1] The most common cancers in the world are breast and lung cancers. [2] There is an annual rise in Eastern Mediterranean region (EMR) cancer from 1 percent to 5 percent, according to the WHO.

[3] The most common cancer in the province of Nineveh, according to the Mosul Cancer Registry, is breast carcinoma. [4]

In predicting the recurrence rate of the disease, the histopathological properties of breast cancer, the patient's personal properties, and the preferences of chemotherapy regimens were previously used. Estrogen receptor (ER) positive breast cancer accounts for 80% of all breast cancer and is a functional predictor of normal breast growth in addition to cancer progression. In addition, ER positivity can predict response to endocrine therapy, whereas progesterone receptor (PR) has a poor predictive value. [5] Patients with breast cancer with estrogen receptor (ER) tumors-positive and/or progesterone receptor (PR)-positive have lower rates of post diagnostic mortality relative to patients with ER and/or PR- negative diseases. [4] Clinical studies have also shown that treatment with adjuvant hormonal and/or chemotherapy regimens improves the survival benefit of women with hormone receptor-positive tumors. [6]

A gene that may play a role in the development of breast cancer is HER2 (human epidermal growth factor receptor. [2] The HER2 gene (also often referred to as HER2/neu proteins) produces HER2 proteins. The receptors on breast cells are HER2 proteins. HER2 receptors usually help regulate how a healthy breast cell develops, divides, and repairs itself. But the HER2 gene does not function properly and makes too many copies of itself in about 10 to 20 percent of breast cancers (known as HER2 gene amplification). [6] All of these extra HER2 genes tell breast cells to generate too many HER2 receptors (HER2 protein

overexpression). This makes breast cells expand and break in an unchecked manner.(5)

In the pathology study, breast cancers with HER2 gene amplification or HER2 protein overexpression are dubbed HER2-positive. Compared to HER2-negative breast cancers, HER2-positive breast cancers tend to develop quicker and are more likely to spread and come back. But there are drugs specifically for breast cancers that are HER2-positive. In assessing the chemical therapeutic strategy in the treatment of breast cancer patients, immunohistochemically examination of ER, PR, and HER2 markers is frequently used along with histopathological grading and staging. [6, 7] In this research, we identified breast cancers with this receptor and followed their effect on recurrence and survival in the province of Nineveh and its neighboring regions to determine if compared to traditional histopathological prognostic factors, the molecular classification of breast cancer provides more survival details. Aim of our study was to discover whether the molecular classification of breast cancer offers more knowledge about survival relative to traditional histopathological prognostic factors.

Methodology: -

This prospective follow-up research was performed at Mosul Oncology Hospital in 2018 on women diagnosed with primary breast cancer this study was carried out during the period from 1st January 2018 till the 1st of January 2021, according to the Iraq Cancer Registry, 297 new breast cancer cases were diagnosed at Mosul Oncology and nuclear medicine Hospital. [8] Patients with invasive breast cancer. [2] who have undergone breast preservation or mastectomy were the criterion for inclusion in this study. [3] They are not severely comorbid. [4] The full immunochemistry outcome of ER, PR and HER2 was observed and the follow-up duration was 2 years.

The classification of pathological mammary tumors (TNM) by the American Joint Committee on Cancer

(AJCC) was used to identify breast tumors [9] and the patients were treated according to international guidelines [10]. This study was performed in compliance with the Helsinki Declaration and approved by the Mosul Medical College Ethics Committee and the Ministry of Health in Nineveh. Medical and patient characteristics, including age of the patient, disease stage, tumor characteristics (status of the lymph node and tissues), method of care and proof of hospital record frequency.

The follow-up of patients was performed on an outpatient basis monthly through the period of study. Clinical interrogation and annual mammography were part of the follow-up examination. A further assessment including a serum calcium blood test, alkaline phosphatase, tumor marker like (CA 15-3), chest and abdominal CT scan and bone scan was conducted when some clinical proof of recurrence or metastasis was suggested.

The status of ER, PR and HER2 expression was assessed by immunohistochemistry and performed on the surgical biopsy. ER and PR were scored for nuclear (not cytoplasmic) staining. Nuclear staining of more than or equal to 1% of tumor cells was considered a positive test, and nuclear staining of less than 1% of tumor cells was considered a negative test [8]. HER2 membrane pattern and staining strength were evaluated and the expression was rated as 0, 1+, 2+, or 3+, according to the American Society of Clinical Oncology / College of American Pathologists guideline [8]. A staining score of 3+ was considered a positive test and tumors with a 2+ score (equivocal) were further evaluated in the Nottingham modification of the Bloom - Richardson grading scheme and the WHO classification system by fluorescence in situ hybridization(FISH) test [11,12].

According to the pattern of ER, PR and HER2 expression, cases were divided into 4 group: first group; ER +ve, PR +ve and HER2 –ve, second group; ER +ve, PR +ve and HER2 +ve, third group; ER-ve, PR-ve and HER2+ve

and fourth group; ER-ve, PR- ve and HER2 –ve (triple negative) [13].

Statistical analysis

SPSS was used to perform data management and statistical research (Version 20; SPSS). The $\chi 2$ test was used to examine the substantial discrepancies between patients in various classes. From the date of the first diagnosis of the disease to the date of death or the last follow-up visit, the average survival period was estimated. The Kaplan-Meier test was used to check the discrepancies in survival between the four groups and to determine the prognostic effect of ER, PR, and HER2 in patients with breast cancer using Cox proportional hazard models. In these models, important prognostic variables were included, such as patient age and tumor level.

Result:

The mean age of all breast cancer patients included in this study at the time of diagnosis was 52.7 years (SD= 11.1, range 24-89 years), out of 297 patients, 37 patients (12.4%) were ≤39 years ,171 patients (57.57%) were between 40-59 years and 89 patients (29.9%) were ≥ 60 years old.

The distribution of the histological types was as follows: 222(74.74%) were Invasive ductal carcinoma (IDC), at first appearance 34 patients (11.44%) were Invasive lobular carcinoma (ILC), 9 patients (3.03%) were mixed (IDC , ILC) and 31 patients (10.43%) were other histological types.

Distribution pattern of ER, PR and HER2 expression in breast cancer samples and its relation with clinic pathological features Based on immunohistochemical study, out of 297 cases, 179 (60.2%) were positive for ER expression and 118 (39.7%) were negative. For HER2 receptors, 177 (59.59%) showed HER2 over-expression and 120 (40.4%) cases showed negative expression. In the present analysis, the distribution of the expression pattern of ER, PR and HER2 markers was as follows: first group 71/297 (23.9%) showed (ER+, PR+, and HER2 -), second group 108/297 (36.36%) showed (ER+, PR+, and HER2+),

third group 70/297 (23.5%) showed (ER-, PR- and HER2+) and finally fourth group 48/297 (16.16%) showed (ER-, PR- and HER2-) (table 1).

The mean age of the first group (ER+, PR+ and HER2-) was 54.11 years (SD 13.4), the mean age of the second group (ER+, PR+ and HER2+) was 52.87 (SD

12.4), the mean age of the third group (ER-, PR- and HER2+) was 53.2 years (SD 12.3) and the mean age of the fourth group (ER-, PR- and HER2-) was 49.75 years, respectively (SD 12.3). The correlation between the age of patients and the pattern of expression of ER, PR and HER2 was statistically important. The p-value amounted to 0.000 (Fig 1).

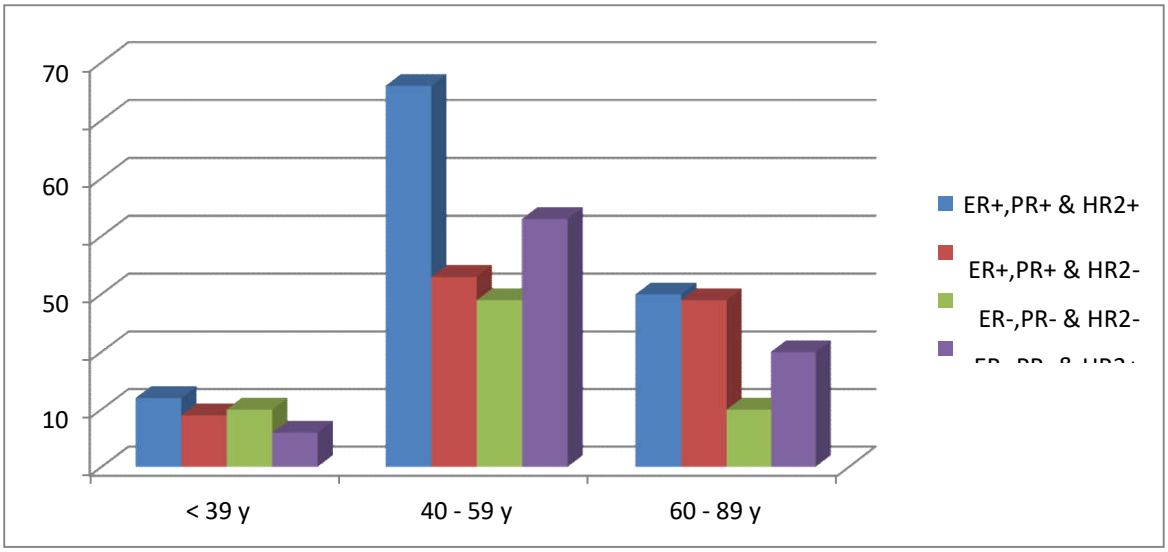

Figure 1: Distribution of age according to the expression sequence of ER, PR & HER2.

Table 1: Correlation of pattern of expression of ER, PR and HER2 with clinic pathologic features of 297 breast cancer cases.

	ER+, PR+ &HR2+	ER+, PR+ &HRE2-	ER-, PR- &HER2-	ER-, PR- &HER2+	total	P value
Number	108	71	48	70	297	
(%)	36.36	23.9	16.16	23.56		

Age						
< 39 y	12	9	10	6	37	0.000
40 - 59 y	66	33	29	43	171	
60 - 89 y	30	29	10	20	89	
Tumor size						
T1	31	15	16	12	74	0.176
T2	60	44	25	36	165	
T3	10	12	8	15	45	
T4	6	3	0	4	13	
Histopathology						
IDC	86	47	36	53	222	0.543
ILC	12	12	4	6	34	
DIC	1	4	3	2	10	
others	9	8	6	8	31	
Lymph node invasion						
N0	13	15	11	22	61	0.005
N1	58	31	23	21	133	
N2	16	13	11	14	54	
N3	17	15	6	7	45	
N4	3	0	0	1	4	
Stage						
I	3	2	1	4	10	0.002
II	40	28	16	24	108	
III	61	38	30	40	169	
IV	4	3	2	1	10	

A significant association was found between the pattern of expression of ER, PR and HER2 with breast cancer lymph node status (P value = 0.005) in which patients in the group (ER+, PR+ and HER2+) and in the group (ER+, PR+ and HER2-) had a higher number of lymph node metastases compared with other patient groups (Table1).

In addition, a significant association was found between the expression pattern of ER, PR and HER2 with breast cancer stage (p value=0.002), the group of patients (ER+, PR+ and HER2+) and the group of patients (ER+, PR+ and HER2-) who had a higher percentage of advanced breast cancer stage than other breast cancer patient groups. No significant association between the ER, PR, and HER2 pattern of expression and the histopathological forms and the size of the tumor (Table 1).

Discussion:

This research analyzes the prognostic effect of ER, PR and HER2 markers in patients with breast cancer separately and combined to accumulate them. Several studies have demonstrated survival benefits of the ER receptor in breast cancer, evidence from the Surveillance Epidemiology End Results Program (SEER) research revealed that in a broad cohort study of women with breast cancer, ER was an independent prognostic factor, and it was also observed that this survival benefits are greatly improved by adjuvant hormone therapy provided to patients with ER positive tumor by minimizing recurrence. [14,15,17,18]

It is well known that overexpression of the HER2 gene is an important indicator of both short total survival and time to relapse in patients with breast cancer. Since 1998, Trastuzumab (Herceptin), which is a humanized monoclonal antibody to the extracellular HER2 domain, has become the standard adjuvant medication in early-stage breast cancer. [19] Trastuzumab has been shown to be an important treatment for increasing survival in patients with early HER2 and metastatic HER2 positive breast cancer. (20.21.22)

The molecular classification of breast cancer, based on immunohistochemical analysis of ER, PR, and HER2, was performed in this study. A subtype of breast cancer was identified in 23.9 %, G1 was detected in 36.36 %, G2 was detected in 23.56 %, and eventually, in 16.16 %, the triple-negative subtype was detected. [23,24] This pattern of expression of these markers is more or less within the rates of expression of other studies in Iraq [1] and other studies abroad. [25, 26] although the pattern of expression of these markers has a high detection rate, this may lead to the variation of genetic predisposition, the variety of risk factors, the technique of immunohistochemistry and the difference in number of markers.

In addition, we find that ER-/PR-/Her2+ breast tumor patients and triple-negative tumor patients have less lymph node metastases and lower final staging, controversial for ER+/PR+/Her2 breast cancer patients and for ER+/PR+/HER+ tumor patients with larger tumor size, higher percentages of lymph node metastases, and higher clinical level. Such findings are consistent with the results of other studies Iraq [1,12,13] but not consistent of studies in London. (27,28)

While some of the patient samples who enrolled in their research did not obtain adjuvant hormone, our result is more identical to the outcome in study at Kirkuk in Iraq [12] and Stockholm in Sweden. [24] Conversely, all ER+ breast cancer patients who were included in our study obtained adjuvant therapy, in addition, some of these studies incorporated CK5, 6 and/or Epidermal growth factor receptor (EGFR) markers in their subtyping. [33, 34] In order to discriminate between highly endocrine sensitive, low proliferation, positive prognosis 'luminal A-like' and less endocrine responsive, the 2015 St Gallen Consensus (International Specialist Consensus on the Primary Therapy of Early Breast Cancer) suggested the evaluation of Ki-67, which is a nuclear marker of cell proliferation that is expressed in all cell cycle phases, barring G0. (27,35)

Conclusion

In all patients with breast cancer, we should use this molecular description in earlier diagnosis for breast cancer, although we need to perform more trials including the evaluation of Ki-67, and include more information for identified subgroups of breast cancer patients.

References:

1- Al Zobair AA, Jasim BI, Al Obeidy BF, Jawher NM. Prognostic impact of hormone and HER2 status on the prognosis of breast cancer in Mosul. Annals of Tropical Medicine & Public Health DOI. 2020.

2- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.

3- Kulhánová I, Bray F, Fadhil I, Al-Zahrani AS, El-Basmy A, Anwar WA, et al. Profile of cancer in the Eastern Mediterranean region: The need for action. Cancer epidemiology. 2017;47:125-32.

4- Taha IA, Younis WH. Clinicopathological analysis of oral squamous cell carcinoma in Iraq During period (2001-2013). Journal of Baghdad College of Dentistry. 2015;27(2):58-65.

5- Bulut N, Altundag K. Does estrogen receptor determination affect prognosis in early stage breast cancers? International journal of clinical and experimental medicine. 2015;8(11):21454.

6- Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast cancer research. 2007;9(1):1-10.

7- Mitri Z, Constantine T, O'Regan R. The HER2 receptor in breast cancer: pathophysiology, clinical use, and new advances in therapy. Chemotherapy research and practice. 2012;2012.

8- Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK. AJCC cancer staging atlas: a companion to the seventh editions of the AJCC cancer staging manual and handbook: Springer Science & Business Media; 2012.

9- Koh W-J, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in

oncology. Journal of the National Comprehensive Cancer Network. 2018;16(2):170-99.

10- Chia S, Burstein H, Vora S. Prognostic and predictive factors in metastatic breast cancer. UpToDate https://www uptodate com/contents/prognostic-and-predictive-factors-in-metastatic-breast-cancer#:~: text= By% 20definition% 2C% 20a% 20prognostic% 20factor, burden. 2020;20.

11- Rakha EA, El-Sayed ME, Lee AH, Elston CW, Grainge MJ, Hodi Z, et al. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. Journal of clinical oncology. 2008;26(19):3153-8.

12- Mahmoud MM. Breast cancer in Kirkuk city, Hormone receptors status (estrogen and progesterone) and Her-2/neu and their correlation with other pathologic prognostic variables. Diyala Journal of Medicine. 2014;6(1):1-14.

13- Al-Hashimi MMY, Wang XJ. Breast cancer in Iraq, incidence trends from 2000-2009. Asian Pacific Journal of cancer prevention. 2014;15(1):281-6.

14- Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T, Eusebi V, et al. Breast cancer prognostic classification in the molecular era: the role of histological grade. Breast Cancer Research. 2010;12(4):1-12.

15- Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. The Lancet. 2013;381(9869):805-16.

16- Liu C, Li H, Zhuo R, Wang L, He L, Ruan Q, et al. Grade-lymph node ratio predicts the survival of breast cancer in different molecular types: A surveillance, epidemiology, and end results population-based analysis. Medicine. 2019;98(28).

17- Bentzon N, Düring M, Rasmussen BB, Mouridsen H, Kroman N. Prognostic effect of estrogen receptor status across age in primary breast cancer. International journal of cancer. 2008;122(5):1089-94.

18- Chatterjee S, Mukherjee MM, Nath NC, Samanta S, Saha AK. An observational study on the incidence of HER-2/neu receptor over-expression and comparison of clinical presentation between HER-2/neu positive and HER-2/neu negative breast cancer. International Surgery Journal. 2017;4(2):506-13.

19- Ulas A, Kos T, Avci N, Cubukcu E, Olmez OF, Bulut N, et al. Patients with

HER2-positive early breast cancer receiving adjuvant trastuzumab: clinicopathological features, efficacy, and factors affecting survival. Asian Pacific Journal of Cancer Prevention. 2015;16(4):1643-9.

20- Scaltriti M, Rojo F, Ocaña A, Anido J, Guzman M, Cortes J, et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. Journal of the National Cancer Institute. 2007;99(8):628-38.

21- Goldvaser H, Korzets Y, Shepshelovich D, Yerushalmi R, Sarfaty M, Ribnikar D, et al. Deescalating adjuvant trastuzumab in HER2-positive early-stage breast cancer: a systemic review and meta-analysis. JNCI cancer spectrum. 2019;3(2):pkz033.

22- Engstrøm MJ, Opdahl S, Hagen AI, Romundstad PR, Akslen LA, Haugen OA, et al. Molecular subtypes, histopathological grade and survival in a historic cohort of breast cancer patients. Breast cancer research and treatment. 2013;140(3):463-73.

23- Haffty BG, Goyal S. Molecular subtyping of early-stage breast cancer: implications for radiation therapy. International Journal of Radiation Oncology• Biology• Physics. 2010;77(5):1293-5.

24- Lindstrom LS, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol. 2012;30(21):2601-8.

25- Tischkowitz M, Brunet J-S, Bégin LR, Huntsman DG, Cheang MC, Akslen LA, et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. BMC cancer. 2007;7(1):1-11.

26- Badowska-Kozakiewicz AM, Sobol M, Patera J, Kozłowski W. Immunohistochemical evaluation of human epidermal growth factor receptor 2 and estrogen and progesterone receptors in invasive breast cancer in women. Archives of medical science: AMS. 2013;9(3):466.

27- Day S, Coombes RC, McGrath-Lone L, Schoenborn C, Ward H. Stratified, precision or personalised medicine? Cancer services in the 'real world'of a London hospital. Sociology of Health & Illness. 2017;39(1):143-58.

28- Garcia-Murillas I, Chopra N, Comino-Méndez I, Beaney M, Tovey H, Cutts RJ, et al. Assessment of molecular relapse detection in early-stage breast cancer.

JAMA oncology. 2019;5(10):1473-8.

29- Goldhirsch A, Winer EP, Coates A, Gelber R, Piccart-Gebhart M, Thürlimann 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 2013. Annals of oncology. 2013;24(9):2206-23.

30- Majid RA, Hassan HA, Muhealdeen DN, Mohammed HA, Hughson MD. Breast cancer in Iraq is associated with a unimodally distributed predominance of luminal type B over luminal type A surrogates from young to old age. BMC women's health. 2017;17(1):1-8.

31- Majid RA, Mohammed HA, Hassan HA, Abdulmahdi WA, Rashid RM, Hughson MD. A population-based study of Kurdish breast cancer in northern Iraq: hormone receptor and HER2 status. A comparison with Arabic women and United States SEER data. BMC women's health. 2012;12(1):1-10.

32- Blows FM, Driver KE, Schmidt MK, Broeks A, Van Leeuwen FE, Wesseling J, et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. PLoS med. 2010;7(5):e1000279.

33- Cubukcu E, Kanat O, Fatih Olmez O, Kabul S, Canhoroz M, Avci N, et al. Prognostic significance of estrogen receptor, progesterone receptor, HER2/neu, Ki-67, and nm23 expression in patients with invasive breast cancer. J BUON. 2013;18(2):359-65.

34- Morigi C. Highlights from the 15th St Gallen International Breast Cancer Conference 15–18 March, 2017, Vienna: tailored treatments for patients with early breast cancer. Ecancermedicalscience. 2017;11.

35- Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Annals of oncology. 2015;26(8):1533-46.