Expression of Estrogen, Progesterone and Human Epidermal Growth Factor Receptors in Breast Cancer in Al-Nassiriya 2014--2015.

Hameed Naeem Musa *
Alaa Jamel Hassan *
Asseel Dhuyool Hasan **
***** Thi-Qar University , Medical college**
****** Thi-Qar Health Directorate / Mensitry of Health.**

Abstract:

Breast cancer is the most common malignancy and is real general well-being issue for ladies all through the world and in Iraq**.** Breast cancer is an extremely heterogeneous disease, There are three predictive markers: estrogen receptors, progesterone receptors and Her2-neu receptors have independent prognostic value in breast cancer. ER expression appears in 80-90 % of patients with breast cancer, while PR expression appear in 70-80 % of cases Her2-neu over expression present in 15-20 % of cases[(1)]. Our study is a cross-sectional study carried out in Thi-qar governorate in Nasiriya city in Al Habbobi hospital –Oncology center**,** 165 cases of patients who were diagnosed during the period of two years (February 2014 - January 2015) with invasive breast cancer were included in this study . The information of each patient were collected and analyzed which include : age of patient, sex, place of residence and tumor related information include grading, staging of tumor, status of receptors(ER, PR, HER2neu receptors). From this study we found The mean age 49±11.1. Most cases were PR+(75.2%) while ER+(72.7%) but most of them were HER2 negative(78.2%). Most patients were in grade II (64.2%) and stage II (50.3%) ,The most common hormonal receptor expression was (ER/PR+ ,HER2-) which accounted for 64.8%.

Regarding to association of hormonal receptor expression with grading and staging of tumor appears that higher grade tumor (II) was observed (76.93%) in type IV (ER/PR-, Her2+) and higher stage (III) was observed (80.95%) in triple negative subtype.

Aim of Study:

It is to evaluate the hormonal receptor status and their association with grading and staging of breast cancer at the time of diagnosis in Al-Nassiriya city.

Introduction:

Breast cancer is the most common malignancy that affects women in developed countries and some developing countries In the US, it is the most common cancer in women; and the second cause of cancer death. In 2007 it accounted for 26% of cancer cases and 15% of cancer death, which translates to 176,296 new cases and 40,515 deaths. [(1)] in 2001, almost 240,000 Women diagnosed with breast cancer , and over

40,000 died from the disease. [2] Breast cancer was the most common tumor seen in Europe in 2006, with 429,900 new cases, representing 13.5% of all new cancers. [3] In Iraq according to the ministry of Health /Iraqi cancer registry 2004, breast cancer occupy the first with 2225 new Cases registered and 15.32% of total cancer cases. [4]

Breast cancer is an extremely heterogeneous disease caused by interactions of both inherited and environmental risk factors which lead to progressive accumulation of genetic and epigenetic changes in breast cancer cells. Although epidemiological evidence support the existence of certain risk factors (e.g., age, obesity, alcohol intake, estrogen exposure, and mammographic density) .The family history of breast cancer remains the strongest risk factor for the disease. Familial forms occupy approximately 20% of all breast cancers and appear to have a distinctive pathogenesis dependent on particular susceptibility gene involved.[4,5]

Although the genes responsible for most familial breast cancers have been identified, approximately half of familial cancers are caused by germline mutation in tumor suppressor genes (TSGs); most of which had functions implicated in preserving genome reliability. These genes include [1] BRCA1 and BRCA2.[6]

Breast cancer is the most widely recognized threatening tumor of ladies woman regularly get from the inward coating of milk conduits (ductal carcinoma) or from the Lobules(lobular carcinoma) that supply the channels with milk.[7]

Estrogen and progesterone receptors expressions are the greatest important and useful predictive factors currently available. Patients with breast cancer whose malignancy totally lacking in ER and PR do not benefit from hormonal treatment [16]. Current assays for ER and PR are performed by using IHC techniques, which have the advantages of not being confounded by endogenous estrogen, can be linked with histological findings to eliminate the likelihood that the assessment was done on noncancerous slide and do not have tumor size as a limiting factor. it is still controversial whether laboratories can correctly report the percentage of positive ER and PR staining.[16] ER/PR status also has some prognostic value; Patients with ER/PR positive tumors also have improved disease-free survival in relation to patients with ER/PR negative tumors with similar stage at 5 years, but this difference is less apparent at 10 years.[17]

HER-2 status is the major predictive factor that determine the benefit from trastuzumab (Herceptin). There is some evidence suggests that HER-2 status is predictive for benefit from anthracycline-based chemotherapy, although this relationship is not certain, particularly with the availability of trastuzumab.[18] Measurement of HER-2 can be performed by either IHC or fluorescent in situ hybridization.

Expression of hormonal receptors

Estrogen and progesterone are two hormones that are required for normal breast function and development, but their unregulated stimulation by extrinsic estrogen such as xenoestrogens can de-regulate the cell cycle and result in breast cell Proliferation, inducing carcinogenicity.[8-10] Estrogen receptors (ERs) are activated by ligands (e.g.,

estrogen, xenoestrogens), and with the help of many cofactors and growth factors can regulate estrogen responsive genes.[19] Also, required for normal breast growth is human epidermal growth factor receptor 2 (Her2), a proto-oncogene, which can mutate into its oncogenic state causing breast carcinogenesis.[20]

The Her2 proto-oncogene which is present in two copies in the normal breast tissue, but in its mutated form there is an increase in the gene copy numbers, also known as Her2 gene amplification or over activation. In its mutated (amplified/overactive) form, it becomes an oncogene (i.e., cancer-causing gene) inducing carcinogenicity of the breast tissue. These tumors present an aggressive phenotype encompassing high tumor proliferation rates, metastasis, and mortality.[21,22]

Importantly, the estrogen receptor (ER) cross communicates with the Her2 receptors at the cellular surface for normal function of the cell, these signaling processes further activate Her2 gene within the nucleus of the cell (Her2 gene expression) and the phosphorylation of the nuclear ER.[23-24]

Furthermore, breast cancer cells have been present to be phenotypically different (e.g., ER+, ER-, Her2+, and Her2-) making breast cancer a heterogeneous disease. It has also observed that for ER positive breast cancers, specifically those with increased Her2 gene copies, the ERs activate Her2 signaling and vice-versa [30]. In Her2 and ER-positive (i.e., Her2+/ER+) breast cancer cells; either Her2 or ER can function as the promoter of cellular proliferation and survival.[28]

In fact, women with an ER-negative status had worse survival outcomes, and were resistant to therapy.[31] Importantly, assessed the Her2 status in women that were using over-the-counter contraceptive pills and the researchers establish that breast cancer aggressiveness and prognosis in these women were positively associated with the overexpression of Her2 oncogene.

HER2, an epidermal growth factor receptor, that locates at chromosome 17q11.2-12, encoding a tyrosine kinase that is composed of three separate regions: an extracellular region (a ligand-binding domain), a transmembrane domain and an intracellular region (a tyrosine kinase domain). Ligand binding leads to receptor dimerization and activation of intrinsic tyrosine kinase activity .Activation of its receptors start downstream signaling pathways which regulate various cellular functions; including cell expansion, apoptosis, angiogenesis and motility.[31]

In spite of the fact that it is not communicated on the cell surface of numerous normal tissues [32] HER2 receptor has turned into vital role for cancer therapy with trastuzumab (Herceptin®). Trastuzumab, a refined monoclonal antibody has active therapy of patients with metastatic breast Malignancy. Studies have found that trastuzumab is especially successive in the treatment of HER2-positive metastatic breast tumor [33]

Table 2.1..ER/PR and HER2 Scoring System and Criteria

The ER/PR Scoring system and Criteria

Scoring system	
0	Negative for receptor
1+	Borderline
2+ to3+	positive for receptor
Criteria	
0	0% nuclear staining
1+	<10% nuclear staining
2+	10%-75% nuclear staining
3+	>75% nuclear staining

HER2 NEU Scoring System and Criteria

Scoring system	
0	Negative
1+	Negative
2+	Weak positive
3+	Positive
Criteria	

O	Negative, no staining is observed or membrane staining is<10% of the tumor cells.
1+	Negative, a faint perceptible membrane staining is detected in >10% of the tumor cells
2+	Weak positive. A weak to moderate complete membrane staining is observed in >10% of the tumor cells
3+	Positive. A strong complete membrane staining is observed in >10% of the tumor cells.

ER-estrogen receptor, PR-progesterone receptor, HER2-human epidermal growth factor receptor

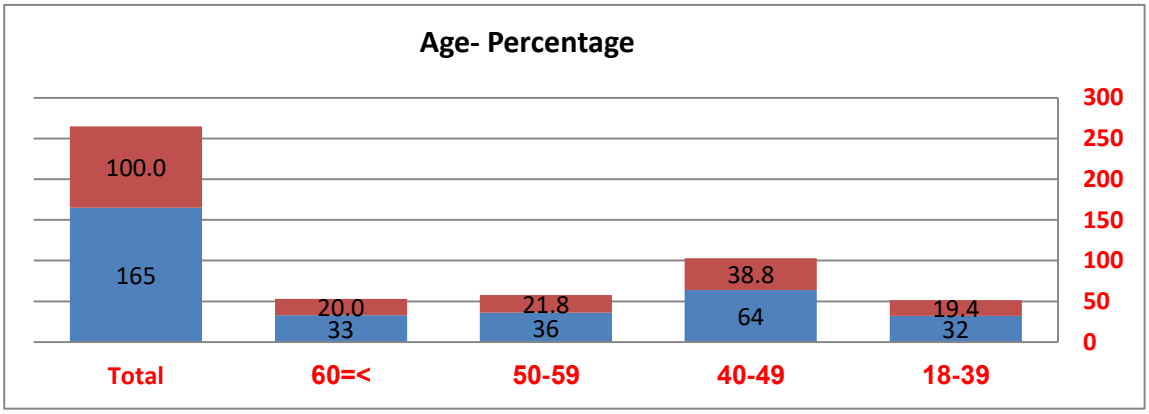
Statistical analysis:

The differences in subjects and characteristics of tumor in this study were analyzed by using SPSS (Statistical Package for Social Sciences) version 22. In all statistical analyses, a P value < 0.05 was considered to be significant.

Results:

Age distribution:

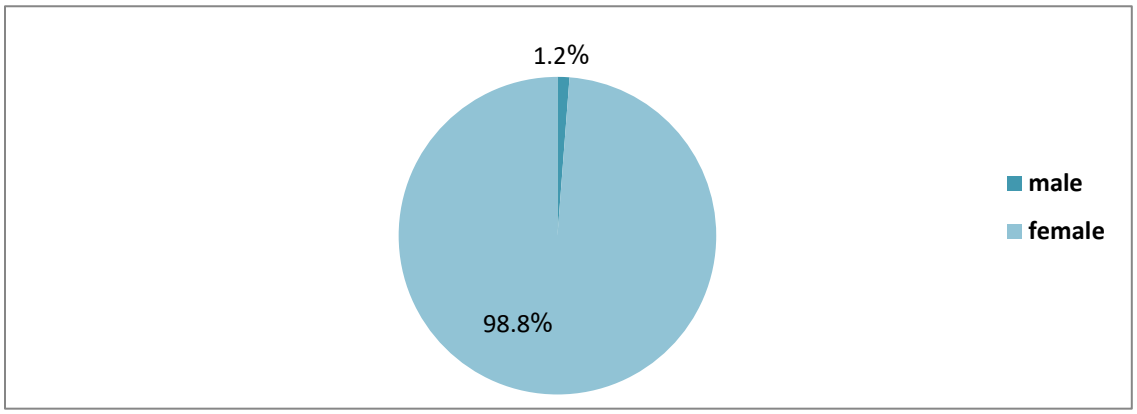
The mean age=49± 11.1, showed that 19.4% of cases were less than or equal to 39 year, 38.8% were (40-49) year, 21.8% were (50-59) year and20% were60 year and more.



A bar chart showing the distribution of cases according to age.

Sex Distribution:

The sex showed that 1.2% males and 98.8% females. So it's the commonest in females but it may occur in males.



Sex Distribution

Residence:

It is shown that 43.6% were living in rural area while 56.4 % in urban area in our city the incidence of disease more common in urban area.

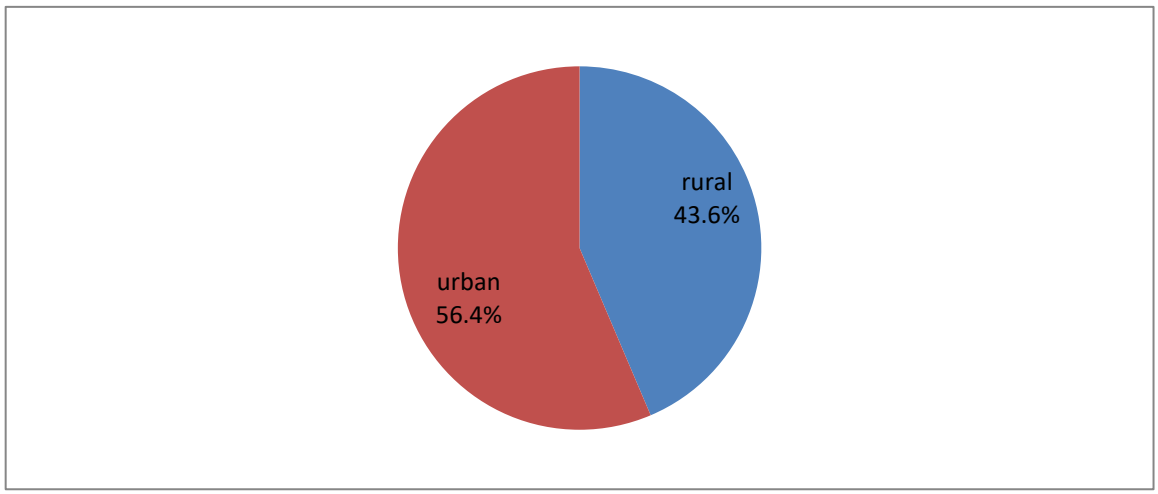


Figure. Residence

Histological grade:

Grading of tumor showed that 10.3% grade I, 64.2% grade II and 25.5% grade III.

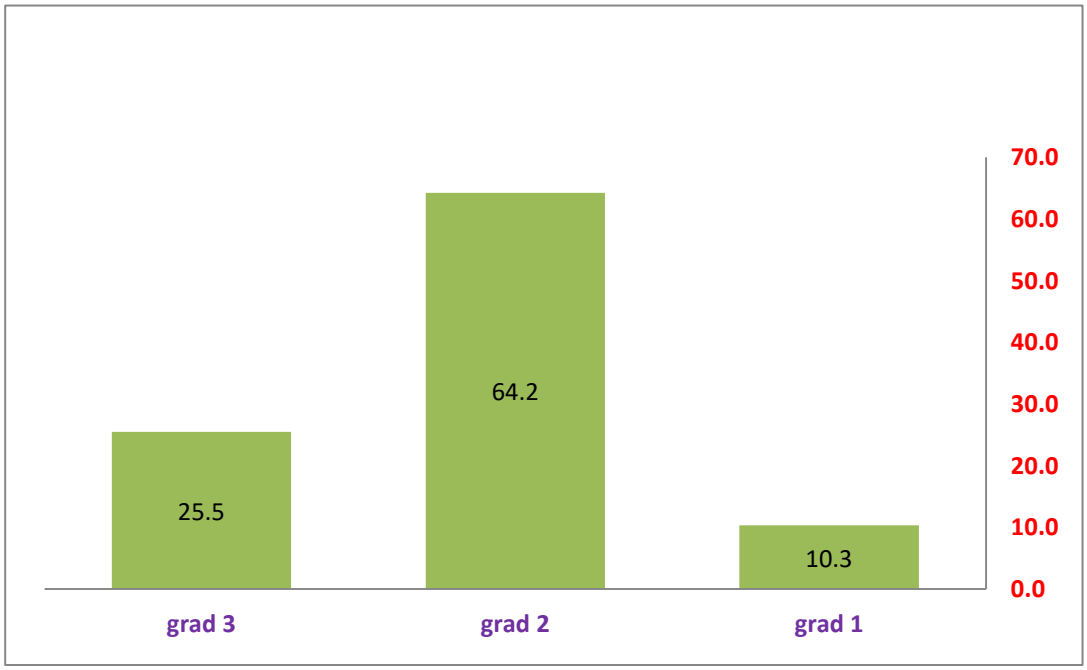


Figure. A Bar chart showing the distribution of cases according to histological grade

Staging of tumour:

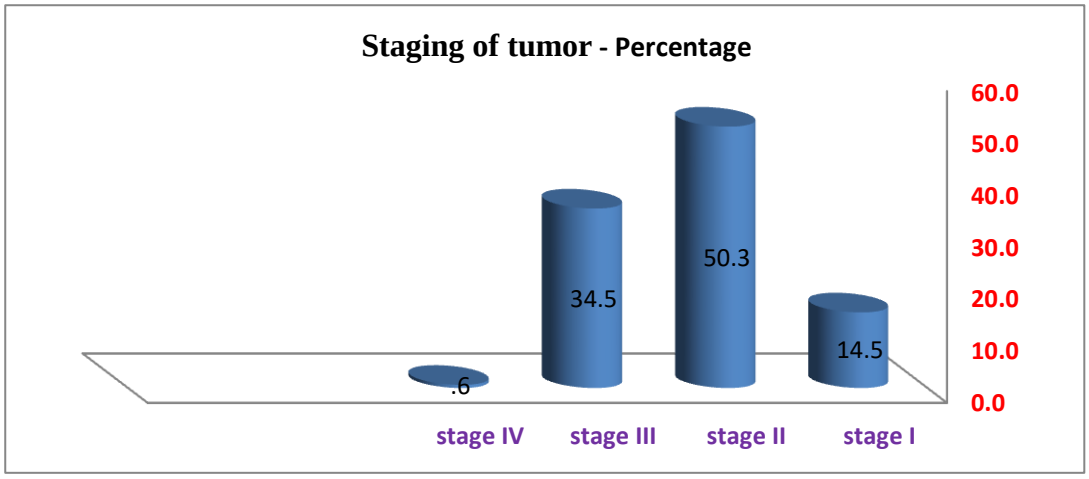


Figure. Staging of Tumour:

Hormonal Receptor Status:

ER status showed that 72.7% positive and 27.3% were

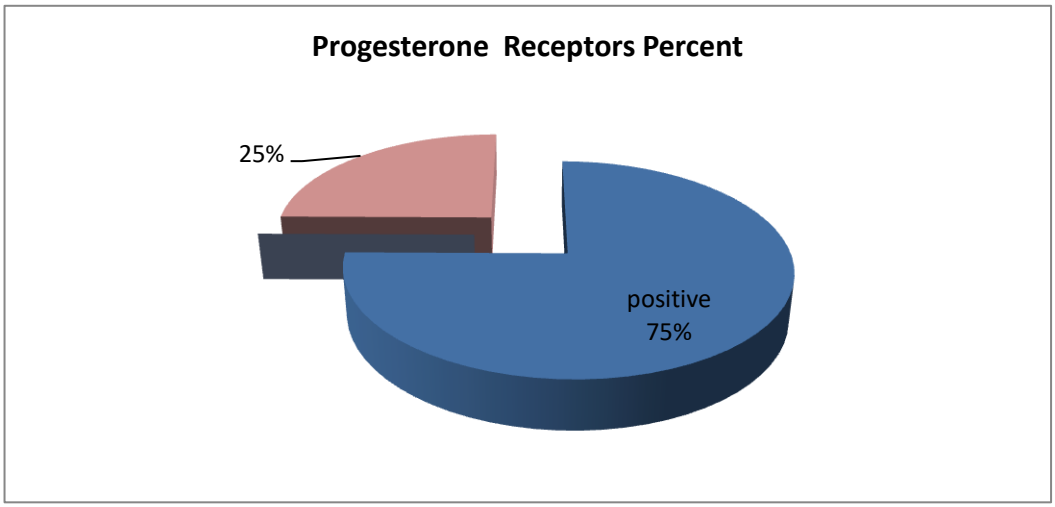
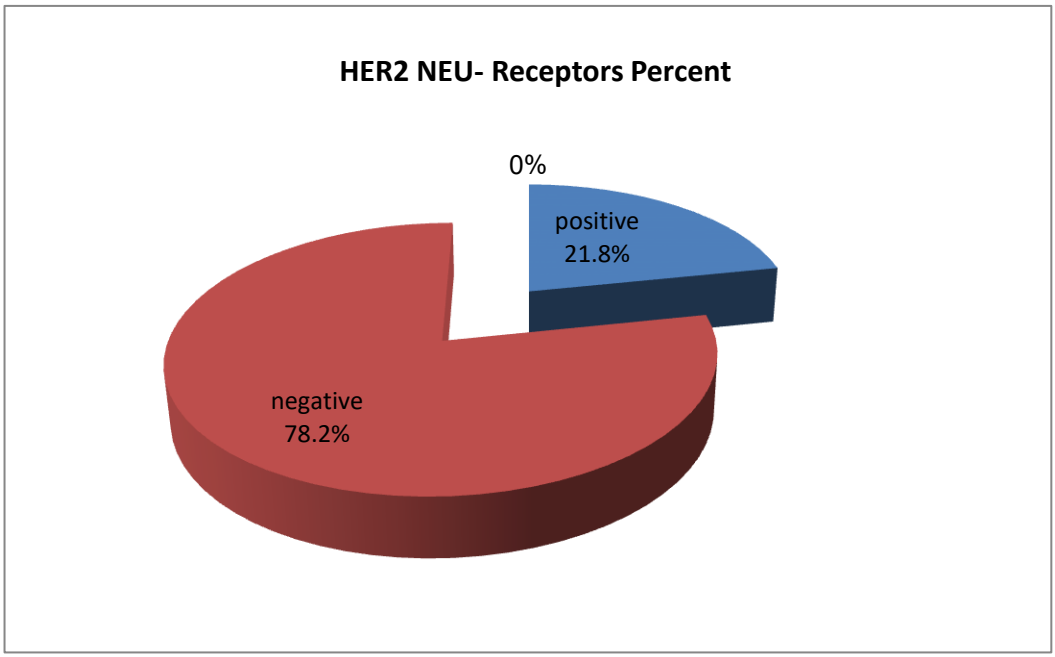


Figure 3.7.A pie chart showing the distribution of cases according to PR status



Pie chart showing distribution of cases according to HER2-NEU

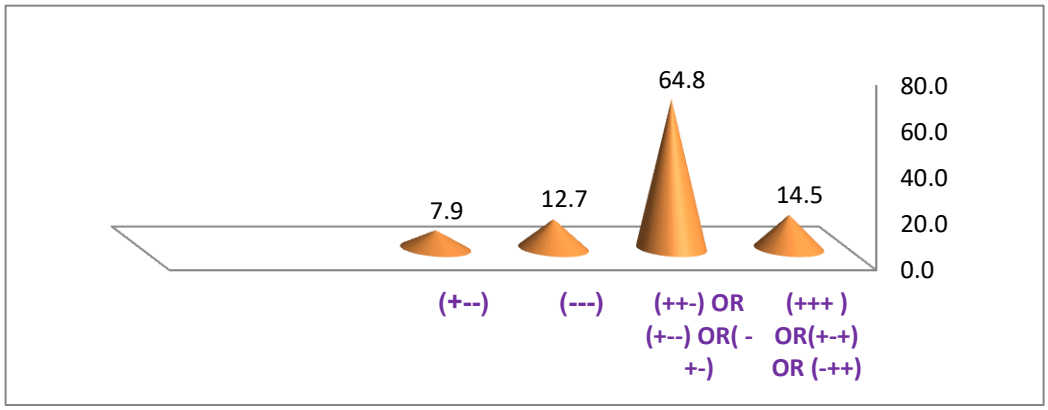


Figure3.9. A bar chart showing the distribution of cases according to hormonal expression

Association grading of tumor with hormonal receptor expression

Histological grade	Hormonal receptor expression				
	ER/PR+,HER2+	ER/PR+,HER2-	ER/PR-,HER2-	ER/PR-,HER2+	p-value
I	0(0%)	13(12.14%)	2(9.52%)	2(15.38%)	0.1855
II	14(58.4%)	70(65.42%)	12(57.14%)	10(76.93%)	0.1855
III	10(41.6%)	24(22.44%)	7(33.34%)	1(7.69%)	0.1855
Total	24(100%)	107(100%)	21(100%)	13(100%)	0.1855

Table3.2: Association staging of tumor with hormonal receptor expression

Staging of tumor	Hormonal receptor expression				
	ER/PR+, HER2+	ER/PR+, HER2-	ER/PR- ,HER2-	ER/PR- ,HER2+	p-value
I	7(29.16%)	16(14.95%)	0(0%)	1(7.69%)	0.0001
II	9(37.5%)	66(61.68%)	4(19.05%)	4(30.78%)	0.0001
III	8(33.34%)	24(22.44%)	17(80.95%)	8(61.53%)	0.0001
IV	0(0%)	1(0.93%)	0(0%)	0(0%)	0.0001
Total	**24(100%)**	**107(100%)**	**21(100%)**	**13(100%)**	

Discussion

The important finding in this study is that nearly any age group may be affected by breast cancer with relatively higher proportion 38.8% of cases was (40-49) years, but it was the least 19.4% below the age of 39 years that means this type of tumor is mostly related to prolong period of breast tissue exposure to the progesterone and/ or estrogen hormones .These results are similar to other study performed in Baghdad which showed that a model age group of (40-49) years with higher percentage 32.55% followed by (50-59) and (30-39) years with the same percentage of (23.25%).[34] The females are mostly affected while male may be affect but usually with early involvement of skin due to little amount of breast tissue found, Male breast cancer account for less than 2% of all cases of breast cancer . Most of patients with breast malignancy were living in urban area (56.4%) ,these results are similar to another study in Iran which found 69.4% of cases living in urban area while 30.6% of them living in rural area.[35] The most possible explanation for this difference is the life style changes occur in urban area Grading of tumor is still one of the important parameter regarding prognosis evaluation.[36]Most of cases are in grade II(64.2%) while low percentage(25.5%) in grade III and the least in grade I(10.3%) ,therefore it is necessary that woman should be educated about breast cancer ,the importance of regular breast self-examination and urgent consultation of physician in case of development of any breast symptom. This will help in early detection of the

disease. These Results were also different from another study in Baghdad which found 38.3% in grade II, 35.8% in grade III and 25.9% in grade I carcinomas.[37]These differences could be the result of inter observer differences. Most of patients are in stage II(50.3%) because of delay in diagnosis and discovery of disease, that means the breast cancer is growing tumor ,but it still in the breast or the growth has only extended to the nearly lymph node , then stage III(34.5%) .But some of them in stage I (14.5%) and very rare in stage IV(0.6%) means that in very rare cases, woman are not diagnosed until reach to stage 1V.These results are different from another study which found that most cases were in stage I(56.4%),while 36.0% were in stage II and 7.7% in stage III.[38]. Most of breast cancer are hormonal receptor dependent estrogen and/or progesterone, we found the tumor was relatively progesterone positive were higher than estrogen receptors which is different from most of researchers who reported that most of breast cancer were estrogen receptors positive . In our results the PR + are 75, 2 % and ER positive are (72, 7 %), so the tumor are more dependent on progesterone rather than estrogen. Different results were seen by study in Baghdad which had shown that (61.9% and 52% positive for ER and PR respectively) [39] Also most of the patients(78.2%) are Her2 –ve, but < 30% are Her2 +ve that differ from other study showed 77.9% ER status positive, 59.1% PR status positive, 17.7% Her2 status positive while 82.3% Her2 status negative.[38] ER and PR status were criteria for sample collection in the present study. Any case without IHC test was excluded from the starting of the study, This is the reason for such difference. In the current study ,Most of the cases were 64.8% ER/PR+ ,Her2- ,This also the same analysis to the previous study[38] that showed 68.9% ER/PR +,Her2- ,7.5% ER/PR- ,Her2 + ,10.2% triple positive,13.4% triple negative. Statistical analysis was done with the Chi-square test (table 1) regarding to association of hormonal receptor expression with grading and staging of tumor, A statistically no significant association could be established between grading of tumor and hormonal receptor expression with P-value (0.185), these results were different from other study was done in India which showed that there is significant association between tumor grade and hormonal receptor expression.[40] A higher percentage of triple negative hormonal receptor expression (ER/PR-,HER2-) was observed in stage III at presentation(80.95%) with p- value 0.001 ,that mean there is positive association between tumor stage and negative hormonal receptor expression .These results are similar to other study which showed that there is significant association between hormonal receptor expression and tumor stage.[38] Finally, one should be aware of the main limitation of the retrospective nature of the current study and the small sample size uses in the study due to incomplete of the data in the case sheets .

Conclusion

1- Breast cancer has hormonal receptor character ER, PR, HER2 receptors.
2- Most cases of breast cancer were living in urban area.
3- Majority of cases presented with grade II and III at the time of diagnosis.

4-Stage II and III were the more frequent among breast cancer cases.

5- Most of hormonal receptor expression in breast cancer are ER/PR+,Her2-

6-Triple negative hormonal receptor status was positively associated with advanced stage.

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الاستدلال عن مستقبلات الاستروجين ، البروجستيرون وعامل النمو البشري لدى مرضى سرطان الثدي في الناصرية 2014- 2015

علاء جميل حسن حميد نعيم موسى اصيل ضيول حسن

الخلاصة

الخلفية : سرطان الثدي هو الورم الخبيث الأكثر شيوعا و مشكلة الصحة العامة للسيدات في جميع انحاء العالم وفي العراق. سرطان الثدي هو مرض متغير الخواص للغاية، هناك ثلاث علامات تنبؤيه: مستقبلات الاستروجين، مستقبلات بروجسترون ومستقبلات عامل النمو عندها قيمة تنبؤيه مستقلة. في 70-80 % من PRفي 80-90% من المرضى بسرطان الثدي، بينما يظهر تعبيرERيظهر تعبير الحالات. مستقبلات عامل النمو موجود في 15-20% من الحالات. لهذاسرطان الثدي يمثّل بشكل افضل بتعبير المستقبل المشترك من التمثيل بمستقبل واحد .علامات الواسم المناعي-الكيميائي النسيجي)،مستقبلات هرمون البروجسترون (العلاقات العامة) ER) من مستقبلات هرمون الاستروجين (IHC( ) يمكن تصنيف التعبير الهرموني لسرطان الثدي الى 4 أنواع فرعية: HER2 ومستقبلات عامل النمو (النوع الاول ثلاثي موجب مستقبلات الهرمونات(هرمون الاستروجين موجب والعلاقات العامة موجب ومستقبلات عامل النمو موجب)؛النوع الثاني (هرمون الاستروجين موجب والعلاقات العامة موجب ومستقبلات عامل النمو سالب)؛ النوع الثالث ثلاثي سالب مستقبلات الهرمونات (هرمون الاستروجين سالب والعلاقات العامة سالب ومستقبلات عامل النمو سالب)والنوع الرابع (هرمون الاستروجين سالب والعلاقات العامة سالب ومستقبلات عامل النمو موجب).

الهدف من الدراسة :

هو تقييم حالة الهرمونات وعلاقتهم بدرجة ومرحلة الورم.

المرضى وطريقة العمل :كان نوع الدراسة دراسة مقطعية في محافظة ذي قارفي مدينة الناصرية في مستشفى الحبوبي مركز الاورام ،تضمنت 165 حالة من المرضى الذين شخصت إصابتهم بسرطان الثدي خلال فترة (كانون الثاني 2014- كانون الاول 2015) **تم ت**جميع معلومات كلّ مريض وتحلّيلها :عمر المريض ،الجنس، مكان الاقامة مستقبلات). ER،PR،her2ومعلومات متعلقة بالورم مثل درجة الورم و مرحلة الورم، ومنزلة المستقبلات .

النتائج: العمري الوسطي = 49 + _ 11.1. وكانت معظم الحالات 75,2% هرمون البروجسترون موجب بينما سالب(78.2٪). كان معظم المرضى من HER2هرمون الاستروجين موجب في (72.7٪)،ولكن معظمهم كانوا موجب و ER / PRالدرجة الثانية (64.2 ٪) والمرحلة الثانية (50.3 ٪)؛كان النوع الفرعي الأكثر شيوعا (سالب) والتي تمثل 64.8٪ her20

بالنسبة لمقارنة التعبير الهرموني للمرض مع درجة ومرحلة الورم لوحظ ان أعلى درجة الورم (الثاني) (76.93٪) (موجب) واعلى مرحلة للورم لوحظت (80.95٪) في سلالة السلبي HER2سالب،ER / PR في النوع الرابع الثلاثي.

الاستنتاجات: سرطان الثدي يمتلك خصوصية مستقبلات هرمونية.الكثير من الحالات توجد في المرحلة الثانية والدرجة الثانية لحظة التشخيص. التعبير الهرموني السلبي متعلق بمرحلة متقدمة من المرض 0ينبغي توجيه الجهود في توحيد أساليب وتطوير اختبارات أكثر وثوقا لتشخيص المرض بمرحلة مبكرة.