

Assessment of Prognostic Value FOXA1 Expression in Breast Carcinoma after Neoadjuvant Chemotherapy: Immunohistochemically Study

Abd Ellatif M. Elbalshy^a, Nihal S. Zafer^a, Ashgan Abo Sarha^b, Naglaa M.Elshazly^b

^aPathology Department, Faculty of Medicine Benha University, Egypt.

^bPathology Department, Medical Research Institute, Alexandria University, Egypt.

Corresponding to:

Dr. Naglaa M.Elshazly.
Pathology Department, Medical Research Institute, Alexandria University, Egypt.

Email: naglaaelshazly@gmail.com

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Abstract:

Background: Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma death in women. Aim and objectives: to determine the expression of FOXA1 in breast carcinoma, to correlate the expression of FOXA1 with hormonal receptors (ER and PR), Her2\neu, Ki67 and pathological response to chemotherapy. **Patient and method:** This retrospective study was carried on 100 controlled, selected cases included seven cases with bilateral breast cancer, eighty-six cases IDC, five cases ILC, ductal carcinoma insitu (DCIS) was three cases, medullary carcinoma three case, two cases papillary and one case tubular. Fifty-six cases of the total cases with positive axillary lymph nodes metastasis. It was performed on formalin-fixed paraffin-embedded tissue blocks of specimens, collected from Pathology Department, Faculty of Medicine, Benha University, from the years (2013-2019). **Result:** Concerning the pathological response was found that, FOXA1 was positive in forty-four (44) out of fifty (50) cases with complete pathological response, twenty-seven (27) out of thirty-seven (37) cases with partial pathological response and seven (7) cases out of thirteen (13) cases with no pathological response. While for (ER), (89) cases are positive out of them (74) case FOXA1 positive, and (PR), (80) cases positive, FOXA1 positivity (68) out of them, however Her-2\neu negative cases were (48) from them (41) case are FOXA1 positive. For Ki-67, fourteen (14) cases show low scoring, while (31) cases has intermediate score and (55) cases has high scoring, FOXA1 positivity out of them (14, 31, 33 cases respectively). **Conclusion:** FOXA1 is a marker of good prognosis in breast cancer as FOXA1 expression associated with complete pathological response, positive hormone receptors and low-intermediate Ki67. **Key words:** FOXA1, Breast carcinoma, Pathological response, Hormonal receptors, prognosis.

Introduction

Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma death in women, with more than 1,000,000 cases occurring worldwide annually^(1,2).

Estrogen receptor expression is an important prognostic and predictive factor in breast cancer. Patients with tumours that express ER have a longer disease-free interval and overall survival than patients with tumours lacking ER expression⁽³⁾. However, not all ER-positive breast cancers behave alike. Knowing why and how some ER-positive breast cancers behave differently than others are important for both research and clinical viewpoint⁽⁴⁾. FOXA1, also named hepatic nuclear factor 3a (HNF3a), is a member of Forkhead box winged-helix transcription factor family^(5,6). It is recognized as a pioneer factor for estrogen receptor (ER) to influence its combination with DNA in estrogen receptor (ER) positive breast cancer patients⁽⁶⁾.

Recent study proved FOXA1 expression can independently predict chemosensitivity of estrogen receptor (ER) positive breast cancer patients⁽⁷⁾ And other suggested low FOXA1 expression to be associated with a good response to neoadjuvant chemotherapy in luminal Her2/neu -negative breast cancer⁽⁸⁾.

The aim of the work was to determine the expression of FOXA1 in breast carcinoma, to correlate the expression of FOXA1 with other established prognostic parameters of breast cancer (Estrogen, Progesterone receptors, Her2/neu and Ki67) and to correlate the expression of FOXA1 with pathological response to neoadjuvant chemotherapy.

Patient and method:

This retrospective study was carried on 100 cases included seven cases with bilateral breast cancer (each considered as one case), eighty-six cases invasive ductal carcinoma (IDC), five cases invasive lobular carcinoma (ILC), ductal carcinoma

in situ (DCIS) was three cases, medullary carcinoma three case, two cases papillary and one case tubular. Fifty-six cases of the total cases with positive axillary lymph nodes metastasis. It was performed on formalin-fixed paraffin-embedded tissue blocks of specimens, collected from Pathology Department, Faculty of Medicine, Benha University, from the 2013 to 2019.

Method: All the studied breast carcinoma patients received the same protocol of neoadjuvant chemotherapy (NACT). All cases underwent surgery 4 weeks after the completion of NACT, either Modified Radical Mastectomy (MRM) or conservative breast surgery (CBS) with or without axillary clearance and sentinel lymph node. The patient with bilateral carcinoma underwent bilateral mastectomy. Lastly all the breast carcinoma patients received radiotherapy (all cases same protocol). Serial 5 µm thick paraffin sections were subjected to the following studies, Routine (H&E) stain, for diagnosis of breast lesion, histological grading of tumors and evaluation of axillary LN metastasis, Routine ER, PR, Her2/neu and KI-67 Immunohistochemical staining and FOXA1 Immunohistochemical staining; one to two drops of the primary monoclonal antibody FOXA1(1:450, DAB plus; DAKO Glostrup, Denmark) prediluted at 1:100 were applied to one section of every case. Slides were incubated in humid chamber for 20 minutes, at room temperature.

Interpretation of immunohistochemical results for FOXA1: (Table 1)

Evaluation of FOX1 expression: According to the results of the present study the normal breast tissue showed nuclear FOXA1. On the other hand, cytoplasmic or both cytoplasmic and nuclear FOXA1 staining was identified in the tumour cells. FOXA1 expression was scored by histoscore procedure, which based on a semi-quantitative scoring system, where the cut off value for

FOXA1 positivity was validated, the numeric final score was generated by the multiplication of percentage and degree of intensity of nuclear expression (scoring = percentage × intensity)⁽⁹⁻¹¹⁾.

The percentage of positive cells was categorized as follows:

0 point: no nuclear expression, 1 point: 1-20%, 2 points: 21-50% and 3 points: 51-100%.

The staining intensity was scored as follows: 1 point: weak intensity, 2 points:

moderate intensity and 3 points: strong intensity.

Based on this semiquantitative scoring system (histoscore procedure); the FOXA1 scoring (percentage × intensity) interpreted as follow: [Table 1]

1. Scores between 0 and 1 were classified as negative
2. Scores ≥ 2 to a maximum of 9 were considered positive.

Table 1: Showing interpretation of FOXA1 expression.

FOXA1 expression	The percentage of positive cells	The staining intensity	Points
Negative (0)	0	-	0
	1-20%	Weak stain	1
	1-20%	Moderate stain	2
Score (+1)	20-50%	Weak stain	2
	1-20%	Strong stain	3
	>50%	Weak stain	3
Score (+2)	20-50%	Moderate stain	4
	20-50%	Strong stain	6
	>50%	Moderate stain	6
Score (+3)	>50%	Strong stain	9

Statistical analysis of the data

Data were analyzed using SPSS software package version 18.0, P value is considered significant if <0.05 at confidence interval 95%. , (SPSS, Chicago, IL, USA)⁽¹²⁾.

Results:

The current study included one hundred (100) cases (80%) with breast carcinoma all of them proved by core biopsy from the breast lesion to be positive for malignant cells and twenty-five (25) normal cases-control cases (20%) underwent reduction mammoplasty.

The study showed that Ductal carcinoma insitu (DCIS) was three (3) cases (3%), Invasive Ductal Carcinoma (NST) IDC was eighty-six (86) cases (86%), six (6) cases (7%) were found to be grade I, sixty-seven (67) cases (77.9%) were grade II and thirteen (13) cases (15.1%) were grade III, Invasive lobular carcinoma ILC was five (5) cases (5%), Medullary carcinoma

was three (3) case (3%), Papillary carcinoma was two (2) case (2%) and Tubular carcinoma was one (1) case (1%) (Table 2).

As regarding the results of FOXA1 positivity, twenty-two (22) cases (22%) were negative and seventy-eight (78) cases (78%) were positive. Different degrees of positivity were observed in the cancer cases. According to the scoring system selected for interpretation of FOXA1 expression the following results were obtained: Eleven (11) cases (11%) FOXA1(+), thirty-six (36) cases (36%) FOXA1 (++) and thirty-one (31) cases (31%) FOXA1 (+++). In tumour tissue, FOXA1 was expressed in the nucleus of cancer cells. In addition, some cells exhibited both nuclear and cytoplasmic FOXA1 positivity especially after neoadjuvant chemotherapy (Table 3, Figure 4-7).

Regarding FOXA1 expression and pathological response, this study revealed

that FOXA1 was positive in forty-four (44) out of fifty (50) cases having complete pathological response and twenty-seven (27) out of thirty-seven (37) cases with partial pathological response, whereas only seven (7) cases out of thirteen (13) cases with no pathological response showed FOXA1 positivity. In the

former group: two (2) cases FOXA1 positivity was weak (+1), while in twenty-two (22) cases FOXA1 positivity was moderate (+2) and in the remaining twenty (20) cases FOXA1 positivity was strong (+3). FOXA1 expression showing a positive statistical significance ($p < 0.019^*$) (Table 4).

Table 2: Histopathological types of breast carcinoma.

Histopathological characters	Frequency	Percent
Types of breast carcinoma	100	100
DCIS	3	3
IDC(NST)	86	86
GI	6	7
GII	67	77.9
GIII	13	15.1
Invasive lobular	5	5
Medullary carcinoma	3	3
Papillary carcinoma	2	2
Tubular carcinoma	1	1

Table 3: Distribution of FOXA1 among the studied cases.

FOXA1	Frequency	Percent
Negative	22	22
Positive	78	78
+	11	11
++	36	36
+++	31	31
Total	100	100

Table 4: Relationship between immunohistochemical FOXA1 expression and pathological response.

	No. of cases	FOXA1 positive (n = 78)				
		No.	%	+1	+2	+3
Pathological response						
No	13	7	9.0	3	2	2
Partial	37	27	34.6	6	12	9
Complete	50	44	56.4	2	22	20
P value		0.019*			0.008*	

p value for association between different categories

*: Statistically significant at $p \leq 0.05$

Table 5: Relationship between FOXA1 expression and Her-2\neu expression.

Her-2\neu expression	No. of cases	FOXA1 positive (n =78)				
		No.	%	+	++	+++
Negative	48	41	52.6	6	15	20
Positive	52	37	47.4	5	21	11
P value		MC p = 0.085		MC p = 0.091		

MC: Monte Carlo p value for association between different categories *: Statistically significant at $p \leq 0.05$

As regard hormonal receptors, this study showed FOXA1 expression was positive in four (4) out of eleven (11) ER negative cases; FOXA1 was weakly expressed (+1) in the four cases, while in the ER positive cases, seventy-four (74) out of eighty-nine (89) cases were FOXA1 positive divided as following: seven (7) cases weak FOXA1 (+1), thirty-six (36) cases moderate (+2) and thirty-one (31) cases showed strong FOXA1 positivity (+3), statistical analysis revealed that there was a highly significant association between ER positivity and FOXA1 expression ($p=0.002^*$), while for PR, FOXA1 expression was positive in only ten (10) out of twenty (20) cases PR negative cases: where FOXA1 expression was weak (+1) in seven (7) cases, moderate (+2) in two (2) cases and strong (+3) in the remaining one (1) case. Whereas in PR positive cases sixty-eight (68) out of eighty (80) showed FOXA1 positivity; the expression was weak (+1) in four (4) cases, moderate (+2) in thirty-four (34) cases and strong (+3) in thirty (30) cases. [Table 24 and Fig. 54, 55] (Table 25, Figure82), with highly significant statistical association between the PR positivity and FOXA1 expression ($p<0.002$) (figure 1,2). Concerning the Her2\neu expression, FOXA1 was positively expressed in forty-one (41) out of forty-eight (48) Her-2\neu negative cases; six (6) cases showed weak FOXA1 positivity (+1), fifteen (15)

cases showed moderate FOXA1 positivity (+2) and twenty (20) cases showed strong FOXA1 positivity (+3). Whereas in Her-2\neu positive tumours FOXA1 was positive in thirty-seven (37) out of fifty-two (52) cases; weak FOXA1 positivity (+1) was seen in five (5) cases, moderate (+2) in twenty-one (21) cases and strong (+3) in eleven (11) cases with no significant statistical association between Her-2\neu positivity and FOXA1 expression ($p=0.091$) (Table 5).

This current study showed that FOXA1 expression was positive in the all fourteen (14) cases with low KI-67 index where FOXA1 expression was moderate (+1) in four (4) cases, and strong (+3) in the remaining ten (10) cases. FOXA1 was expressed positively in the all thirty-one (31) intermediate KI-67 index cases, were FOXA1 positive divided as following: four (4) cases weak FOXA1 (+1), thirteen (13) cases moderate (+2) and fourteen cases (14) showed strong FOXA1 positivity (+3). Cases with high KI-67 index FOXA1 positive expression was in thirty-three (33) cases out of fifty-five (55) in which seven (7) cases showed weak FOXA1 positivity (+1), nineteen (19) cases showed moderate FOXA1 positivity (+2) and seven (7) cases showed strong FOXA1 positivity (+3), statistical analysis revealed that there was a very high significant association between low-intermediate KI-67 index and FOXA1 expression ($p=0.001^*$) (figure 3).

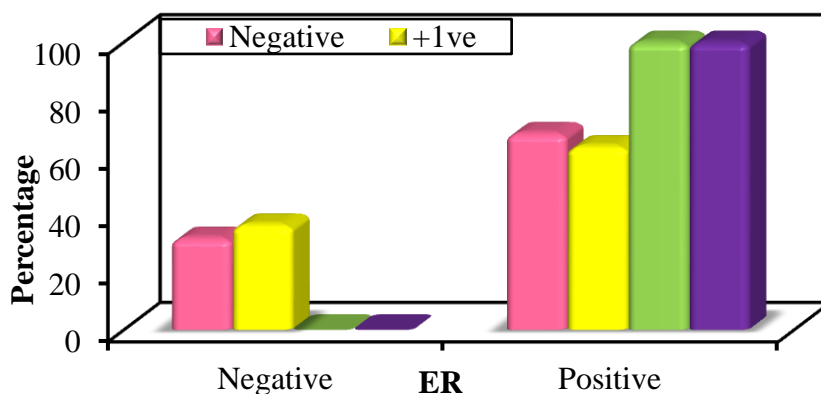


Figure 1: Relation between FOXA1 and ER

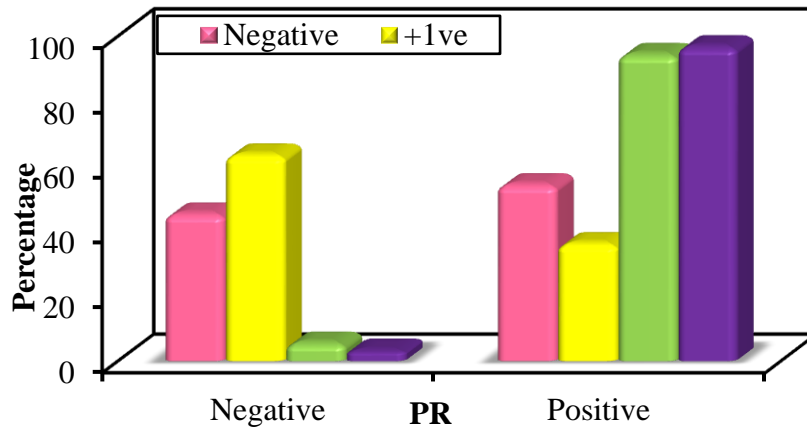


Figure 2: Relation between FOXA1 and PR

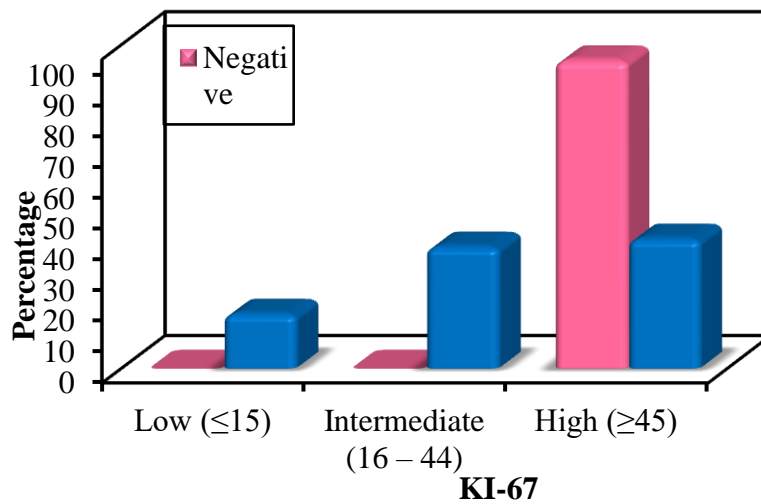


Figure 3: Relation between FOXA1 and KI-67

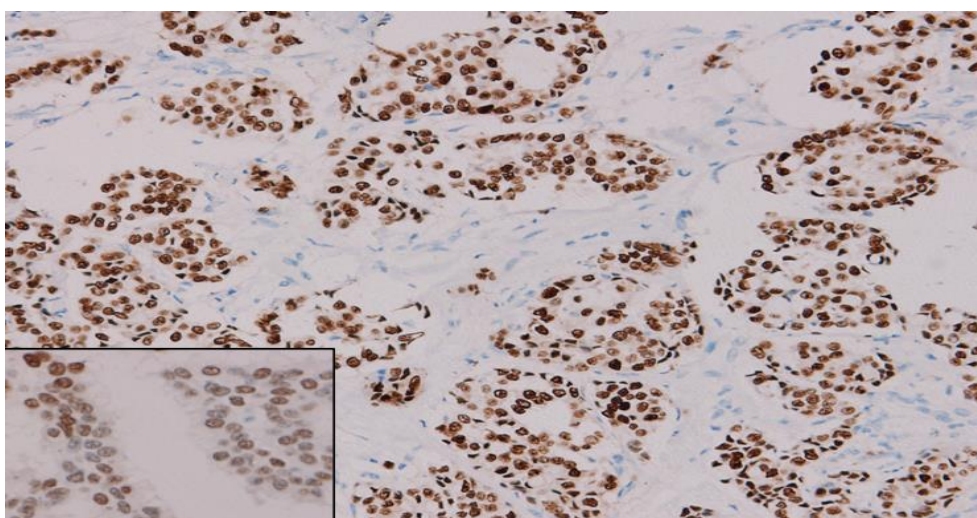


Figure 4: IDC grade II showing moderate (++) nuclear FOXA1 immunostaining, core biopsy. (X100, Inset X400).

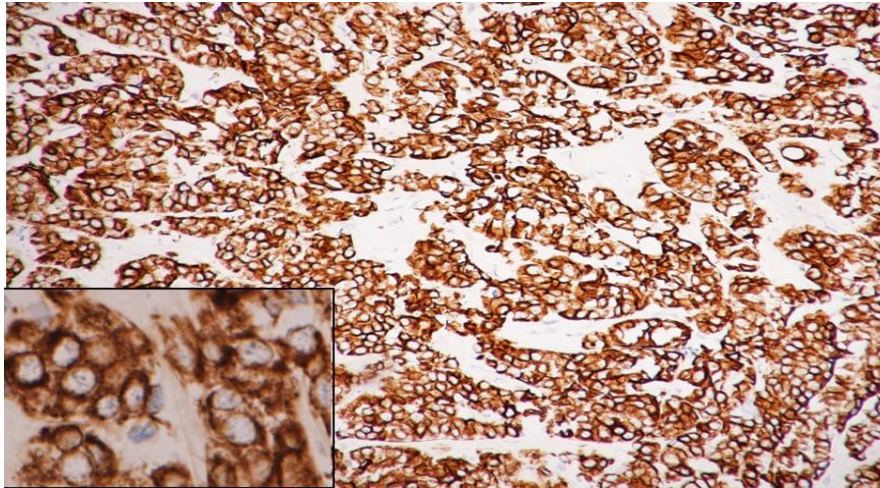


Figure 5: IDC grade II showing strong (++) nuclear FOXA1 immunostaining, MRM. (X100, InsetX400).

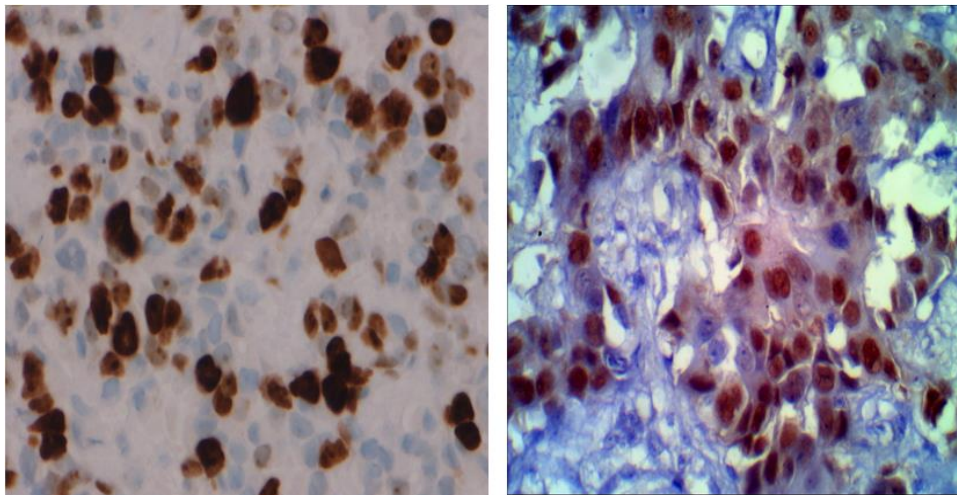


Figure 6: Strong (+3) cytoplasmic and nuclear FOXA1 immunostaining in grade II IDC, MRM. (X400).

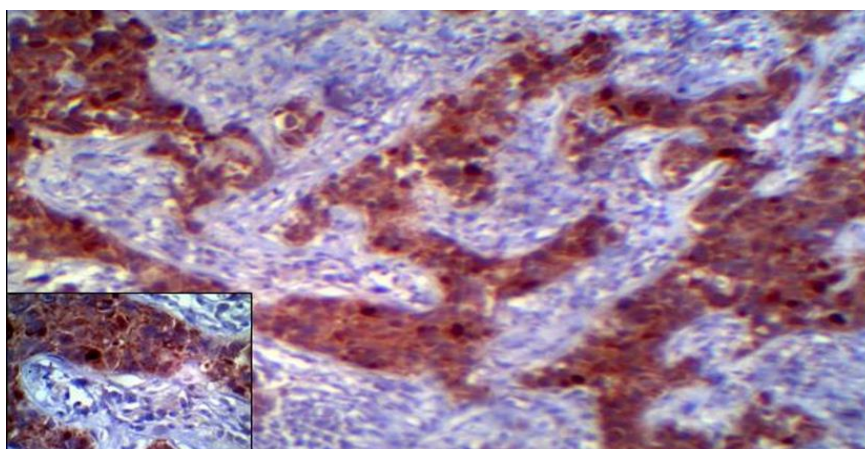


Figure 7: IDC grade II showing strong (+3) cytoplasmic positivity for FOXA1, with occasional nuclear labelling. (X200, InsetX400)

Discussion:

In women worldwide, the most common malignant neoplasm is breast cancer, with a frequent risk of 1 out of every 8 women⁽¹³⁾. It is the second common cause of malignancy associated death following lung cancer in women^(1,2,14,15) with 2,261,419 new cases and 684,996 deaths worldwide in 2020, despite major improvements in terms of prevention, diagnosis and treatment⁽¹⁶⁾.

In Egypt, breast cancer is the first among female cancers as it represents 37% of all female cancers and showed recently an appreciable increase in annual incidence rate thus represents an important public health problem⁽¹⁶⁾.

Breast carcinoma is considered as a disease in which its clinical development and prognosis are variable. So FOXA1 can be consider as one of the most promising members of molecular and immunohistochemical markers for the evaluation of the behavior of malignancy^(11,13).

In the present study, the immunohistochemical expression of FOXA1 was represented as nuclear in normal epithelial cells and cancer cells respectively. On the other hand, nuclear or both nuclear and cytoplasmic FOXA1 immunostaining were identified in the tumour cells after neoadjuvant chemotherapy.

Same results reported by others as; they observed that FOXA1 nuclear staining expression was observed in a few luminal epithelial cells of the normal breast, while FOXA1 expression after neoadjuvant chemotherapy can be identified in cancer cell cytoplasm only or nuclear and cytoplasm^(18,19).

In the present study, seventy-eight (78) out of one hundred (100) cases 78% showed positive FOXA1 expression. This was in line with previous studies, who found that 92.6%, 85.9%, 84.6%, and 71.2% respectively of the cases expressed FOXA1^(11,17-19).

On the other hand, others found 43%, 45.7%, 41.5% and 58.9% of cases respectively with positive FOXA1, this may be due to difference in number of cases included in each study and/or difference in scoring method for FOXA1⁽²⁰⁻²³⁾.

In the present work and regarding the pathological response, there was a statistically significant correlation between FOXA1 expression and pathological response ($p < 0.019^*$) as out of the seventy-eight (78) FOXA1 positive cases forty-four (44) (56.4%) showed complete pathological response.

In accordance with the results of the current work, many studies showed that FOXA1 expression was positively correlated chemosensitivity and pathological response⁽¹⁹⁾. Also, recently documented that, high FOXA1 expression was correlated with increased tumor sensitivity to chemotherapeutic agents^(10,11,24). While, results obtained by others, confirmed that high levels of FOXA1 expression were associated with a low rate of pathological complete response⁽¹⁸⁾.

Regarding hormonal receptor status (ER and PR), in the present study there was a highly significant association between FOXA1 expression and hormonal receptors positivity ($p = 0.002^*$) and ($p < 0.002^*$) respectively. Similarly, in the medical literature, most publications report a very strong correlation between FOXA1 expression and that of ER and PR in breast cancers^(20-23,25), confirmed by two meta-analysis^(26,27).

FOXA1 can either stimulate or suppress growth. It works as a stimulator by binding to chromatinized DNA, opening the chromatin, and enhancing (ER) binding to its target genes. FOXA1 does more than just change the way ER works. Additionally, it connects directly to the promoter of the ESR1, which is required for BC cells to produce ER mRNA and protein. Therefore, FOXA1 is necessary for both ER activity and expression. Two potential growth inhibitory repressor

mechanisms were discovered: stopping the spread of metastatic disease and differentiating ER pathway regulation⁽¹⁸⁾.

On the other hand, FOXA1 reduced the development of cells and blocked the ER pathway in ER positive cells⁽²³⁾.

ER is expressed in the majority of breast cancers and is positively correlated with FOXA1 expression, yet its role in breast cancer is less understood⁽²⁵⁾.

In the current study and in agreement with others, no significant association was detected between Her-2/neu positivity and FOXA1 expression ($p=0.091$)^(10,17,18).

But others reported that, there was a statistically significant association between FOXA1 expression and Her-2/neu negative cases^(21,23). This contradiction may be due to difference in cutoff point.

While other study reported that, overexpression of FOXA1 has been demonstrated to be strongly associated with Her-2/neu overexpression breast tumors⁽¹¹⁾.

In the present study, there was a very high significant association between low-intermediate Ki-67 index and FOXA1 expression ($p=0.001^*$), that is in line with numerous studies, which demonstrated that, FOXA1 expression was negatively correlated with Ki-67^(4,28,29).

In this study, clinicopathological evidences have been provided to indicate that FOXA1 expression is associated with good prognosis in breast cancer. Collectively, the significant associations between FOXA1 with complete pathological response, positive hormonal status (ER and PR), low Ki-67; that FOXA1 expression is a marker of good prognostic value. This is supported by other studies⁽¹⁷⁻²³⁾.

Conclusion:

FOXA1 is a marker of good prognosis in breast cancer.

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