Original paper

Association Between ER And HER2neu Status with Various Sonographic Findings in Breast Cancer

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Abstract

Introduction: Diagnostic ultrasonography is used as a radiological modality for assessing clinically suspected mammary lesions based on certain radiological criteria.
Objectives: This study was conducted to investigate the association between ultrasound based radiological findings and biological markers (estrogen receptor ER and HER2\NEU) in invasive mammary carcinoma.
Materials and methods: In this study 100 samples were collected retrospectively; each sample consist of one Hematoxylin and Eosin (H&E) stained histological section of invasive mammary carcinoma diagnosed by core needle biopsy together with the relevant immunohistochemical sections for ER and Her2Neu. The histological and immunohistochemical sections were carefully reviewed by two independent pathologists for assigning appropriate grading by using Nottingham modification of Bloom-Richardson system and an appropriate immunohistochemical scoring. For each sample, patient age, cytological report and the relevant sonographic data were extracted from the patient clinical request forms in the archive of data. The results were statically correlated by using chi square test.
Results: The study enrolled 100 histological sample of invasive mammary carcinoma diagnosed by core needle biopsy, 52% from the right breast and 48 % from the left one, age range of patient was from 28 to 80 years with a mean age of 53 years. 64 % were estrogen receptor positive, 54% were HER2\NEU positive. There was a significant statistical correlation between ER and HER2\NEU positivity with the ultrasonic features of positive axillary lymph node metastasis. While a non-statistical relationship was achieved between ER and HER2\NEU positivity with various sonographic findings in invasive mammary carcinoma.
Conclusion: Ultrasound based findings of a primary malignant breast mass are of no help to predict ER and HER2 status of invasive mammary carcinoma.
Keywords: Invasive mammary carcinoma, estrogen receptor, HER2\NEU, Sonography

Introduction

Invasive mammary carcinoma is regarded as the most common type of female cancer worldwide [(1)]. Indeed, mammary carcinomas are a different group of pathological lesions having a great diversity in histological and immunohistochemical features as well as biological behavior [(2)]. In situ breast cancer in which malignant cells are still within their confines with an intact basement membrane is the precursor lesion, it is either ductal or lobular, their discrimination is characteristically based upon architectural and cytologic features of the lesions rather than their topographic features (location) within the mammary ductal-lobular parenchymal system. Furthermore, Invasive mammary carcinomas consist of two main histological types of no prognostic significance, invasive ductal and lobular cancer, each with a characteristic histology allowing for microscopic identification. [(3)]
Each main histological type was further classified into different histological variants, accordingly breast cancer prognosis, treatment response and clinical outcome can be highly variable [(4)].
Recognizing the heterogeneity of this cancer type is the first step in an attempt to personalize breast cancer therapy. A grading system was introduced depending on the percentage of tubular formation, atypia and mitosis that is closely linked to prognosis [(5)] however identification of further prognostic predictors has a great effect on therapy personalization of this common type of cancer. [(6-7)]
"Gene expression profile" provides a further clarification of the heterogeneity of invasive mammary cancer. Accordingly, breast cancer with ER positivity is further classified as "luminal A", which is associated with HER2 negativity and

"luminal B," which is associated with HER2 positivity. Furthermore, breast cancer with ER negativity is also classified into an "HER2-over expressed" and the so-called "basal-like" subtype. (8)

The clinical significance of molecular classification of mammary cancer remains under extensive investigation (9). Testing the status of PR receptor in invasive mammary cancer remains a debated issue in clinical oncology and many laboratories do not test it routinely according to Breast cancer data set of the" Royal College of Pathologists" (10, 11). Another very important issue in the era of breast cancer treatment is the assessment of" HER2" oncogene. Amplification of HER2 gene which is detected by immunohistochemical expression was reported in nearly 20% of breast cancer and associated with a biologically aggressive disease (12). However, the introduction of the targeted drug," trastuzumab", an anti HER2 therapy and their proved pharmaceutical efficacy in HER2 positive cancer leads to a significant changes in the prognosis of HER2 positive breast cancer.(13)

Diagnostic ultrasonography is often used as a radiological modality for assessing clinically or radiologically suspected mammary lesions based on certain radiological criteria, it is regarded as an effective screening method for radiological identification of occult cancers in dense breasts particularly in women below 35 years old, it has a high sensitivity for diagnosing mammary cancers particularly with a recent technical advance in transducer designing (14).

BI-RADS "(Breast Imaging-Reporting and Data System)" is a widely a accepted strategy for risk assessment described by" American College of Radiology" as a formal reporting system in breast radiology depending on certain radiological features (15) "Percutaneous core needle biopsy" (CNB) under ultrasound guide has become the standard diagnostic tool widely used nowadays for primary histological diagnostic approach of invasive mammary cancer successfully replacing fine needle aspiration cytology (FNA) as well as excisional biopsy (16).

This study was conducted to investigate the association between breast sonographic findings and biological markers (ER and HER2\NEU) in an attempt to find an ultrasound based radiological signs that can predict hormone receptor positivity and HER2\NEU immunoreactivity in the most common cancer in a sample of Iraqi women.

Materials and methods

This study was conducted at Al Massa breast center, one of the private breast center units at Bagdad. In this study100 samples were collected retrospectively from the laboratory department during one year period (from July 2022 to July 2023). Each sample consists of one Hematoxylin and Eosin (H&E) stained histological section of invasive mammary carcinoma diagnosed by core needle biopsy together with the relevant immunohistochemical sections for ER and Her2Neu. The histological and immunohistochemical sections were carefully reviewed by two independent pathologists for assigning appropriate grading by using Nottingham modification of Bloom-Richardson system and an appropriate immunohistochemical scoring (6,13).

For each sample, patient age, cytological reports (provided by ultrasound guided fine needle aspiration) together with the relevant radiological data regarding sonographic findings were extracted from the patient clinical request forms in the archive of data. These include site, margins, echo pattern, calcification, axillary lymph node status and final BIRAD category.

The inclusion criteria included only samples with a positive radiological signs of axillary lymph node metastasis, that have cytological confirmation by Ultrasound guided fine needle aspiration and those with complete radiological and immunohistochemical data.

The exclusion criteria included samples with equivocal HER2/NEU results and those with missing radiological and immunohistochemical data.

Statistical association was done by using chi square test to compare between different variables; a P-value of less than 0.05 was considered a statistically significant. The age range of the participants was presented as means ± standard deviation (SD).

In this study photomicrographs were taken using a camera (Leica Icc 50E/Wetzlar, Germany). Histological examination was done by using a light microscope (leica DM500 / Wetzlar, Germany).

This study was approved by the ethical committee of the Al Massa center, reference number (1212-2023) and subjected to its institutional policy regarding the ethical consideration.

Result

The study enrolled 100 histological sample of invasive mammary carcinoma (figure 1) diagnosed by core needle biopsy 52% from the right breast and 48 % from the left one, age range of patient was from 28 to 80 years with a mean age was 53 years. 64 % were estrogen receptor positive (figure 2), 54% were HER2\NEU positive (figure 3).

Association between ER receptor status and the radiological features of positive axillary lymph node metastasis revealed a significant statistical relationship, while a non-significant statistical relationship was achieved between ER status and BIRAD category, radiological calcification, echogenicity, radiological margins as shown in table 1.

Association between HER2\NEU status and radiological features of positive axillary lymph node metastasis revealed a significant statistical relationship, while a non-significant statistical relationship was achieved between HER2\NEU status and BIRAD category, radiological calcification, echogenicity, radiological margins as shown in table 2

Table1. Association between ER status and various sonographic findings

	Axillary nodal status		BIRAD category		Radiological calcification		Echogenicity		Radiological margins	
	positive	negative	BIRAD IV	BIRAD V	Presence of calcification	Absence of calcification	Hypoechoic	Complex cystic	Speculated margin	Microlobulated margin
ER positive	28	36	16	20	14	50	62	2	48	16
ER negative	26	10	36	28	12	24	34	2	26	10
Total	54	46	52	48	26	74	96	4	74	26
P value	0.006		0.256		0.209		0.354		0.761	

Table2. Association between HER2\NEU status and various sonographic findings

	Axillary nodal status		BIRAD category		Radiological calcification		Echogenicity		Radiological margins	
	positive	negative	BIRAD IV	BIRAD V	Presence of calcification	Absence of calcification	Hypoechoic	Complex cystic	Speculated margin	Microlobulated margin
HER2 positive	40	14	24	30	16	38	52	2	44	10
HER2 negative	14	32	28	18	10	36	44	2	30	16
Total	54	46	52	48	26	74	96	4	74	26
P value	< 0.001		0.101		0.369		0.869		0.064	

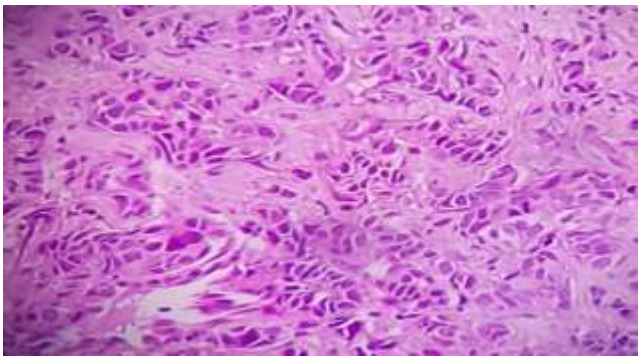

Figure1. (X100) H&E histological sections GradeIII invasive ductal carcinoma (NOS)

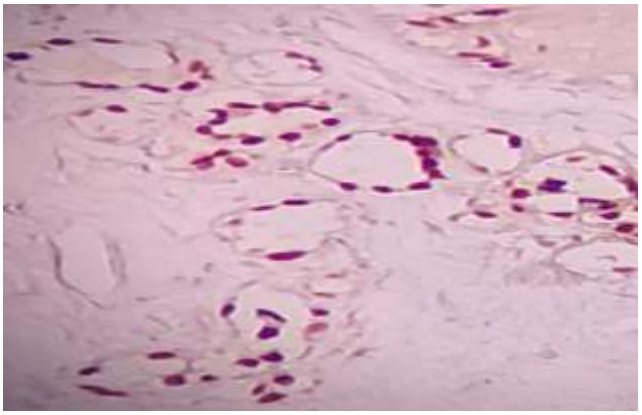

Figure 2. (X100): ER positive invasive ductal carcinoma

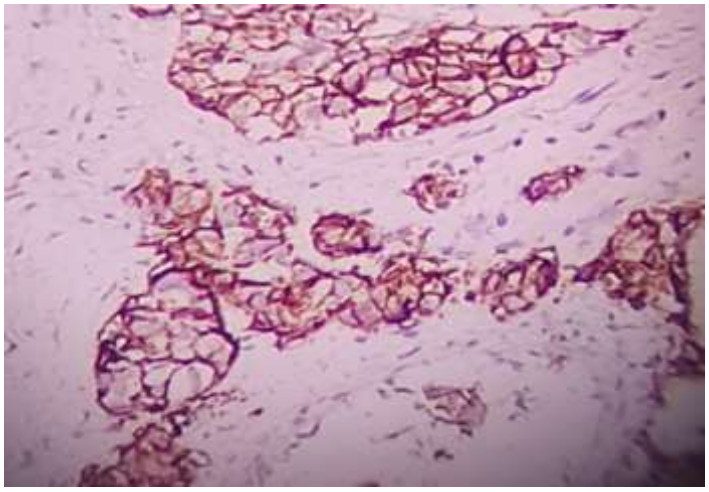

Figure 3(X100): HER2\NEU positive invasive ductal carcinoma

Discussion

BI-RADS "(Breast Imaging-Reporting and Data System)" is a risk stratifying categories developed by" American College of Radiology" that include reporting schema for breast radiology by ultrasound, mammography and magnetic resonance image (MRI). Accordingly, Seven categories were assigned , "BI-RADS 0": incomplete, "BI-RADS 1": negative "BI-RADS 2": benign, "BI-RADS 3": probably benign, "BI-RADS 4": suspicious for malignancy "BI-RADS 5": highly suggestive of malignancy, "BI-RADS 6": known case of breast cancer proved by tissue biopsy. Sonographic features often used for assessment of axillary lymph node status include heterogenous echogenicity, shape, size, margins, cortical thickness, and lack of fatty hilum, abnormal vascular patterns on Doppler study (17).

This study showed that there was a significant statistical association between ER receptor positivity and HER2\NEU positivity with the radiological finding of positive axillary lymph node metastasis, these results were in agreement with the results of Mohson (18) in regard to HER2\NEU positivity and Ayad (19) in regard to ER positivity. In this study all breast cancer appeared irregular in shape with either speculated or microlobulated margins, the majority 96% were hypoechoic and only 4% had complex cystic and solid patterns. However Kim et al (20) which used a larger sample size found that not all breast cancers have irregular shape and some were hypoechoic and isoechoic, these variations in results may be due to variation in sample size. Calcification within the tumor was present in 26% of invasive mammary carcinoma in this study , a similar percentage was found in as study done by Kim et al. (20) This study also found that there was no statistical relationship between ER and HER2\NEU positivity with various sonographic characteristics of a primary malignant breast mass as mentioned above , surprisingly there is conflicting data in the literature regarding this association. Kim et al (20) found that there was a significant association between ER receptor status and echogenicity in breast sonography, hypoechoic and complex cystic -solid patterns were more frequently present in ER negative cancers.

Unlike this study, a significant correlation between HER2\NEU with sonographic or mammographic calcifications was reported by other studies (20,21,22) which may be due to different radiological modality used in these studies.

Limitation

The results of the present study were based on a retrospective analysis in a single center with lack of many relevant clinical information as in any retrospective study. Another limitation was a discussion- related due to small numbers of studies with a similar aim for comparison and extensive discussion.

Conclusions

There was a significant statistical association between ER and HER2\NEU positivity with the simultaneous presence of axillary lymph node metastasis. While there was a non-statistical relationship between ER and HER2\NEU positivity with various sonographic findings in invasive mammary carcinoma. Thus, with the exception of radiological features of positive axillary lymph node metastasis, ultrasound-based findings of a primary malignant breast mass are of no help to predict ER and HER2 status in invasive mammary carcinoma.

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