RESEARCH ARTICLE

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Massively Invasive Ductal Breast Cancer: Association Between Mammographic Features and the HER2-enriched Molecular Subtype

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Abstract

Objectives: This study aimed to determine whether there were differences in mammographic characteristics (mass size and margin of the mass) between the HER2-enriched and non-HER2-enriched molecular subtypes of breast cancer.

Methods: A total of 142 individuals with mammographically verified masses and histopathologically diagnosed invasive ductal breast cancer were detected (HER2-enriched: n=29; HER2 non-enriched: n=113). Mammographic features related to HER2 molecular subtype were analyzed. According to the TNM staging criteria, patients with masses on mammography were divided into ≤2 cm (T1) and >2 cm (T2 and T3) groups. The margin characteristics of the mass detected by mammography were divided into spiculated and nonspiculated groups.

Results: Histopathological sampling was performed on the lesions of 142 patients with breast cancer who had mass lesions associated with invasive ductal carcinoma on mammography; 29/142 (20.4%) were HER2-enriched and 113/142 (79.5%) were non-HER2-enriched. On univariate analysis; HER2-enriched molecular subtype rates were significantly higher in tumor size ≤2 cm [17/60 (28.3%)] than in those >2 cm [12/82 (14.6%)] (p=0.007) and HER2-enriched molecular subtype rates were significantly higher in nonspiculated lesions [20/61 (32.7%)] than in spiculated lesions [9/81 (11.1%)] (p<0.001). No significant associations were observed between patients age and HER2-subtypes.

Conclusion: Small tumor sizes and non-spiculated masses were more likely to be HER2 molecular subtype. This study presents a predictive model that combines tumor size and nonspiculated mass mammographic characteristics. This model has the potential to determine the HER2-enriched subtype of breast cancer before surgery.

Keywords: Mammography, invasive ductal breast cancer, human epidermal growth factor receptor subtypes

Introduction

Breast cancer is the primary cause of cancer-related mortality in women globally, as well as the second leading cause of cancer-related death in the United States.[1] A highly distinct tumor that contains multiple subgroups. Based on the immunohistochemical expression of hormone receptors, these subtypes are commonly divided into four categories: progesterone receptor-positive (PR+), human epidermal growth factor receptor 2-positive (HER2+), and estrogen receptor-positive (ER+), which is defined by the absence of expression of any of the aforementioned receptors triple-negative breast cancer.[2]

About 15-25% of breast cancers express human epidermal 2 HER2, and the status of this receptor is primarily important for selecting the best course of treatments.[3] Chemotherapy combined with dual HER2 blockage with lapatinib/trastuzumab or neoadjuvant trastuzumab appears to be particularly beneficial for HER2-enriched subtypes.[4] Breast cancer radiogenomics investigation identified relationships between genetic subgroups and imaging abnormalities.[5] On mammography, patients with HER2-enriched breast cancer were more likely to show up with a non-spiculated lump.[6]

Clinical studies have shown that mammography screening is associated with reduced breast cancer mortality. However, screening healthy individuals is also associated with undesirable effects, such as women with false-positive results being recalled for additional imaging. Advocates of more aggressive screening strategies aim to maximize the benefits of early detection, while advocates of less frequent screening aim to reduce false-positive assessments, anxiety, and costs for patients who will never develop breast cancer. The World Health Organization has recommended that mammography screening begin at age 40 in well-resourced settings.[7-9]

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The HER2-enriched molecular subtype determines the medications and treatment modalities are advised.[10] Sometimes sampling artifacts, tiny biopsy specimens, or inoperability make it impractical to obtain enough tissue for examination prior to therapy initiation. In this situation, our study will be useful for decision-making. As a result, we aimed to explore the relationships between the HER2-subtype and mammographic features.

Methods

Ethics committee approval was obtained from the Erzincan Binali Yıldırım University, Mengücek Gazi Training and Research Hospital Research Committee (number: 2023-9/3, session: 3, date: 09.03.2023) for this study, and the Helsinki principles were adhered to during the study. Because of the retrospective study design, no additional informed consent forms were obtained from the patients. Between January 2018 and January 2023, patients with histopathologically confirmed invasive ductal breast cancer were screened from the institutional database. A total of 142 patients with mass lesions on mammography were included in the study. Mammographic characteristics (mass size and margin of the mass) and histopathological information (HER2-enriched molecular subtype and non-HER2-enriched molecular subtype) of the patients were recorded. The study included patients of all ages.

A consensus was reached after two radiologists who were blinded to the histological characteristics evaluated the mammography images for this study. The margin characteristics of the mass detected in the patients mammography were divided into spiculated and nonspiculated groups based on previous studies.[6,11] Lesions with lines radiating from their edges are called spiculated masses. If the lesion margins were circumscribed, microlobulated, obscured or indistinct were called non-speculated.

According to the TNM staging criteria, patients with masses on mammography were divided into ≤2 cm (T1) and >2 cm (T2 and T3) groups.

The tumor pathology reports of the patients were reviewed. The pathology reports were recorded as HER2-enriched and non-HER2-enriched molecular subtypes.

Statistical Analysis

The chi-square test (using Statistical Package for the Social Sciences software, version 15.0) was used to evaluate the correlation of HER2-enriched molecular subtype status with age and pathologic characteristics. Differences between breast cancers with and without HER2-enriched molecular subtypes were determined using the chi-square test, as well as univariate and multivariate binary logistic regression analyses. P<0.05 was considered statistically significant.

Results

As a result of histopathological sampling of the lesions of 142 breast cancer patients who had mass lesions related to invasive ductal carcinoma on mammography; 29/142 (20.4%) were reported as HER2-enriched and 113/142 (79.5%) were reported as non-HER2-enriched.

On univariate analysis, HER2-enriched molecular subtype rates were significantly higher in tumor size ≤2 cm [17/60 (28.3%)] than in those >2 cm [12/82 (14.6%)] (p=0.007) (Table 1).

On univariate analysis, HER2-enriched molecular subtype rates were significantly higher in nonspiculated lesions [20/61 (32.7%)] than in spiculated lesions [9/81 (11.1%)] (p<0.001) (Table 2).

Our results showed that small tumor sizes and non-spiculated masses were more likely to be HER2 molecular subtype.

No significant associations were observed between patient age and HER2 subtype (Table 3).

Table 1. Association between tumor size and HER2 subtypes

Tumor size	Non-HER2 enriched n (%)	HER2 enriched n (%)	Whole population (n)	Chi-square p value
≤2 cm	43 (71.7%)	17 (28.3%)	60	0.007*
>2 cm	70 (85.4%)	12 (14.6%)	82	

HER: Human epidermal growth factor receptor, n: Number, %: Percentage, *: Statistical significance

Table 2. Association between mass margin and HER2 subtypes

Margin of mass	Non-HER2 enriched n (%)	HER2 enriched n (%)	Whole population (n)	Chi-square p value
Spiculated mass	72 (88.9%)	9 (11.1%)	81	<0.001*
Non-spiculated mass	41 (67.3%)	20 (32.7%)	61	

HER: Human epidermal growth factor receptor, n: Number, %: Percentage, *: Statistical significance

Table 3. Age distribution of the HER2 subtypes

Age	Non-HER2 enriched n (%)	HER2 enriched n (%)	Whole population (n)	Chi-square p value
<35	7 (87.5%)	1 (12.5%)	8	0.751
35-69	101 (78.9%)	27 (21.1%)	128	
≥70	5 (83.3%)	1 (16.7%)	6	

HER: Human epidermal growth factor receptor, n: Number, %: Percentages

Discussion

The molecular characterization of breast cancer has led to a better understanding of the disease. Anti-HER2-targeted medicines have greatly improved the HER2-subtype, which has been associated with poor prognosis in seminal studies on cancer genetics.[12] An analysis of prior data indicated that compared with female patients with HER2-negative breast cancer, those with HER2-positive breast cancer who were treated with trastuzumab had a markedly better prognosis.[13]

The spiculation of malignant breast lesions often occurs because of substantial desmoplastic response. This feature is commonly observed in invasive breast cancer during mammography and serves as a valuable criterion for the clinical identification of the disease.[6,14] Imaging studies have revealed that grade 1 and 2 breast cancers exhibit a stromal response characterized by a spiculated margin.[15] Mammographic features have the ability to visually represent the characteristics of the breast tumor phenotype without the need for invasive procedures.[16] Recent studies have shown that masses with a spiculated margin are more frequently observed in patients with luminal A subtype than in other subtypes.[17,18] In addition, Liu et al.[6] noted that breast tumors with HER2 overexpression do not have a spiculated margin although the exact reason remains unclear. Our study showed that the rates of the HER2-enriched molecular subtype were considerably greater in nonspiculated than in spiculated lesions.

No statistically significant correlation between HER2/neu expression and tumor growth has been shown in earlier research.[19-22] Nevertheless, our investigation revealed a notable increase in the prevalence of the HER2-enriched molecular subtype in tumors 2 cm compared with larger lesions. These findings are consistent with those of Nie et al.[4], Bhagat et al.[23], and Almasri and Hamad.[24]

Study Limitations

Our study has some limitations. This study did not include other mammographic characteristics, such as microcalcification. It is appreciated that HER2 overexpression was not observed in most invasive lobular carcinomas, and invasive lobular carcinomas were not included in the study. Our study is retrospective, and data were collected from a single center. On the other hand, the predictive value of mammographic features was modest.

Conclusion

In conclusion, this study presents a predictive model that combines tumor size and nonspiculated mass mammographic characteristics. This model has the potential to determine the HER2-enriched subtype of breast cancer before surgery. Our study indicated that the tumor size was 2 cm, and it was more probable for the nonspiculated mass to belong to the HER2 molecular subtype. Radiologists should purposely search for this mammography finding to inform referring clinicians of the presence of this feature.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Erzincan Binali Yıldırım University, Mengücek Gazi Training and Research Hospital Research Committee (number: 2023-9/3, session: 3, date: 09.03.2023) for this study, and the Helsinki principles were adhered to during the study.

Informed Consent: Because this was a retrospective study, informed consent was not required by the ethics committee.

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