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Evaluation of Breast Conserving Surgery According to Molecular Subtypes in Kurdish Females

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Abstract

Background & objectives:
The most frequently occurring cancer in women is breast cancer, and various treatment methods are available. Thus, we aimed to correlate between molecular subtype and the suitability of performing breast-conserving surgery.

Methods: This retrospective cross-sectional study was conducted on 300 women with primary breast cancer, but without distant metastasis, from 2016 to 2022. These women had undergone either breast-conserving surgery or mastectomy. Patients were interviewed directly to obtain the necessary data, and their data were recorded on a questionnaire.

Results: The most common age group at diagnosis was 45-50 years, and the mean age for menarche was 13.3±1.3 years. Of the patients, 9% were single, 15% were nulliparous, and 76.7% had practised breastfeeding. The most common type of cancer was invasive ductal carcinoma, with ductal carcinoma in situ (82%). The molecular subtype and type of surgery were significantly correlated (p=0.041). Of the sample, 66.7% underwent breast-conserving surgery, with the highest rate (87%) being done in the triple-negative molecular subtype. Additionally, there was a significant correlation between the tumour focality and the postoperative margin (p<0.001).

Conclusions: Triple-negative cases were the most suitable for breast-conserving surgery among the molecular subtypes and had the highest rate of free margin. In contrast, unifocal breast cancers had the least involvement in margin postoperatively.

Keywords: Breast cancer, Breast-conserving surgery, Cross-sectional study, Margin involvement, Molecular subtype

Introduction

Breast cancer is the most common cancer in females and the top cancer-related death among women.[1] It is the second most frequent cancer globally, with nearly 1.7 million new patients recorded yearly, 25% of all cancer patients. The incidence rate of breast cancer varies from region to region, ranging from 19.4 cases per 100,000 in East

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Africa to 89.7 cases per 100,000 in West Europe.[2] Breast cancer is a diverse set of diseases with different subtypes, each possessing unique biological characteristics that cause variable responses to treatment and clinical outcomes.[3] The molecular subtype should be evaluated when deciding on the type of approach because conventional clinical criteria such as tumour grade, size, lymph node state, and surgical margin are insufficient as sole prognostic markers.[4]

There are five molecular subtypes based on estrogen receptor (ER), progesterone receptor (PR), and Human epidermal growth factor receptor 2 (HER2) status,[3-5] including:

- Luminal A: ER +ve, PR +ve, Ki67 <14%, HER2 -ve
- Luminal B (HER2 negative): ER +ve, PR -ve and/or Ki67 >14%, HER2 -ve
- Luminal B (HER2 positive): ER +ve, any PR and Ki67, HER2 overexpressed
- HER2 overexpressed: ER and PR -ve, HER2 +ve, and Ki67
- Basal-like: ER and PR -ve, HER2 -ve, and Ki67

For early-stage breast cancer, breast-conserving surgery (BCS) is the standard surgical treatment that involves the removal of the whole cancerous breast tissue and a margin of tissue surrounding the tumour.[6,7] Mastectomy and BCS have comparable long-term survival rates. Still, BCS results in significantly better cosmetic outcomes [8] and enhances the quality of life by decreasing the likelihood of disfiguring surgery.[9] Critical clinical factors such as the tumour size, margin status, and multifocality of the lesion must be considered before deciding to perform BCS.[10]

Neoadjuvant chemotherapy (NACT) is a primary or preoperative chemotherapy that uses systemic medicines to treat patients before their cancer is surgically removed.[10] It was first utilized to change locally advanced inoperable tumours into tumours amenable to excision. It was then expanded to operable early-stage breast cancer to improve the eligibility for BCS among women with bulky tumours.[10] It has allowed more breast-conservation treatment (BCT) in locally progressed and early-stage cancers.[11]

When complete pathological response or tumour regression to a single nidus is obtained after chemotherapy, BCS is a viable option. However, in certain malignancies, cancer may exhibit a widespread pattern of persistent, multifocal microscopic disease spread throughout the original tumour volume.[12] It enhances the aesthetic result of selected breast conservation patients by allowing lower quantities of breast tissue to be removed.[12] It can also eliminate micrometastatic illness in regional lymph nodes and sometimes modify the axilla management plan.[13] Therefore, this study was designed to find which group of breast cancer molecular subtypes was more suitable for BCS.

Patients and methods

This retrospective, cross-sectional study was performed on 300 Kurdish females aged 50 years or younger with breast cancer who underwent surgery either before chemotherapy or after neoadjuvant therapy and were on follow-up from 1st January 2016 to 1st May 2022 at Hiwa Hematology/Oncology Hospital, Sulaimaniyah, Iraq. Patients with stage IV disease, male gender, and menopause were excluded. Women were interviewed face to face, verbal consent was taken from them, and their investigations were reviewed and recorded. The study concentrated on the type of breast cancer and the hormonal status of their tumours. Thus, patients were divided into five subgroups according to ER, PR, HER2, Ki67, and TNM staging. All underwent surgery, and the postoperative HPE and the need for surgery were considered. The operations were performed by general surgeons who were experienced in

breast surgery. Intraoperative frozen section was not done for patients, and most patients did not have intra-lesional clip insertion before starting chemotherapy.

The Statistical Package for Social Sciences (SPSS, version 26) evaluated the data. Categorical variables were reported as frequencies and percentages, while numerical variables were presented as means and standard deviations (SD). Fisher's exact test was used instead of the chi-square test if the expected frequency (value) was less than five or more than 20% of the table's cells. A p-value of ≤ 0.05 was considered statistically significant.

Moreover, the study protocol was approved by the Research Protocol Ethics Committee of the Kurdistan Higher Council of Medical Specialties (KHCMS), and approval was obtained from the hospital's research committee.

Results

Three hundred women with breast cancer, who had been operated on, were included in the study. Most (90.3%) patients were married; the largest proportion (36%) were aged 45-50 at diagnosis. The mean±SD age of menarche was 13.3±1.3 years. Most of the patients (76.7%) had a history of breastfeeding, and 8% had a surgical

Table (1): Basic characteristics of the studied samples.

Variable	No.	%
Marital status		
Single	27	9.0
Married	271	90.3
Divorced	2.0	0.7
Age at diagnosis (Years)		
25-29	15	5.0
30-34	26	8.7
35-39	63	21.0
40-44	88	29.3
45-50	108	36.0
Mean (SD)	41.2	5.8
Age of menarche (Years)		
10-12	76	25.3
13-15	211	70.3
16-17	13	4.3
Mean (SD)	13.3	1.3
Breastfeeding		
Yes	230	76.7
No	70	23.3
Past surgical history		
None	276	92.0
Benign	12	4.0
Malignant	12	4.0
Parity		
Nulliparous	45	15
Parous	255	85
Total	300	100

The most common type of breast cancer was invasive ductal carcinoma (IDC), with ductal

carcinoma in situ (DCIS) representing 82% of the patient (Figure 1).

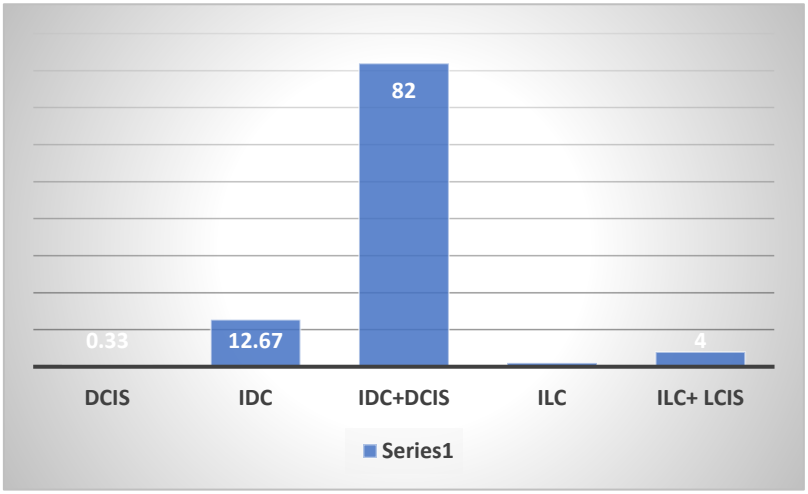

Figure (1): Types of breast cancer among studied patients.

The patient's breasts were mostly dense breast ACR 3 (75.67%), while the least was ACR 1 type using mammography, as shown in Figure (2).

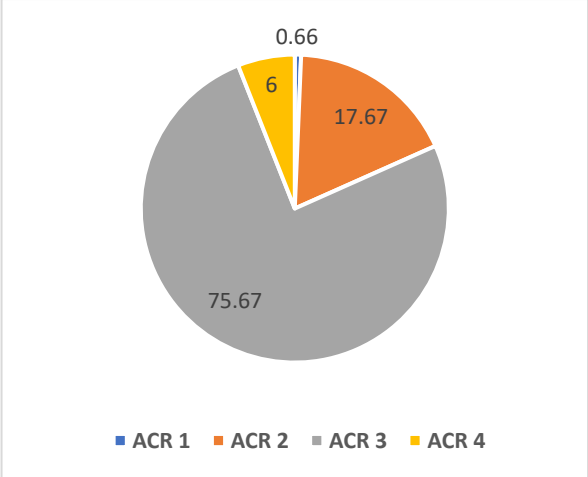

Figure (2): Patient's breast density by mammography.

Table (2) indicates that most patients (39%) had luminal B subtype, while the least had HER2 overexpression (low) (0.33%). The rate of BCS was 66.7% in the patients, with the highest rate (87%) in the triple-negative molecular subtype. Mastectomy was done for 44.9% of women with luminal B-HER2+ subtype with the least rate (13%) in the triple-negative molecular subtype. Hence, a significant correlation (p=0.041) was observed between the type of surgery performed and the breast cancer molecular subtype.

Table (2): Type of surgery by molecular subtype.

Molecular subtype	BCS	Mastectomy	Total	p value
	Number, %			
Luminal A	55 (67.9)	26 (32.1)	81 (27)	0.041*
Luminal B	81 (69.2)	36 (30.8)	117 (39)	
Luminal B - HER2+	38 (55.1)	31 (44.9)	69 (23)	
HER2 overexpression (low)	0.0 (0.0)	1.0 (100.0)	1.0 (0.33)	
HER2 overexpression (high)	6.0 (66.7)	3.0 (33.3)	9.0 (3.0)	
Triple-negative	20 (87.0)	3.0 (13.0)	23 (7.66)	
Total	200 (66.7)	100 (33.3)	300 (100.0)	

*: Significant difference using Fisher's exact test. BCS: Breast-Conserving Surgery

Table (3) shows that tumour margin involvement was presented in 14.8% of women with the luminal A molecular subtype and 10.3% with the luminal B subtype, while no patient with HER2 overexpression had any tumour margin involvement. Thus, there was a significant (p=0.043) correlation between tumour margin and molecular subtype of cancer in studied women.

Table (3): Tumour margin status by molecular subtype.

Molecular subtype	Tumour margin				p value
	Involved	Free	Close	Total	
	Number, %				
Luminal A	12 (14.8)	64 (79.0)	5.0 (6.2)	81 (27)	0.043*
Luminal B	12 (10.3)	102 (87.2)	3.0 (2.6)	117 (39)	
Luminal B - HER2+	4.0 (5.8)	60 (87.0)	5.0 (7.2)	69 (23)	
HER2 overexpression (low)	0.0 (0.0)	0.0 (0.0)	1.0 (100.0)	1.0 (0.33)	
HER2 overexpression (high)	0.0 (0.0)	7.0 (77.8)	2.0 (22.2)	9.0 (3.0)	
Triple-negative	1.0 (4.3)	21 (91.3)	1.0 (4.3)	23 (7.66)	
Total	29 (9.7)	254 (84.7)	17 (5.7)	300 (100.0)	

*: Significant difference using Fisher’s exact test.

Table (4) demonstrates that most patients (63.67%) had unifocal breast cancer, which made them highly suitable for BCS, and only 4.7% of them required revision surgery due to margin involvement. When breast cancer was diagnosed as 'multifocal', the tumour margin was positive for cancer cells in 20.3% of the patients. In contrast, in cases diagnosed as 'multicentric', the tumour margin was involved in 15.6%

Table (4): Tumour margin status by histopathological examination of the excised mass.

Locality	Tumour margin				p value
	Involved	Free	Close	Total	
	Number, %				
Unifocal	9.0 (4.7)	174 (91.1)	8.0 (4.2)	191 (63.66)	<0.001*
Multifocal	13 (20.3)	45 (70.3)	6.0 (9.4)	64 (21.33)	
Multicentric	7.0 (15.6)	35 (77.8)	3.0 (6.7)	45 (15)	
Total	29 (9.7)	254 (84.7)	17 (5.7)	300 (100.0)	

*: Significant difference using Fisher's exact test.

Our results showed that most (52%) patients had stage II A breast cancer, and the least (6.7%) had stage III. In addition, T2 masses had the highest rate of margin involvement (48.3%), whereas T0 masses had the lowest (3.4%). Therefore, no significant (p=0.606) correlation was seen between the involvement of the tumour cells in the margin and the pathological tumour size, as demonstrated in Table (5).

Table (5): Pathological tumour size after treatment by margin involvement.

Pathological tumour size after operation	Margin involvement				p value
	Involved	Free	Close	Total	
	Number, %				
0	1.0 (3.4)	7.0 (2.8)	1.0 (5.9)	9.0 (3.0)	0.606
1	11 (37.9)	92 (36.2)	7.0 (41.2)	110 (36.7)	
2	14 (48.3)	134 (52.8)	8.0 (47.1)	156 (52.0)	
3	3.0 (10.3)	17 (6.7)	0.0 (0.0)	20 (6.7)	
Ductal carcinoma in situ	0.0 (0.0)	4.0 (1.6)	1.0 (5.9)	5.0 (1.7)	
Total	29 (100.0)	254 (100.0)	17 (100.0)	300 (100.0)	

Discussion

Several factors affect the rate of breast-conserving surgery, including tumour size, the surgeons' preferences, patients' choices, and the availability of radiotherapy. The success of BCS is heavily influenced by anatomical parameters related to the tumour, such as tumour size, margin status, the number of lesions and the distance between them.[6]

The trend toward conserving breast has increased lately[7], which can also be seen in this study where the rate of BCS was 66.7% and for mastectomy was 33.3%. This study's most common molecular subtype was the luminal B subtype (39%). The absence of a specific drug and the aggressive biological characteristics of triple-negative breast cancer have led to debates about the possibility of performing BCS in this subtype. Nevertheless, recorded data from

cancer registries and prospectively collected data have indicated that BCS and mastectomy have similar long-term overall survival rates in patients with triple-negative breast cancer.[6] This study found a noteworthy difference between the molecular subtypes and the type of surgery performed. Specifically, most patients with triple-negative breast cancer had the highest rate of BCS (87%). This finding is in line with another research that showed the rate of BCS in the triple-negative subtype to be identical to, and even more than, the rates in ER-PR positive/HER2 negative and ER-PR negative/HER2 positive patients, respectively.[6] So, it is an excellent guide to the type of surgery to assess the molecular subtype of breast cancer beforehand.

Achieving an adequate margin, as it stands, remains to be the strongest predictor for recurrence.[14] Tumour size was not significantly correlated with margin involvement in this study (p=0.606). The patients with involved margins were T3 (10.3%), T2 (48.3%), and T1 (37.9%). This finding contradicts results from another study where there was a more rate of positive surgical margins in patients with stage T3 (42.9%) and T2 (16%) cancer, as compared to those with stage T1 (5.1%) cancer.[15]

Unifocal masses had the least (4.7%) involved margin histopathologically. They required minor revision surgery, while multifocal masses had a higher (20.3%) margin involvement rate with a significant correlation between the margin facility and the need for revision surgery (p<0.001). These results contradict another study which showed no significant difference in margin involvement between unifocal (10.6%) and multifocal (17.2%) masses (p=0.167).[6]

Conclusion

We concluded that the most suitable breast cancer molecular subtype for breast-conserving surgery was triple negative cases with the highest free margin rate. Additionally, postoperatively, unifocal breast cancers had the least margin involvement and were more suitable for breast-conserving surgery. The limitation of the study was funding shortage, difficulty reaching the patients, and the patients who received neoadjuvant systemic therapy did not have intralesional insertion clip before treatment.

Conflict of interest

There is no conflict of interest.

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