A RETROSPECTIVE COHORT STUDY ON BREAST CANCER: DETERMINANT FACTORS IN A SINGLE-CENTER MILITARY HOSPITAL IN JORDAN (KING HUSSEIN MEDICAL CENTER)

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ABSTRACT

Background:Breast cancer is a highly prevalent and heterogeneous form of cancer in women. Despite its global impact, limited research has been conducted on breast cancer in the Jordanian population. Understanding the factors influencing surgical choices and outcomes is crucial for optimizing treatment strategies. Therefore, this study aimed to describe samples of breast cancer collected from the Jordanian population that underwent wide local excision and axillary clearance or modified radical mastectomy.

Methods: We conducted a retrospective, single-center observational study from 2007 to 2014, at the King Hussein Medical Center (KHMC). The study included 447 breast cancer patients, who underwent modified radical mastectomy (MRM) or wide local excision and axillary clearance (WLE&AC). Demographic and clinicopathological data were collected, including surgical procedure, neoadjuvant chemotherapy, histology, tumor size, lymph vascular invasion (LVI), and hormone receptor status.

Results: The cohort comprised 99% females, with a median age of 52.0 years. Neoadjuvant chemotherapy was received by 14% of patients. MRM was chosen by 93% of patients, while 7% underwent WLE&AC. Positive lymph nodes and lymph node ratio (LNR) were significantly higher in the MRM group. Tumor size was also larger in the MRM group. LVI was associated with higher tumor grade, HER2 positivity, and larger tumor size. Patients with LVI were less likely to undergo adjuvant chemotherapy. Hormone receptor status was associated with LVI presence.

Conclusion: This study provides insights into breast cancer management in the Jordanian population, emphasizing the impacts of neoadjuvant chemotherapy, LVI, and hormone receptor status on treatment decisions and outcomes.

Keywords: breast cancer, patients' outcomes, oncology

JRMS DECEMBER 2025 VOL 33 (3):10.12816/0062298

INTRODUCTION

Breast cancer has emerged as the most prevalent form of cancer in women and displays considerable heterogeneity at the molecular level. According to GLOBOCAN 2020 data, breast cancer ranks among the most frequently diagnosed cancers globally and is placed as the fifth leading cause of cancer-related deaths. The estimated number of new cases worldwide is approximately 2.3 million. [1], [2] Breast cancer is influenced by a substantial number of risk factors, comprising both modifiable factors (including but not limited to) such as hormonal therapies, physical activity, alcohol and smoking history, and chemical exposure, as well as non-modifiable factors such as female gender, age, previous family history, genetic mutations, and others. [3], [4]

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The treatment for breast cancer typically involves a combination of surgery, radiation therapy, chemotherapy, and hormone therapy. Prognosis and therapy selectioncan be influenced by various clinical and pathological features. Breast-conserving surgery (BCS), often referred to as lumpectomy or wide local excision (WLE), allows for the removal of tumor tissue while preserving the healthy breast tissue, and is often combined with plastic surgery procedures. [5] On the other hand, mastectomy involves the complete removal of breast tissue, and might be followed by breast reconstruction. Despite the apparent benefits of BCS, those who undergo BCS might exhibit a higher likelihood of requiringa subsequent mastectomy. [6] The European Society for Medical Oncology (ESMO) guidelines for breast cancer treatment consider treatment options based on factors such as tumor size, the feasibility of surgery, histology, and the patient's preference for preservation. [7] Lymph node ratio (LNR), which is the ratio of positive lymph nodes to the total number of excised axillary lymph nodes, is seen to be a potential prognostic marker of breast cancer. Inaddition, LNR has been identified as a high-risk feature in patients undergoing mastectomy.[8] Hormone receptors also play a major role in breast cancer, since around 80% of breast cancer patients have been classified asestrogen receptor (ER)-positive, with 65% also being tested positive for progesterone receptor (PR). [9] In this study, we aimed to describe samples of breast cancer collected from the Jordanian population who have undergone WLE&AC or modified radical mastectomy (MRM), and to investigate the association between procedure type and clinicopathological characteristics.

METHODS

Study Design We conducted a retrospective, single-center, observational study to investigate the clinical and demographic characteristics of patients with breast cancer, and to evaluate the association between these factors and the choice of surgical procedure: MRM or WLE&AC during 2007 to 2014 at the King Hussein Medical Center (KHMC).

Additionally, the study assessed the relationship between various pathological features and the presence of lymph vascular invasion (LVI). Patients with no local advancement underwent BCS, while patients with locally advanced tumors, lymph node involvement, and large tumor size underwent neoadjuvant chemotherapy. This study was conducted in accordance with ethical guidelines and was approved by the relevant institutional review board.

DATA COLLECTION

Demographic data were collected for age and sex. Clinicopathological data were collected for the following variables: type of surgical procedure (WLE&AC or MRM), neoadjuvant chemotherapy,sentinel lymph nodes (SLN), adjuvant chemotherapy, tumor focality, histology, size, grade, presence of LVI, presence of perineural invasion (PNI), Paget status, ER status, progesterone receptor status (PR), and Human epidermal growth factor 2 (Her2) status. Imunohistochemical (IHC) staining assays were utilized to determine the status of ER, PR, and HER2 in the samples. For cases with borderline HER2 staining (+2), additional analysis was conducted using fluorescence in situ hybridization (FISH).

STATISTICAL ANALYSIS

Continuous variables were expressed as median, along with first and third quartile (Q1-Q3). Categorical variables were summarized using frequencies and percentages. To investigate the correlation between demographic, clinical, and operative variables with mortality risk-groups, the Wilcoxon (Mann-Whitney U) test was utilized for continuous variables. For categorical variables with a category count of less than 5, the chi-squared (X^2) test or Fisher's exact test was employed. A significant difference was considered if the p-value was less than 0.05. All statistical analyses were performed using R software (version 4.2.3, Vienna, Austria).

RESULTS

A total of 444 samples were included, of which 439 (99%) were females and 5 (1%) were males. The median age was 52.0 (43.0-61.0), whereas 64 (14%) patients were on neoadjuvant hemotherapy. Most patients had grade 2 and 3 tumors, as seen in 216 and 188 (49% and 43%) patients,
respectively. Median tumor size was 3.85 (2.5-5.0) and Paget disease was positive for 32 (7%) patients. HER2 was positive for 85 (19%) patients, while most patients 76% (n=339) were ER-positive, and 318 (71%) were PR positive. Median harvested LNs were found to be 17.0 (13.0-22.0), of which median positive nodes were 2.0 (0.0-7.0) and median LNR was 0.12 (0.0-0.41). Most patients (51% or n=228) had LVI, and 122 (27%) had perineural invasion. **Table 1** shows the clinical and demographic characteristics of all included patients.

Table I: Baseline Characteristics of All Included Samples

Characteristic		N = 4471
Age, Median (Q1-Q3)		52.0 (43.0-61.0)
Sex		
Female		439 (99%)
Male		5 (1.1%)
Neoadjuvant Chemotherapy		64 (14%)
SLN		9 (2.0%)
Type of surgery		
MRM		415 (93%)

MRM		415 (93%)
WLE&AC		30 (6.7%)
Focality		
Left		215 (49%)
Right		228 (51%)
Type		
Cribriform		4 (0.9%)
IDC		371 (84%)
IDC+CRI		1 (0.2%)
ILC		50 (11%)
LCIS		2 (0.5%)
Micropapillary		3 (0.7%)
Mixed		6 (1.4%)
Mucinous		1 (0.2%)
Neuroendocrine		1 (0.2%)
Papillary		2 (0.5%)
Tubular + Cribriform		1 (0.2%)
Grade		
1		33 (7.6%)
2		216 (49%)
3		188 (43%)
Size, Median (Q1-Q3)		3.85 (2.5-5.0)
Positive LNs, Median (Q1-Q3)		2.0 (0.0-7.0)

Total LNs, Median (Q1-Q3)		17.0 (13.0-22.0)
LNR, Median (Q1-Q3)		0.12 (0.0-0.41)
LVI		228 (51%)
PNI		122 (27%)
Paget		32 (7.2%)
ER		339 (76%)
PR		318 (71%)
Her2		85 (19%)
1Mean (SD); n (%)		

The majority of patients (93% or n=415) underwent MRM, whereas 30 (7%) underwent WLE&AC. Tumor grade and focality did not differ significantly across groups, as shown in Table 2. Positive LNs, LNR and tumor size were significantly higher in the MRM group, as shown in **Figure 1A-B**.

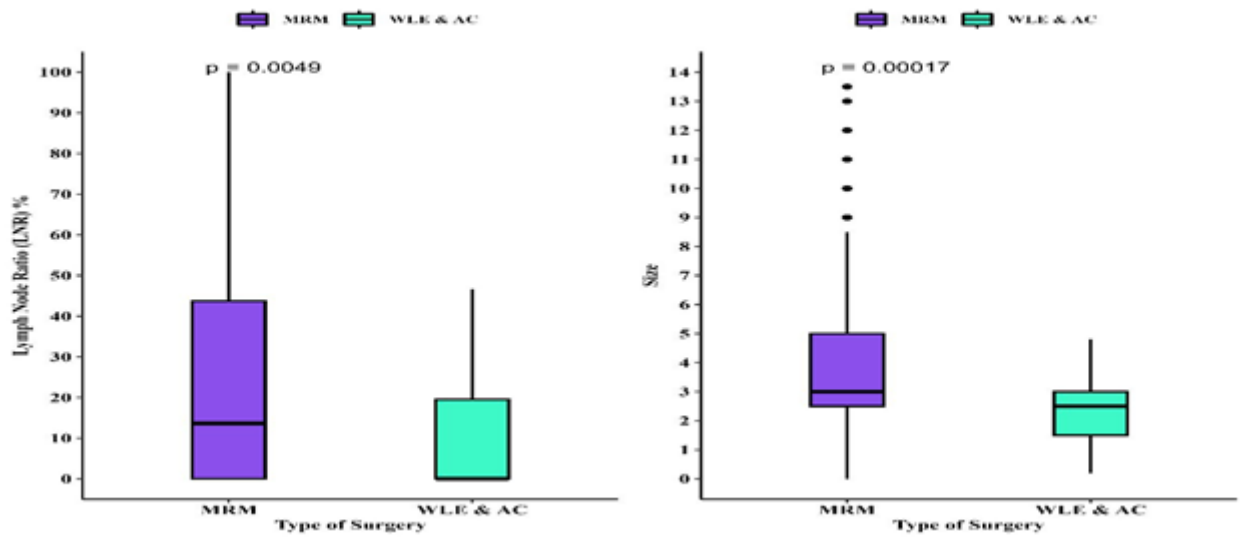

Figure I: Boxplots Showing Pathological Factors Associated with WLE&AC and MRM: A) LNR representing number of positive LNs among the total LNs retrieved was significantly higher among samples who underwent MRM; **B**) Tumor size was significantly larger in MRM patients

Table2:Clinical and Pathological Characteristics of Patients who Underwent WLE&AC and MRM

Characteristic	**MRM**, N = 415*1*	**WLE&AC**, N = 30*1*	**p-value***2*
Age, Median (Q1-Q3)	52.0 (43.00, 61.00)	50.0 (42.50, 61.50)	0.594
Sex			>0.999
Female	409.00 (98.79%)	30.0 (100.00%)	
Male	5.00 (1.21%)	0.00 (0.00%)	
Neoadjuvant Chemotherapy	58.00 (14.01%)	6.00 (20.00%)	0.416
SLN	1.00 (0.24%)	8.00 (30.77%)	<0.001
Focality			0.312
Left	204.00 (49.16%)	11.00 (39.29%)	
Right	211.00 (50.84%)	17.00 (60.71%)	
Histology			0.797
Cribriform	4.00 (0.97%)	0.00 (0.00%)	
IDC	343.00 (83.05%)	28.00 (96.55%)	
IDC+ Cribriform	1.00 (0.24%)	0.00 (0.00%)	

IDC+ Cribriform	1.00 (0.24%)	0.00 (0.00%)	
ILC	49.00 (11.86%)	1.00 (3.45%)	
LCIS	2.00 (0.48%)	0.00 (0.00%)	
Micropapillary	3.00 (0.73%)	0.00 (0.00%)	
Mixed	6.00 (1.45%)	0.00 (0.00%)	
Mucinous	1.00 (0.24%)	0.00 (0.00%)	
Neuroendocrine	1.00 (0.24%)	0.00 (0.00%)	
Papillary	2.00 (0.48%)	0.00 (0.00%)	
Tubular + Cribriform	1.00 (0.24%)	0.00 (0.00%)	
Grade			0.315
I	29.00 (7.11%)	4.00 (13.79%)	
II	201.00 (49.26%)	15.00 (51.72%)	
III	178.00 (43.63%)	10.00 (34.48%)	
Size, Median (Q1-Q3)	3.00 (2.50, 5.00)	2.50 (1.50, 3.00)	<0.001
Positive LNs, Median (Q1-Q3)	2.00 (0.00, 7.00)	0.00 (0.00, 2.75)	0.003
Total LNs, Median (Q1-Q3)	18.00 (13.00, 22.00)	11.50 (7.00, 17.00)	<0.001
LNR, Median (Q1-Q3)	0.13 (0.00, 0.44)	0.00 (0.00, 0.20)	0.005
LVI	214.00 (51.57%)	14.00 (46.67%)	0.604
PNI	112.00 (27.05%)	10.00 (33.33%)	0.457
Paget	31.00 (7.51%)	1.00 (3.33%)	0.713
ER	312.00 (75.18%)	27.00 (90.00%)	0.066
PR	294.00 (70.84%)	24.00 (80.00%)	0.284
Her2	81.00 (19.57%)	4.00 (13.33%)	0.402

[1]Median (Q1-Q3); n (%)

[2]Wilcoxon rank sum test; Fisher’s exact test; Pearson’s Chi-squared test

LVI was seen in 228 (51%) patients, whereas 217 (49%) did not show LVI. The proportion of patients who underwent adjuvant chemotherapy was significantly associated with the absence of LVI, as shown in Table 3. Grade 3 was significantly associated with presence of LVI, whereas grades 1 and 2 were higher in the absence of LVI. Tumor size and LNR were significantly higher in samples with LVI. In addition, perineural invasion was significantly associated with the presence of LVI. The absence of LVI was significantly linked to ER status, representing 80% of cases without LVI (174 cases), while the presence of LVI was associated with 65% of PR-positive cases (148 cases) as shown in **Table 3**.

Table3: Clinical and Pathological Characteristics among Samples with LVI

Characteristic	No, N = 2171	Yes, N = 2281	p-value2
Age, Median (Q1-Q3)	50.00 (43.00, 60.00)	52.00 (43.00, 61.00)	0.549
Sex			0.678
Female	213.00 (98.61%)	226.00 (99.12%)	
Male	3.00 (1.39%)	2.00 (0.88%)	
Neoadjuvant Chemotherapy	26.00 (12.04%)	38.00 (16.67%)	0.165
SLN	3.00 (1.41%)	6.00 (2.63%)	0.506
Type of surgery			0.604
MRM	201.00 (92.63%)	214.00 (93.86%)	
WLE&AC	16.00 (7.37%)	14.00 (6.14%)	
Focality			0.267
Left	99.00 (45.83%)	116.00 (51.10%)	
Right	117.00 (54.17%)	111.00 (48.90%)	

Type			0.096
Cribriform	4.00 (1.85%)	0.00 (0.00%)	
IDC	174.00 (80.56%)	197.00 (87.17%)	
IDC+CRI	0.00 (0.00%)	1.00 (0.44%)	
ILC	26.00 (12.04%)	24.00 (10.62%)	
LCIS	2.00 (0.93%)	0.00 (0.00%)	
Micropapillary	1.00 (0.46%)	2.00 (0.88%)	
Mixed	4.00 (1.85%)	2.00 (0.88%)	
Mucinous	1.00 (0.46%)	0.00 (0.00%)	
Neuroendocrine	1.00 (0.46%)	0.00 (0.00%)	
Papillary	2.00 (0.93%)	0.00 (0.00%)	
Tubular + Cribriform	1.00 (0.46%)	0.00 (0.00%)	
Grade			<0.001
I	27.00 (12.74%)	6.00 (2.67%)	
II	120.00 (56.60%)	96.00 (42.67%)	
III	65.00 (30.66%)	123.00 (54.67%)	
Size, Median (Q1-Q3)	3.00 (2.00, 4.00)	3.50 (2.50, 5.35)	<0.001
Positive LNs, Median (Q1-Q3)	0.00 (0.00, 2.00)	5.00 (1.00, 9.50)	<0.001
Total LNs, Median (Q1-Q3)	17.00 (12.00, 22.00)	18.00 (13.00, 22.00)	0.298
LNR, Median (Q1-Q3)	0.00 (0.00, 0.17)	0.31 (0.07, 0.55)	<0.001
PNI	24.00 (11.11%)	98.00 (42.98%)	<0.001
Paget	7.00 (3.23%)	25.00 (11.06%)	0.001
ER	174.00 (80.18%)	165.00 (72.37%)	0.053
PR	170.00 (78.34%)	148.00 (64.91%)	0.002
Her2	28.00 (12.90%)	57.00 (25.11%)	0.001

DISCUSSION

Breast cancer remains a significant global health challenge, with high prevalence and heterogeneity at the molecular level. Hence, in this study, we have highlighted the prominence of breast cancer in Jordan, where 2.3 million new cases are estimated worldwide, thus making it imperative to understand the factors affecting treatment choices and outcomes. The study has also The study cohort consisted predominantly of females (99%), in line with the higher incidence of breast cancer among women. [10] The mean age of 52 indicates a cohort that spans a range of ages, consistent with the diverse nature of breast cancer demographics. Notably, 14% of patients were on neoadjuvant chemotherapy, highlighting the significance of this treatment modality in managing locally advanced or aggressive tumors. In a study from Jordan of 346 patients who received neoadjuvant chemotherapy protocol, showed a pathologic complete response of 25% of the cases, and it was characterized by the absence of any invasive cancer in the breast tissue at the time of surgery [11]. Since the 1970s, neoadjuvant chemotherapy has been utilized to shrink large or locally advanced tumors, enabling the possibility of breast-conserving surgery and mitigating the need for mastectomy. [12] Esserman et al. in the I-SPY 1 Trial assessed the effect of neoadjuvant chemotherapy upon achieving pathologic complete response (pCR) in breast cancer patients. Their study showed that the highest pCR rate of 45% was seen in HER2-positive patients, whereas the lowest rate of 9% pCR was seen in HER2-negative patients [13],[14].

LVI stands as a significant marker of high tumor aggressiveness in various cancers, showing a significant association to breast cancer with larger tumor size, higher grades, higher TNM staging, and presence of LN metastasis. [15] In concordance with the literature, our findings suggest that patients with LVI showed a significantly higher tumor grade and size, positive HER2 status, and LNR. Ryu et al. found that LVI was associated with a significantly worse prognosis and overexpression of HER2 receptor; further, LVI-positive tumors did not achieve any pCR with regard to neoadjuvant chemotherapy. [16] SLN biopsy was performed in 89% of patients who underwent WLE&AC surgery. Performing a simultaneous SLN biopsy during the primary surgery has been found to significantly spare those patients for whom an initial diagnosis of ductal carcinoma in situ (DCIS) is upgraded to invasive carcinoma upon final histological evaluation, thereby obviating the need for a secondary surgical procedure. [17] In addition, 43% of patients who underwent WLE&AC had adjuvant chemotherapy, whereas 21% of those who underwent MRM needed adjuvant chemotherapy. Bleicher et al. demonstrated in their study of 5,685 non-metastatic breast cancer patients that adjuvant therapy together with neoadjuvant chemotherapy and other factors are associated with prognostic prediction in conservative breast cancer surgeries. [18]

LNR, calculated as the ratio of the total number of positive LNs to the total number of LNs retrieved, is shown to be significantly associated with breast cancer prognosis. In our study, both LNR and a number of positive LNs were significantly higher in patients undergoing MRM. Nonetheless, Saxena et al. discovered that LNR independently predicted breast cancer prognosis post-neoadjuvant chemotherapy, albeit with lesser prognostic efficacy compared to N stage. On the other hand, Kim et al. challenged the prognostic

significance of LNR among patients who had undergone neoadjuvant chemotherapy. Consequently, the prognostic role of LNR for breast cancer patients' post-neoadjuvant chemotherapy remains a subject of ongoing debate.[19], [20], [21] While the results provide valuable information, there exist several limitations to be considered. The study is retrospective, which may introduce biases and confounding factors. Additionally, the single-center nature
of the study could limit the generalizability of the findings to broader populations. The associations between various pathological features and clinical outcomes highlight the importance of considering these factors in treatment planning and prognosis. Further research is warranted to explore the underlying mechanisms driving these associations and to validate the findings in larger, more diverse cohorts.

In conclusion, our study elucidates the complex interplay between clinical and pathological characteristics in breast cancer patients and their potential influence on surgical treatment decisions, particularly between MRM and WLE&AC. Factors such as tumor size, lymph node involvement, and presence of LVI were found to be significantly associated with the choice of surgical procedure, underscoring their importance in clinical decision-making strategies.

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