

# The Relationship between Clinico-Pathological Variables and Axillary Lymph Node Status in Breast Cancer in a Single Cancer Center in Jordan

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## ABSTRACT

**Objective:** To determine the relationship between axillary lymph node involvement and clinico-pathological variables in a single cancer center in Jordan.

**Methods:** This retrospective study was conducted in Al-Hussein Hospital in Amman from Jan 2011 till Jan 2013. This study revised the histopathology reports of 204 patients who all underwent modified radical mastectomy for invasive breast cancer. Various clinico-pathological factors of age, estrogen/progesterone receptor status, tumor size, histological type and grade were statistically correlated with lymph node involvement using contingency tables and P values.

**Results:** Axillary lymph node involvement was noted in 152 (74.5%) with an average of five nodes involved (range 1-41). Mean age was 51.3 years. Around eighty percent of patients were above 40 years old and had involved lymph node whereas only twenty percent were below 40 years with involved lymph node. Average tumor size was 3.5cm with 67.1% between 2-5cm (T2). The most common tumor type and grade was invasive ductal carcinoma (NOS) (170 patients (83.3%)) and grade 2 (119 patient (58.3%)). The Majority of tumors were both ER and PR positive 75%. Tumor grade, size and histological type significantly correlated with lymph node involvement whereas age and receptor status had no significant correlation.

**Conclusion:** The majority of patients in our centre present with node positive breast cancer. In a Jordanian population, as has been demonstrated in the world literature, there is a statistically significant relation between axillary lymph node involvement and tumor, size, grade and type and that age is not an independent predictor for node positivist.

**Key words:** Axillary metastasis, Breast cancer, Lymph node involvement, Prognostic factors.

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### Introduction

Many studies have demonstrated that node positive breast cancer patients have a worse prognosis in comparison to node negative breast cancer patients in terms of five year survival and recurrence. Lymphnode (LN) involvement is the

most important prognostic factor in breast cancer, and may also be a marker of tumor biology indicating a worse phenotype in node positive breast cancers. The question of whether breast cancer in our region differs from breast cancer in Europe and USA in terms of younger patients,

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**Table I:** AJCC 7<sup>th</sup> Ed. Classification

<b>Classification of Invasive Breast Cancer Tumor Type:</b>				
<b>Types</b>	<b>IDC</b>	<b>ILC</b>	<b>Paget disease</b>	<b>Undifferentiated</b>
<b>Subtypes</b>	NOS			
	Medullary with lymphocytic infiltrate			
	Comedo			
	Mucinous			
	Papillary			
	Tubular			
	Scirrhous			
	Inflammatory			
	Other			

**Table II:** Elston-Ellis Score

<b>Score</b>	<b>Tubule formation</b>	<b>Mitotic Count</b>	<b>Nuclear pleomorphism</b>
1	Majority of tumor >75%	0-9 mitosis/ 10 HPF	Small regular uniform cells
2	Moderate degree 10-75%	10-19 mitosis/ 10 HPF	Moderate nuclear size and variation
3	Little or none <10%	20 or > mitosis/10 HPF	Marked nuclear variation
Combined Histologic Grade (Addition of score for each category)			
Low grade (I)		3-5	
Intermediate grade (II)		6-7	
High grade (III)		8-9	

**Table III:** Lymph node involvement

	0 (N0)	1-3 (N1)	4-9 (N2)	>9 (N3)	
Number of Patients	52	69	49	34	204
Total patients with positive LN			152	74.51%	
Total patients with negative LN			52	25.49%	
			204		

smaller tumor size with LN involvement is yet to be answered. This paper studies the relationship of various factors such as age, grade of tumor, size of tumor, histopathological type of tumor, estrogen receptor, progesterone receptor and both receptor combination with LN involvement in Jordanian population. The aim was to find factors that can be adjusted if LN correlation found. Earlier screening age, selective estrogen receptor modulators administration, or probable axillary ultrasound beginning at a certain age may pose benefit in the future for early detection of LN involvement which may influence the prognosis in breast cancer patients in our region.

## Methods

A retrospective study conducted in Al-Hussein Hospital in Amman from Jan 2011 till Jan 2013. Patients who were excluded were patients who underwent previous surgery to the breast or axilla, patients who took neoadjuvant chemotherapy, patients who underwent sentinel LN dissection and patients with skin or chest wall involvement (T4). This study revised the

histopathological reports of 204 cases that underwent mastectomy and axillary clearance for invasive breast cancer. The factors that were correlated with LN involvement were estrogen and progesterone receptor status, tumor size, age of patients, tumor histological type and tumor histological grade. The invasive breast cancer histopathological type classification used was the American Joint Committee on Cancer (7<sup>th</sup> ED) (AJCC) (see Table I). The grading system used was the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system (see Table II). Immunohistochemical staining assays were used for progesterone receptor (PR) and estrogen receptor (ER) status reporting. The statistical analysis used contingency tables and Fisher's exact test for calculating P value for significance. A P value of <0.05 was considered significant with a confidence interval of 95%.

## Results

Out of the 204 cases of breast cancer reviewed, 152 (74.5%) patients had axillary LN involvement (see Table III). The range of LN

involved ranged from 1- 41 LN with an average of 5. Sixty nine (33.8%) patients had 1 to 3 LNs involved (N1), Forty nine (24%) patients had 4-9 LNs involved (N2) whereas only thirty four (16.6%) patients had more than 9 LNs involved (N3). Mean age of patients was 51.3 years (range 26-79 years). Thirty seven patients (18.1%) were below 40 years (see Table IV), while patients aging between forty and sixty and patients over sixty years were one hundred and thirteen (55.4%) and fifty four (26.5%) respectively. Regarding histopathological grade, one hundred and nineteen (58.3%) patients had grade 2 which was the commonest tumor grade (see Table V). The average tumor size was 3.5cm (range 0.2-12cm). Thirty six (17.6%) patients had tumors below 2cm (T1) while 137(67.1%) patients had tumor size between 2 and 5 cm (T2) and only 31(15.1%) patients had a tumor size over 5cm (T3) (see Table VI). One hundred seventy (83.3%) patients had IDC (NOS) which was the most common tumor (see Table VII). As for ER and PR receptor status, most of the tumors were both ER and PR positive in 75% (see Table VIII). There was a significant P value when correlating grade of tumor, size of tumor, and tumor histological type with LN involvement in the study (see Tables V-VII). The most common tumor histological type that had positive axillary LN involvement was IDC (NOS) (see Table VII). The other factors (Age, receptor status) had no significant correlation with LN involvement but noticeably patients with an age group of 40-60years had the highest LN involvement in all age groups and patients with receptors positive (ER, PR) status had more LN involved than patients with receptor negative status. (See Tables VIII-X)

## Discussion

In Jordan, breast cancer is the most common cancer affecting women accounting for 37.4%.<sup>(1)</sup> Treatment consists of surgery to the breast and axilla and may offer a 10 year survival of over 90% if the patients are diagnosed in early stages. Some of the complications of axillary dissection are hematoma, seroma, parasthesia, weakness in the upper limb, wound infection and pain. However, the value of the information from the

excision lies in prognosis, local control and determining the need for chemotherapy afterwards. While in western countries breast cancer with positive nodes constitutes less than 40% of cases due to effective screening and earlier diagnosis, in our study around 75% of patients were found to have positive LN post axillary dissection. The other 25% did not benefit from this procedure and may only endure its complications.

### **Age and LN involvement:** (Table IV)

The patients were divided into 3 groups; patients younger than 40, patients within the age group 40-60 years and patients older than 60 years. One hundred and thirteen patients (55.4%) were in the group 40-60 years. Positive LN was also the highest in this age group (54.6%) but there was no significant relation between age and LN involvement in our study. The notion that most of our diagnosed patients with breast cancer with positive LN are at the same age as when we begin screening poses a question of efficacy of starting screening at the age of 40years. When reviewing the literature, contrasting results are seen in studies correlating age and LN involvement. In a study by Ashturkar *et al.*<sup>(3)</sup> there was no significant relationship between age and race and LN involvement. However, Ivkovic-Kapicl *et al.*<sup>(4)</sup> in 2006, claimed that among patients with breast cancer, younger patients have a higher incidence of axillary nodal metastasis than older patients.

### **Histological Grade and LN involvement:** (see Table V)

Multiple studies have shown an independent prognostic significance of grade in breast cancer.<sup>(5)</sup> It was even combined to LN stage and tumor size in prognostic indices such as in Nottingham prognostic index (NPI) and Kalmar prognostic index (KPI). In NPI, LN stage and grade have equal weight value while in KPI, grade has twice the weight value of LN stage. Others proposed grade to be incorporated in breast cancer staging, however, this was opposed due to concerns regarding its prognostic value in small tumors. In our study, the patients were divided into 3 groups according to the Elston-

**Table IV:** Age & LN involvement

Age	No of cases	+ve LNI	% LN+ve from same category	% LN+ve from Total +ve LN	-ve LNI	P value
<40 years	37	31	83.8%	20.4%	6	NS
40-60 years	113	83	73.5%	54.6%	30	
>60 years	54	38	70.4%	25%	16	
	204	152		100%	52	

**Table V:** Histological grade and LN involvement

Grade	No of cases	+ve LNI	% LN+ve from same category	% LN+ve from total +ve LN	-ve LNI	P value
I	33	21	63.6%	13.82%	12	0.0007 Significant
II	119	82	68.9%	53.94%	37	
III	52	49	94.2%	32.24%	3	
	204	152		100%	52	

**Table VI:** Size of tumor and LN involvement

Size	No of cases	+ve LN	% LN+ve from same category	% LN+ve from total +ve LN	-ve LN	P value
<=2cm (T1)	36	20	55.6%	13.16%	16	0.01 Significant
2-5 cm (T2)	137	106	77.4%	69.74%	31	
>5 cm (T3)	31	26	83.9%	17.10%	5	
	204	152		100%	52	

Ellis score (see Table II). One hundred and nineteen patients (58.3%) had grade II tumors which are tumors with intermediate grade. More than half of those patients (53.94%) had positive LN involved. A strong relation between grade and LN involvement was seen in this study with a significant P value. In a multivariate analysis study by Emad A. *et al.*,<sup>(5)</sup> they found that higher grade of tumor was associated with worse prognosis and shorter disease free survival (DFS) and this was independent of other prognostic variables such as LN stage and tumor size.

**Size of tumor and LN involvement:** (see Table VI)

The patients were divided into three groups according to TNM classification; patients with tumor size below or equal to 2cm (T1), patients with tumor size 2-5cm (T2) and patients with tumor size over 5cm (T3).

More than two thirds of patients had a T2 or T3 tumor size which is a relatively advanced tumor. This can be explained by late presentation by the patient due to social factors, late referral from remote areas or patient assumption that painless breast lumps are not significant for investigation in our cultural beliefs. It is interesting to notice that only 13.6% of patients presented with a small tumor (T1) and LN involvement. This concedes with other studies which report that T1 tumors have less than 18-38.5% rate for axillary LN involvement, while grossly enlarged tumors

have an increased rate of axillary metastasis and those patients have decreased survival.<sup>(3)</sup> In our study, there was a strong relation between size and LN involvement and the P value was significant. In a study by Soerjomataram *et al.*<sup>(6)</sup> it was concluded that tumor size is one of the strongest prognostic indicators even after 20years of follow up and that survival is influenced by tumor size. This was asserted when comparing survival between a group of node negative patients with tumor size 2-5cm and another group of patients with node negative and smaller tumor size(<2cm). The survival was shorter for patients with larger tumor size (T2).

Another study by Webster *et al.*<sup>(7)</sup> in 2005 concluded that larger tumour size was also related to the presence of LN metastases.

**Tumor Histological Type and LN involvement:** (see Table VII)

More than two thirds of cases had IDC tumor type. Eighty six percent of all positive LN involved was of IDC type. Our study showed a strong relation between IDC and LN involvement with a significant P value. Special type tumors (invasive tubular, invasive papillary, invasive mucinous, invasive medullary, mixed) have a favorable outcome and the percentage of LN involved in this group was very low (3.29%). A study Ashturkar *et al.*<sup>(3)</sup> found a significant correlation between histological type and lymphnode involvement where in his study the

**Table VIII:** ER Receptor Status and LN involvement

ER	No of cases	LN+ve	% LN+ve from same category	% LN +ve from total +ve LN	LN-ve	P
ER+ve	176	130	73.9%	85.53%	46	NS
ER -ve	28	22	78.6%	14.47%	6	
	204	152		100%	52	

**Table IX:** PR Receptor Status and LN involvement

PR	No of cases	LN +ve	% LN+ve from same category	% LN +ve from total +ve LN	LN -ve	P
PR+ve	159	115	72.3%	75.66%	44	NS
PR-ve	45	37	82.2%	24.34%	8	
	204	152		100%	52	

**Table X:** Combined Receptor Status and LN involvement

	No of cases	LN+	% LN+ve from same category	%LN + from total +ve LN	LN -ve	P value
ER+ PR +	153	110	71.9%	72.37%	43	NS
ER - PR+	6	5	83.3%	3.29%	1	
ER+ PR-	23	20	87%	13.16%	3	
ER- PR -	22	17	77.3%	11.18%	5	
	204	152		100%	52	

most common tumor correlated with this finding was also IDC.

#### **Receptor Status and LN involvement:**

The patients were classified into 3 groups, the first group combined ER status with LN involvement (see Table VIII). In this group 85% of patients with node positive tumor had a positive ER status; however, there was no significant relation between ER status and LN involvement.

The second group combined PR status with LN involvement (See Table IX). In this group 75% of patients with node positive tumor had a positive PR status; however also, there was no significant relation between PR status and LN involvement. A study by Ali Pourzand *et al*<sup>(8)</sup> in 2011 also did not find a significant relation between ER or PR status and LN involvement, but found a statistically significant relation between negative PR status and human epidermal growth factor 2 (Her2) over expression.

The third group combined ER and PR status with LN involvement (See Table X). In this group, one hundred and fifty three (75%) patients had both receptors positive, of those patients 110 (72.37%) had positive LN involvement. However, our study failed to show a significant relationship between combined ER & PR receptor status and LN involvement. However, a study by Ashturkar *et al*<sup>(3)</sup> showed that negative ER and PR status was significantly associated with low risk of axillary node metastasis.

However, the significance of the ER, PR receptor status remains in predicting the response to hormonal treatment and offers an alternative to patients with positive receptor status whom cannot take chemotherapy.

#### **Conclusions**

The study showed a strong relation between histological grade, histological type, and size of tumor with LN involvement but failed to show a significant relation with receptor status and age. Patient and tumor characteristics noticed in the study were: patients were mostly in the Age group 40-60years, tumor size between 2-5cm (T2), and histological type mostly IDC in over 80%. Seventy five percent of these tumors are ER, PR receptor positive. Our findings if validated by other larger studies may provide better understanding of breast cancer biology in Jordan.

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