Factors Affecting Axillary Lymph Node Involvement in Breast Cancer

Ayman A. Albatanony, (MD)[1]; Asem F. Moustafa, (MD) [1] and Ali G. Hydara, MBBCh[2]

[1]General Surgery Department, Faculty of Medicine, Menoufiya University, Egypt.
[2]General Surgery Department, Tanta Cancer Center, Tanta, Egypt.
alihydara69@yahoo.com

Abstract: Objectives: to detect factors affecting axillary lymph node (LN) metastasis in breast cancer. **Background:** Surgical dissection is the accepted mode of staging the axilla in breast cancer. However, the associated morbidity has led researchers to look at less invasive options so Proper prediction of factors influencing axillary lymph node positivity is very important to detect proper surgical interference **Methods:** This study is a prospective, comparative, randomized and descriptive study it includes 40 patients Certain factors related to the primary tumor recorded including: (tumor size, lymphovascular invasion, body mass index (BMI), family history, histologic type, tumor grade and positivity or negativity for estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor 2 HER2neu) and relation between these factors and percentage of positive axillary lymph nodes recorded. **Results:** there are factors that are highly predicator of axillary lymph node metastasis in breast cancer as age of patient of (p value 0.048) tumors larger than 2cm (p value 0.048). With positive lymphovasularinvasion (p value 0.036). Her 2neu positive tumors (p value 0.011) at upper outer quadrant (p value 0.008) obese patient (p value 0.046). Tumorhistopathology. **Conclusion:** young patients with tumors larger than 2cm with positive lymphovasular invasion Her 2neu positive tumors at upper outer quadrant obese patient tumor lobular carcinoma and mixed ductal and lobular have higher incidence of positive axillary lymph nodes so these factors should be considered in treatment.

Key words: Axilla, axillary node clearance, Breast cancer, Lymph nodes, Palpation.

1. Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in women worldwide, accounting for 23% of total cancer cases and 14% of all cancer related mortalities. Currently, the life time risk of developing breast cancer for women is 1/8. However, more than 40% of the affected patients are currently more than 65 years of age and remarkably, this group accounts for almost 60% of the total deaths from breast cancer. [1]

Axillary lymph node metastases are the single most important prognostic factor for breast cancer survival. [2]

Presence of axillary lymph node metastases is also of vital importance for staging offering local disease-control, and postoperative planning. Axillary lymph node clearance remains the gold standard for evaluating metastases. National guidelines state that ''all invasive breast cancers should have an axillary procedure. [3]

Multiple attempts have been made to identify predictors of axillary nodal involvement that could lead to more selective use of axillary dissection. Several patient and tumor characteristics have been associated with risk of axillary nodal involvement in patients with invasive breast cancer (such as tumor size, lymphovascular invasion, histologic type, tumor grade, age, body mass index, family history, hormone receptor status, and human epidermal growth factor receptor 2 (HER-2)/neu status). Axillary lymph node dissection is the current standard of surgical care to reduce axillary recurrence. The purpose of this procedure is to eliminate any cancer cells that may be residing in these lymph nodes. [4]

The aim of this study to evaluate factors affecting axillary lymph node metastasis as tumor size, lymphovascular invasion, histologic type, tumor grade, age, body mass index, family history, hormone receptor status, and human epidermal growth factor receptor 2 (HER-2)/neu statusand role of these factors in detecting type of axillary surgery and adjuvant treatment.

2. Materials and Methods

A clinical prospective study of 40 patients, each with early breast cancer. They were admitted to Department of General Surgery, Menoufia University and all patients undergo modified radical mastectomy or conservative breast surgery and axillary evacuation. All resected tissues sent to histopathological examination.

Certain factors related to the primary tumor recorded including: (tumor size, lymphovascular invasion, histologic type, tumor grade, body mass

index, family history and positivity or negativity for estrogen, progesterone receptors and HER2neu) this study Inclusion criteria were (Female patients, pathologically proven breast cancer). And Exclusion criteria were (patient who receive any neoadjuvant medication, male breast cancer and number of lymph node dissection less than 10). Informed consents were obtained from all patients included in the study which were approved by the local ethics committee of general surgery department of faculty of medicine Menoufia University. All the patients included in this study were subjected to the following Preoperative assesment (Complete metastatic workup was done Necessary laboratory investigation, imaging study (Plain X-ray, abdominal Ultrasonography and Echocardiography) were done All patients had had Intraoperative assessment of (Operative time, amount of blood loss and injury to axillary vein, thoraco-

dorsal nerve or long thoracic nerve). And Postoperatively assessment of (Time to remove drain, wound infection and seroma formation).

The results had been collected, evaluated, calculated, tabulated and statistically analyzed using a computer statistical package (International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 22.0. Armonk, United States of America: IBM Corp.) with a significant P value ≤ 0.05%.

3. Results
this study include 40 patient 12 patient was less than 45 years old and 28 patient more than 45 years old we found that patient less than 45 years old have high percentage of positive axillary lymph node than patient more than 45 years old and the result is statistically significant (p value 0.048) Table (1).

Table (1): Relation between age (years) and percentage of +ve axillary L.Ns (n = 40)

	Age (years)		MW	P
	≥45 (n = 12)	>45 (n = 28)		
+ve axillary L.Ns Min. – Max. Mean ± SD. Median	3.85 – 100.0 37.68± 35.23 25.0	0.0 – 63.64 17.66± 19.45 12.02	101.5*	0.048*

MW, p: U and p values for Mann Whitney test for comparing between the two groups
*: Statistically significant at p ≤ 0.05

Table (2): Relation between BMI (Kg/m2) and percentage of +ve axillary L.Ns. (n = 40)

	BMI (Kg/m2)		MW	P
	≤25 (n = 23)	>25 (n = 17)		
+ve axillary L.Ns Min. – Max. Mean ± SD. Median	0.0 – 91.43 18.49± 25.07 5.88	0.0 – 100.0 30.66± 27.33 23.81	123.0*	0.046*

MW, p: U and p values for **Mann Whitney test** for comparing between the two groups
*: Statistically significant at p ≤ 0.05

Table (3): Relation between site and percentage of +ve axillary L.Ns (n = 40)

	Site					H	P
	UOQ (n = 10)	LOQ (n = 6)	UIQ (n = 9)	LIQ (n = 6)	Retro areolar (n = 9)		
+ve axillary L.Ns Min. – Max. Mean ± SD. Median	0.0 – 100.0 54.52 ± 33.08 60.77	0.0 – 42.86 25.14 ± 14.94 29.0	0.0 – 33.33 13.70 ± 13.15 5.0	0.0 – 25.0 14.64± 8.86 15.36	0.0 – 15.79 4.37± 5.27 3.85	13.933*	0.008*

H, p: H and p values for **Kruskal Wallis test**   *: Statistically significant at p ≤ 0.05
UOQ: Upper outer quadrant   LOQ: Lower outer quadrant   UIQ: Upper inner quadrant
LIQ: Lower inner quadrant

This study include 40 patient there are 23 patient with body mass index less than 25 and this is the normal body weight and 17 patient with body mass index more than 25 and these are obese patient we found that obese patient have high percentage of positive axillary lymph node than normal body weight patient and the result is statistically significant (p value 0.046) Table (2).

This study include 40 patient there are 10 patient have tumor at upper outer quadrant of breast, 6 at lower outer quadrant 9 at upper inner quadrant 6 at lower inner quadrant and 9 retroareolar we found the higher incidence of positive axillary lymph nodes occur with upper outer quadrant followed by lower outer quadrant and the result is significant (p value 0.008) Table (3).

This study include 40 patient 6 patients of tumor size 2 cm or less and 34 more than 2 cm in size we found that tumor more than 2cm have higher incidence of positive axillary lymph nodes than tumors less than 2 cm this result is statistically significant (p value 0.048). Table (4).

This study includes 40 patient 8 patient ER receptor at their tumor was negative and 32 positive we found that negative tumors have higher incidence of positive axillary lymph nodes than positive but this

statistical result is insignificant (p value0.734) Table (5).

This study includes 40 patient 8 patient PR receptor at their tumor was negative and 32 positive we found that negative tumors have higher incidence of positive axillary lymph nodes than positive but this statistical result is insignificant (p value0.734). Table (5).

This study includes 40 patient 34 patient Her2neu at there tumor was negative and 6 positive we found that positive tumors have higher incidence of positive axillary lymph nodes than negative this statistical result is significant (p value0.011). Table (5).

This study have 40 patient 21 patient do not have lymphovascular invasion at tumor and 19 have lymphovasular invasion we found that presence of lymphovascular invasion increase incidence of positive axillary lymph nodes and this result is statstically significant (p value 0.036) Table (5).

This study have 40 patient 32 patient have tumors of histopathological type invasive ductal carcinoma, 4 invasive lobular carcinoma 4 mixed we found that lobular and mixed type have higher incidence of positive axillary lymph nodes than ductal and this result is statistically significant (p value 0.025). Table (5).

Table (4): Relation between size (cm) and percentage of +ve axillary L. Ns (n = 40)

	Size (cm)		MW	P
	<2 (n = 6)	2 – >5 (n = 34)		
+ve axillary L.Ns Min. – Max. Mean ± SD. Median	0.0 – 15.79 5.09 ± 5.80 4.42	0.0 – 100.0 26.94 ± 27.32 20.09	50.0*	0.048*

MW, p: U and p values for **Mann Whitney test** for comparing between the two groups
*: Statistically significant at p ≤ 0.05

Table (5): Relation between (estrogen receptor (ER), progesterone receptor (PR), Her2neu, lymph vascular invasion, histopathological type, grade and family history) and percentage of +ve axillary L.Ns (n = 40)

		Min. – Max	Mean ± SD	Median	MW or H	P value
Estrogen receptor (ER)	Negative (n = 8)	0.0 – 68.0	25.64 ± 25.91	20.67	118.0	0.734
	Positive (n = 32)	0.0 – 100.0	23.17 ± 26.94	16.23		
Progesterone receptor (PR)	Negative (n = 8)	0.0 – 68.0	25.64 ± 25.91	20.67	118.0	0.734
	Positive (n = 32)	0.0 – 100.0	23.17 ± 26.94	16.23		
Her2neu	Negative (n = 34)	0.0 – 100.0	17.69 ± 20.95	12.02	35.0*	0.011*
	Positive (n = 6)	0.0 – 91.43	57.54 ± 30.50	63.96		
Lymph vascular invasion	No (n = 21)	0.0 – 63.64	13.10 ± 15.16	6.67	122.50*	0.036*
	Yes (n = 19)	0.0 – 100.0	35.34 ± 31.36	31.25		
Histopathological type	Invasive duct carcinoma IDC (n = 32)	0.0 – 100.0	18.30 ± 24.84	8.93	7.349*	0.025*
	Invasive lobular carcinoma ILC (n = 4)	0.0 – 64.29	49.19 ± 17.50	50.0		
	Mixed IDC + ILC (n = 4)	28.0 – 68.0	49.19 ± 17.50	50.38		
Grade	Low (n = 32)	0.0 – 100.0	24.59 ± 27.58	16.23	116.50	0.696
	High (n = 8)	0.0 – 64.29	19.95 ± 22.41	15.36		
Family History	Negative (n = 34)	0.0 – 91.43	22.19 ± 24.77	14.56	83.50	0.481
	Positive (n = 6)	0.0 – 100.0	32.03 ± 36.04	27.50		

4. Discussion

Breast cancer is the most common cancer in women worldwide. It is also the principle cause of death from cancer among women globally. Despite the high incidence rates, in Western countries, 89% of women diagnosed with breast cancer are still alive 5 years after their diagnosis, which is due to early detection and treatment. Axillary node involvement is the most significant and durable prognostic factor for women with breast cancer because nodal metastases double the risk of distant disease and influence therapeutic decisions the use of systemic adjuvant chemotherapy is often determined by the presence or absence of axillary lymph node metastases. Donegan[5]

Multiple attempts have been made to identify predictors of axillary nodal involvement that could lead to more selective use of axillary dissection. Several patient and tumor characteristics have been associated with risk of axillary nodal involvement in patients with invasive breast cancer such as. (Tumor size, lymphovascular invasion, histologic type, tumor grade and positivity or negativity for estrogen, progesterone receptors and HER2). Gill et al [3]

This study includes 40 patients presented with operable breast cancer All Patients undergo modified radical mastectomy or conservative breast surgery and axillary evacuation. All resected tissues sent to histopathological examination. All factors mentioned before related to the primary tumor recorded and relation between these factors and percentage of positive axillary lymph nodes was done.

In our study age is a protective factor for axillary lymph node metastasis. Axillary lymph node metastases decrease in old age explanation of this that Breast cancer is a hormone related disease, and the hormone levels of the body change with age. Mamounas [6]

Breast cancer has a somewhat different biologic behavior in older patients versus younger patients. Advancing age is associated with more favorable tumor biology and the most important that the number of tumor- infiltrating lymphocytes in breast cancer decreases with age. Zavagno et al [7] this result regarding relation between age of patient and percentage of positive axillary lymph nodes agreed with the result of *Ling et al* [8], *Jamal* [9] and Chisthi et al [10] in there study.

In this study mean of percentage of positive axillary lymph nodes is higher in obese patients than in normal body weight patients' explanation of this result that in obese women, aromatization of and rostenedione in the adipose tissue is the major source of estrogen production and this may result in enhanced tumor growth. Furthermore, obese and postmenopausal patients show decreased levels of sex hormone-binding globulin, thus increasing free

estradiol available to target tissues Porter et al [11] and this result agreed with Chisthi et al [10] also controversial results have been obtained. In the Porter and colleagues study, an elevated risk of lymph node metastasis in association with increasing BMI was found Similarly Porter et al [11], in a study of 176 node-positive breast cancer patients, a significantly increased risk of early axillary metastases was found in the obese group Daniell et al [12], Schapira and colleagues also showed more common axillary lymph node involvement in obese postmenopausal patients than in leaner cases with unfavorable prognosis. Schapira et al [13]. Keskinetal in therestudy show no relation between body mass index and axillary lymph node metastasis and this not agreed with this study. Keskin et al [14]

In this study tumors in upper outer quadrant have higher level of axillary lymph node metastasis followed by tumors at lower outer quadrant, and the explanation of this that These findings appear consistent with the anatomy of lymphatic drainage in the breast; tumors in the inner quadrants are more likely to have alternative drainage to the internal mammary chain. *Olivotto* et al [15].

Chisthi et al [10] agreed with this study but Brenin et al [16] Study says that there is no significant relation between site of tumor and axillary lymph node metastasis.

In this study tumors larger than 2cm have higher incidence of axillary lymph node metastasis than tumors less than 2 cm in size explanation of this is that large size of tumor reflects the size of the invasive component and small tumors may have insitu component also larger tumors may predict node positivity because of occult histologic lymphatic invasion. Brenin et al [16] This statistical result agreed with Abner et al [17] in there study but Chisthi et al [10] says that there is no relation between size and axillary lymph node metastasis.

In this study estrogen and progesteron receptor negative tumors has more axillary lymph node metastasis than estrogen and progesterone positive patients but in our statistical result are not significant explanation of this that ER and PR receptor have role in transcriptional activation of the genes required for tumor growth Harrell et al [18] and Nouh et al [19] agreed with our study but [20], [4] and Donegan [5] not agreed with our study.

In this study Her 2neu expression is an important predicator for positivity of axillary lymph nodes and explanation of this that Her 2neu is a member of the epidermal growth factor receptor family that is involved in the regulation of cell growth, proliferation, and differentiation of tumor cells Positive expression in cancer cells indicates strong proliferative ability, rapid disease progression it is therefore an important

early indicator of poor prognosis and metastasis of breast cancer Harrell et al [18]. Chisthi et al [10] and Elsayed et al [21] agreed with our study but Almasri et al [22] in there study say that Her 2neu expression not significant at axillary lymph node metastasis.

In this study lymphovascular invasion is an important predicator for axillary lymph node metastasis and explanation of this that cancer cell emboli move in bulk through lymphovascular system to LN Harrell et al [18].

Chisthi et al [10], and Barth et al [23] agree with this study but Chu et al [24] reported that lymhovascular invasion statistically insignificant regard axillary lymph node metastasis.

In this study mean of positive axillary lymph nodes increase in lobular carcinoma and mixed lobular and ductal more than in ductal carcinoma and the explanation of this statistical result that It has been demonstrated that loss of expression of the cell–cell adhesion molecule E-cadherin in invasive lobular carcinoma (ILC) may decrease adhesiveness of cells and facilitate this type of infiltration *Lehr et al* [25] The morphologic features of lobular carcinoma differ from those of ductal carcinoma. ILC is characterized by small, round cells that are bland in appearance and have scant cytoplasm, which infiltrate the stroma in single file and surround benign breast tissues in a targeted manner *Li* et al [26] Infiltration typically does not destroy anatomic structures or incite a substantial connective tissue response. By virtue of their distinctive growth pattern and biology, lobular carcinomas often fail to form distinct masses that can easily be diagnosed by palpation or mammography. This can make early diagnosis challenging *Yeatman* et al [27]. Lobular carcinomas may have increased risk for multifocal and multicentric distribution, bilaterality and for metastatic spread to axillary lymph node and distant metastasis *Toikkanen et al* [28]. Chisthi et al [10] agree with this study but Gill et al [3] not agreed with this study as his study reported that incidence of axillary lymph node metastasis increase in ductal than in lobular and mixed carcinoma.

In this study statistical analysis reported that incidence of axillary lymph node metastasis increase in tumor grade 2 than in tumor grad 3explanation of this that grade 2 tumors cells tend to be slow growing which may indicate that the invasive tumor growth cycle is longer and this increase opportunity of lymphovascular invasion. Liu et al [29] but in our study this statistical result is not significant. Some studies agreed with this as Chisthi et al [10] and other studies not agreed with this in statistical analysis of their study as *Jamal* [9].

In this study positive family history is predicator for positivity of axillary lymph node but this statistical result is not significant and the explanation of this that small subset of women with positive family histories have germ line mutations linked to metastatic propensity. *Yeatman* et al [27]. Some studies agree with this result as Harrell et al [18] but Chisthi et al [10] not agreed.

Conclusion

In conclusion this study reported factors that are highly predicator of axillary lymph node metastasis in breast cancer as young age of patient tumors larger than 2cm with positive lymphovasular invasion Her 2neu positive tumors at upper outer quadrant obese patient tumor lobular carcinoma and mixed ductal and lobular so these factors should be considered in type of surgery, axillary evacuation neoadjuvant chemotherapy adjuvant treatment.

Correspondence Author:
Name: Ali Gamal Hydara, MBBCh.
Address: Tanta, Gharbyia governorate, Egypt.
E-mail address: alihydara69@yahoo.com

References
1. *Siegel, R.; Ma, J.; Zou Z.; Jemal*, A. Cancer statistics. *CA Cancer J. Clin.*2014,*64*, 9–29.
2. Vinh-Hung V, Verschraegen C, Promish DI. Ratios of involved nodes in early breast cancer. Breast Cance Res 2004;6: R680–8.
3. Gill PG, Luke CG, Roder DM. Clinical and pathological factors predictive of lymph node status in women with screendetectedbreast cancer. The Breast 2006;15:640–8.
4. *Yip CH, Taib NA, Tan GH: Predictors of axillary lymph node metastases in breast cancer: Is there a role for minimal axillary surgery? World J Surg2009. 33:54–57.*
5. Donegan WL. Tumor-related prognostic factors for breast cancer. CA Cancer J Clin1997; 47:28–51.
6. Mamounas EP. Age and lymph node status in breast cancer: not a straightforward relationship. (2009) *J Clin Oncol*, 27, 2900-1.
7. Zavagno G, Meggiolaro F, Pluchinotta A: Influence of age and menopausal status on pathologic and biologic features of breast cancer. Breast2000 9:320-328,.
8. *Ling Li and Li-Zhang Chen. Factors Influencing Axillary Lymph Node Metastasis in Invasive Breast Cancer Asian Pacific Journal of Cancer Prevention,2012. Vol 13*.
9. *Jamal K. AL-Qaisy*. Factors Predicting Positive Axillary Lymph Nodes Metastasis in Primary Breast Cancer in Women Anb Med J Vol.10 No.2 Spt. 2012; 62-68.
10. Chisthi MM, Kuttanchettiyar KG. Clinico - pathological profile of axillary lymph node status

in early breast carcinoma - a tertiary care centre experience. Int Surg J 2016;3:776-80.

11. Porter GA, Inglis KM, Wood LA, Veugelers PJ. Effect of obesity on presentation of breast cancer. Ann Surg Oncol2006;13:327-332. 9.

12. Daniell HW, Tam E, Filice A. Larger axillary metastases in obese women and smokers with breast cancer an influence by host factors on early tumor behavior. Breast Cancer Res Treat 1993;25:193-2010.

13. Schapira DV, Kumar NB, Lyman GH, Cox CE. Obesity and body fat distribution and breast cancer prognosis. Cancer 1991;67:523-528.

14. O. Keskin, S. Aksoy, T. Babacan, F. Sarici, N. Kertmen, M. Solak, *et al*, Obesity and nodal status in breast cancer JBUON 2013; 18(4): 826.

15. *Olivotto IA, Jackson JS, Mates D. Prediction of axillary lymph node involvement of women with invasive breast carcinoma: a multivariate analysis. Cancer 1998; 83: 948–55.*

16. Brenin D R, Manasseh D, El-Tamer M, Troxel A, Schnabel F, Ditkoff B A, et al. Factors correlating with lymph node metastases in patients with T1 breast cancer. Ann Surg Oncol2001;8(5):432-7.

17. Abner AL, Collins L, Peiro G, Recht A, Come S, Shulman LN, et al. Correlation of tumour size and axillary lymph node involvement with prognosis in patients with T1 breast carcinoma. Cancer 1998;83:2502-8.

18. Harrell JC, Dye WW, Allred DC. Estrogen receptor positive breast cancer metastasis: altered hormonal sensitivity and tumor aggressiveness in lymphatic vessels and lymph nodes. Cancer Res 2006;66:9308–15.

19. Nouh, M.A.; Ismail, H.; El-Din, N.H.; El-Bolkainy, M.N. Lymph node metastasis in breast carcinoma: Clinicopathological correlations in 3747 patients. *J. Egypt. Natl. Cancer Inst.* 2004, *16*, 50–56.

20. Chua B, Ung O, Taylor R. Frequency and predictors of axillary lymph node metastases in invasive breast cancer. ANZ J Surg2001;71:723–8.

21. Elsayed M Ali1, Ahmed R. H. Ahmed2, Ayman M. A. Ali3 Correlation of Breast Cancer Subtypes Based on ER, PR and HER2 Expression with Axillary Lymph Node Status Cancer and Oncology Research 2014,2(4):51-57.

22. Almasri, NM and Al Hamad M. Immunohistochemical evaluation of human epidermal growth factor receptor 2 and estrogen and progesterone receptors in breast carcinoma in Jordan. Breast Cancer Res2005.,7:598-604.

23. Barth A, Craig PH, Silverstein MJ. Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. Cancer.1997;79:1918-22.

24. Chu KU, Turner RR, Hansen NM, Brennan MB, Bilchik A, Giuliano AE. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? Ann Surg. 1999;229:536-41.

25. *Lehr HA, Folpe A, Yaziji H, Kommoss F, Gown AM. Cytokeratin 8 immunostaining pattern and E-cadherin expression distinguish lobular from ductal breast carcinoma. Am J Clin Pathol.2000, 114: 190-196.*

26. *Li CI, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE. Changing incidence rate of invasive lobular breast carcinoma among older women. Cancer.2000, 88: 2561-2569. 10.1002/1097-0142(20000601)88:11<2561: AID-CNCR19>3.3. CO;2-O.*

27. *Yeatman TJ, Cantor AB, Smith TJ, Smith SK, Reintgen DS, Miller MS, et al. Tumor biology of infiltrating lobular carcinoma. Implications for management. Ann Surg. 1995, 222: 549-559. discussion 559–561.*

28. *Toikkanen S, Pylkkanen L, Joensuu H. Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma. Br J Cancer.1997, 76: 1234-1240.*

29. Liu S, Dontu G, Mantle ID. Hedgehog signaling and Bmi-1 regulate self-renewal of normal and malignant human mammary stem cells. Cancer Res 2006;66: 6063–71.

6/6/2017