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Lymph Node Metastasis in Breast Carcinoma: Clinicopathologic Correlations in 3747 Patients

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ABSTRACT

Background: Histological axillary node involvement (ANI) evaluated by axillary dissection remains the most accurate predictive factor for patients with invasive breast cancer. Axillary node involvement implies the necessity of systemic adjuvant treatment and locoregional irradiation.

Aim of the study: Is to detect the relative frequency of node positivity in relation to histopathology through studying a large mastectomy series.

Material and methods: This study included 3747 mastectomy specimens performed at NCI Cairo in the period 1993-2003. In each case we assesed the age at time of diagnosis, pathologic tumor size and number, histologic subtype (including grade), tumor location, number of lymph nodes dissected and number of positive nodes (burden of node positivity).

Results: Females constituted 96.8% of cases, 60.7% of them were premenopausal. The mean age was 47.1±10.5 years. Tumor size ranged from 0.5 to 20 cm. The global ANI rate in the entire cohort was 70.6%. In univariate analysis, five variables were significantly correlated to ANI, these were laterality, multiplicity, tumor size, histologic subtype and grade, while multiplicity, tumor size, histologic subtype and grade correlated significantly with metastatic burden. Multivariate analysis showed that older women (40-60 and > 60 years) have at least half the risk of developing LN metastasis compared to those < 40 years with the odds of 0.51 (0.35-0.73) and 0.31 (0.18-0.55), respectively. Tumor size > 2 cm put the women with breast cancer at 3 (if 2 -5 cm) to 9 (if > 5 cm) folds of developing lymph node (LN) metastasis. Tumor size > 5 cm increases the likelihood of higher metastatic burden (> 3 +ve nodes) with odds of 1.5 (1.24-1.9). Unfavorable histology also, increases the liklihood of more positive nodes to the double when compared to favourable histology.

Conclusions: The results of this study reflected the unfortunate presentation of breast cancer patients. In addition, some factors could be used as useful guidlines in the management of those patients. These factors include age, tumor size and histologic type of the tumor.

Key Words: *Breast cancer - Mastectomies - Axillary lymph node metastatses - Burden of node positivity - Favorable - Unfavorable histology.*

INTRODUCTION

Breast cancer is the most common cause of cancer deaths among women worldwide. Incidence rates are high in more developed countries, whereas, rates in less developed countries and in Japan are low but are lately increasing [1]. It is the most common malignancy in females and is second only to lung cancer as a cause of cancer death in females. In Egypt, breast cancer is the most common cancer in females constituting 33% of all female cancers [2].

The natural history and prognosis of primary breast cancer vary considerably from patient to patient. Some patients present with very indolent disease and are either cured by local therapy or survive for many years even after developing metastasis. In other patients, the disease follows an aggressive, rapidly progressive course that is refractory to treatment. This heterogeneity in the clinical course of breast cancer is mirrored by great variability in many parameters [3].

Lymph node (LN) involvement is the most common important prognostic factor in the absence of distant metastasis. Node positive patients, who constitute 25-40% of the cases, in the west, have poor prognosis when compared to node negative breast cancer patients. However, up to 30% of node negative breast cancer will recur after five to ten years of their initial diagnosis [4,5]. This work aims at determining the relative frequency of node positivity in relation to some clinical and histopathologic parameters through studying a large series of mastectomies.

MATERIAL AND METHODS

A total of 3755 mastectomies were performed at the National Cancer Institute (NCI), Cairo University, in the period from 1993 to 2003. Eight cases were excluded from this study being sarcomas. Retrieval of clinical and pathological data from the computer data-base of the surgical pathology unit for the 3747 patients were performed. Clinical data included age, sex and laterality of breast involved. Pathologic data included histopathologic type, size of the tumor, number of tumors, grade and LN status. T was followed according to the TNM, UICC (T1 tumors ≤ 2 cm, T2 > 2-5 cm and T3 tumors > 5 cm). Nodal metastatic burden divided the cases with positive LNs into two groups: a group with ≤ 3 positive LNs and a second group with > 3 positive LNs. Micrometastasis was defined when the LNs showed metastatic deposits less than 2 mm.

Statistical analysis: Univariate analysis was performed using Chi-square and Fisher's exact tests for testing proportion independence. In the multivariate logistic regression analysis we used one model with backward regression for LN status as an outcome variable and another for metastatic burden as the dependent variable. Odds ratio (OR) calculated the relative risk of either having positive nodes or higher metastatic burden. p value was considered significant if ≤ 0.05.

RESULTS

Out of the 3747 cases analyzed, 3628 were females (96.8%) and 119 were males (3.2%). Age of the patients ranged from 15 to 87 years. The mean age of females was 47.0±10.4 years and of males was 50.4±11.6 years. Two thousand one hundred and thirty six (58.9%) of the female patients were below the age of 50 years and were considered premenopausal, while, 1491 cases (41.1%) were 50 years or older and were considered postmenopausal. In 1527 cases (40.8%) lumpectomy was performed prior to mastectomy with no residual tumor left in the breast. The majority of cases (2145, 57.3%) were presenting by a single tumor. Only 113 cases (3.1%) showed multiple tumors. The average tumor size was 2.8±3.0 cm with a range of 0.5-20.0 cm and a median of 3 cm. Out of the 3747 cases, 38 (1.0%) were carcinoma in situ; of these 36 were ductal and 2 were of the lobular type. Cases categorized as favorable histology were 139 (3.7%), while, the unfavorable histology included 3570 cases (95.2%). The relative frequency of different histopathologic types are detailed in (Table 1).

The LN, metastasis was evident in 2646 (70.6%) of the total cases, while 1101 cases (29.4%) were free of metastasis.

Node positivity was not correlated to menopausal status ($p = 0.2$). In a univariate analysis, when stratifying our study group into categories < 40 years, 40-60 years and > 60 years a significant difference in LN positivity was found. The younger age group had the highest positivity (74.5%) compared to 69.8% and 67.7% in the older groups respectively, $p = 0.02$ (Table 3). On multivariate analysis with LN positivity as the dependent variable, age of the patients was found to influence LN positivity. The liklehood (odds) of having positive nodes in patients aged 40-60 years and > 60 years compared to those < 40 years was 0.51 (0.35-0.73) and 0.31 (0.18-0.55), respectively and $p < 0.001$.

Laterality of breast cancer was found to be correlated to node positivity on both univariate and multivariate analysis (Tables 3,5).

Size of tumor appears to be a determintal factor in LN metastasis. In this series; 71.6% of T1 tumors metastasized to LN and increased to 75.4% in T2 tumors and 85% in T3 tumors ($p < 0.001$) (Table 3).

Mastectomies with a single tumor were more negative for LN metastasis (24.1%) than mastectomies with multiple tumors (12.4%) (Table 3).

Node metastasis was evident in 36% (50 cases) of the favorable histology group. Unfavorable histology, had LN metastasis identified in 2593 cases (72.6%) (Table 2). Applying a univariate analysis, the difference was highly significant ($p < 0.001$) (Table 3). On multivariate analysis, histology was not correlated to LN positivity (Table 5).

Node positivity showed marked increase with the increase of tumor grade, as 49.3% of grade 1 tumors were node positive compared to 72.4% of grade 2 and 76.8% of grade 3 ($p < 0.001$) (Table 3). Grading system was not applicable in 357 cases of breast carcinoma and was not available for 8 cases.

Metastatic burden was neither statistically different among pre and postmenopausal patients nor among different age categories by both univariate (Table 4) and multivariate analysis (Table 6). Similarly, no significant relation was observed between laterality and metastatic burden.

Again, the node metastasis burden was higher in mastectomies with multiple tumors with borderline significance, $p = 0.06$ (Table 4).

About 62% of T1 tumors metastasized to >3 LN in contrast to 74.3% of T3 tumors ($p < 0.001$) (Table 4). In Tables (5,6) T stage sustained its effect on both LN positivity and metastatic burden with tumors > 5cm having about 9 folds probability of positivity and 1.5 folds of > 3 positive nodes compared to those ≤ 2cm.

The nodal metastatic burden was different among the carcinoma in situ, favorable and unfavorable histology groups. None of the carcinoma in situ cases showed LN affection of more than 3 LNs. This is in contrast to 46% of the favorable histology and 62.8% of the unfavorable histology cases that showed positivity in more than 3 LN ($p = 0.004$) (Table 4). On multivariate analysis, the likelihood of having > 3 positive nodes was 2.2 (1.1-4.3) with unfavorable histology compared to favorable one (Table 6).

A progressive increase was observed when comparing node metastasis burden versus tumor grade. Fourty seven percent of node positive grade 1 tumors showed involvement of >3 LNs. Node positive grade 2 and 3 tumors metastasized to >3 LNs in 62% and 66% of cases, respectively ($p = 0.059$) (Table 4).

Table (1): Relative frequency of histopathologic types in 3747 mastectomy cases.

Item	No.	%
Carcinoma in situ:	(38)	(1.01)
Ductal	36	0.96
Lobular	2	0.05
Favorable histology:	(139)	(3.71)
Medullary	55	1.47
Mucinous	51	1.36
Intracystic papillary	15	0.40
Cribriform	9	0.24
Tubular	4	0.11
Adenoid cystic	3	0.08
Secretory (juvenile)	2	0.05
Unfavorable histology:	(3570)	(95.28)
Invasive duct	3298	88.02
Invasive lobular	191	5.10
Paget's	49	1.31
Undifferentiated	10	0.27
Mixed invasive and lobular	9	0.24
Signet ring adenocarcinoma	9	0.24
Apocrine carcinoma	3	0.08
Adenosquamous	1	0.03

Table (2): Relative frequency of nodal metastasis in relation to histopathologic type.

Item	No.	%
Carcinoma in situ	3	7.9
Favorable histology:	(50)	(36.0)
Medullary	17	30.9
Mucinous	16	31.4
Intracystic papillary	7	46.7
Cribriform	4	44.4
Tubular	2	50.0
Adenoid cystic	2	66.7
Secretory (juvenile)	2	100.0
Unfavorable histology:	(2593)	(72.6)
Invasive duct	2405	72.9
Invasive lobular	138	72.3
Paget's	30	61.2
Undifferentiated	5	50.0
Mixed invasive and lobular	5	55.6
Signet ring adenocarcinoma	7	77.8
Apocrine carcinoma	2	66.7
Adenosquamous	1	100.0

Table (3): Lymph node positivity in relation to some clinicopathologic parameters#.

Item	No.	% node +ve	*p* value
Sex:			0.07
Male	119	63.0	
Female	3628	70.9	
Menopausal status:			0.21
Premenopausal	2136	71.6	
Postmenopausal	1491	69.5	
Age categories:			0.02*
< 40	793	74.5	
40-60	2481	69.8	
> 60	353	67.7	
Laterality:			< 0.001**
Right	1609	99.1	
Left	1799	40.7	
Bilateral	20	0.0	
Tumor size:			< 0.001**
T1	317	71.6	
T2	1248	75.4	
T3	655	85.0	
Multiplicity:			0.006**
Single tumor	2145	75.9	
Multiple tumors	113	87.6	
Histology:			< 0.001**
In situ carcinoma	38	7.9	
Favorable histology	139	36.0	
Unfavorable histology	3570	72.6	
Histopathologic grade:			< 0.001**
Grade I	69	49.3	
Grade II	2822	72.4	
Grade III	499	76.8	

* p is significant ≤ 0.05 and **highly significant ≤ 0.01.
# Data regarding age was not available in 120 cases, laterality in 319 cases, size of tumor in 1527 cases with lumpectomies prior to mastectomy and grade was not available in 357 cases.

Table (4): Nodal metastatic burden in relation to some clinicopathologic parameters.

Item	No. of node +ve cases	1-3 +ve nodes %	> 3 +ve nodes %	*p* value
Sex:				0.61
Male	75	34.7	65.3	
Female	2566	37.5	62.5	
Menopausal status:				0.49
Premenopausal	1522	37.1	62.9	
Postmenopausal	1034	38.4	61.6	
Age categories:				0.27
< 40	590	35.3	64.7	
40-60	1727	37.9	62.1	
> 60	239	41.0	59.0	
Laterality:				0.12
Right	1594	38.8	61.2	
Left	728	35.4	64.6	
Tumor size:				< 0.001**
T1	225	35.8	62.2	
T2	941	36.2	64.2	
T3	556	25.7	74.3	
Multiplicity:				0.06
Single tumor	99	24.2	75.8	
Multiple tumors	1626	33.5	66.5	
Histology:				0.004**
In situ carcinoma	3	100.0	0.0	
Favorable histology	50	54.0	46.0	
Unfavorable histology	2588	37.1	62.9	
Histopathologic grade:				0.06
Grade I	34	52.9	47.0	
Grade II	2038	38.0	62.0	
Grade III	382	34.0	66.0	

Table (5): Stepwise logistic regression results for variables that significantly correlated to lymph node status (being positive).

Variables in the equation					
Variable	*ß*	S.E.	*p* value	OR	(95% CI)
Age < 40 years:					
(40-60)	-0.6792	0.1838	0.0002	0.51	(0.5-0.73)
> 60 years	-1.1615	0.2846	0.0000	0.31	(0.18-0.55)
Left side	-4.7561	0.3685	0.0000	0.009	(0.004-0.02)
Tumor size ≤ 2 cm:					
2-5 cm	1.3266	0.4202	0.0016	3.77	(1.65-8.59)
> 5 cm	2.1931	0.4355	0.0000	8.96	(3.82-21.0)
Constant	3.9712	0.5352	0.000		

ß stands for regression coefficient, SE = Standard error, CI = Confidence interval, *p* is significant at 0.05 level, OR = Odds ratio (relative risk of node positivity).

Table (6): Results of logistic regression analysis for variables that significantly correlated to metastatic burden (> 3 +ve nodes).

Variables in the equation					
Variable	*ß*	S.E.	*p* value	OR	(95% CI)
Unfav. histology	0.7723	0.3497	0.03	2.2	(1.10-4.3)
Tumor size > 5 cm	0.4269	0.1000	< 0.001	1.5	(1.24-1.9)
Constant	-2.5505	1.0735	0.02		

Unfav = Unfavorable.

DISCUSSION

Axillary node involvement (ANI) remains to be an essential prognostic factor for breast cancer patients as it implies the necessity of systemic adjuvant treatment and locoregional irradiation [6]. Axillary dissection itself contributes to improve local disease control and may increase survival, however, it is not a hassle free procedure since 20-25% of patients undergoing this procedure will suffer from long term side effects. The fact that the prevelance of screening and imaging techniques resulted in the diagnosis of breast cancer while the primary lesions are small, increased the demand for a predictive index of ANI in operable breast cancer [6,7].

One of the points which is not clearly identified is the relation of tumor histologic type to the subsequent risk of ANI. Reviewing a large mastectomy series may enlighten this aspect and subsequently verifies its independent relevance to ANI. In this study, ANI was observed in 70.6% of the cases. This is a very high figure if compared to large cohort studies as that done by Olivotto [8] and his colleagues on 4660 cases and reported a 35.5% positivity rate. Similarly, Chua et al. [9] reported a 41% positivity rate. However, a comparable high rate of ANI positivity (64%) was reported by De Laurentiis et al. [7] who studied 2076 patients with operable breast cancer.

The highest node positivity was observed in secretory, adenosquamous, signet ring ductal and lobular carcinomas in a descending order where it varied between 100% and 72.3%. With the exception of juvenile (secretory) carcinomas, all other histologies are considered unfavorable. Van Hoeven and his collegues [10] found that in low grade adenosquamous carcinoma, LN metastasis was extremely rare. While, 10-15% of pure squamous cell carcinomas have axillary node metastasis. Nineteen to 25% of those with chondro-osseous elements have axillary node metastasis [11]. Though, the only 2 cases of secretory carcinoma in this study showed LN metastasis, other studies found metastasis in 15% of their cases [12].

When lumped together, breast cancer cases with favorable histology showed node positivity rate which was half that of the unfavorable histology group, 36% and 72.2%, respectively. Carcinoma in situ showed node positivity in only 7.9% of cases. Ductal carcinoma remains to be the most common histologic type, in this series, it constituted 88.8%, while others reported a range of 40 to 75% [13]. Olivotto et al. [8] in their study on 4660 cases divided their cases only into ductal, lobular and others. They showed a higher node positivity rate in lobular carcinoma compared to ductal carcinoma. This was not the case in the present study, where both ductal and lobular carcinomas showed an almost equal increased ANI rates of 72.9% and 72.3%, respectively. However, Cutuli et al. [6] showed more ANI rates in ductal carcinoma compared to lobular carcinoma (27.5% and 22.7%, respectively) in their study on 893 patients with tumors less than 3 cm. Similarly, a lower frequency of axillary nodal metastasis in invasive lobular carcinoma than in invasive duct carcinoma has been reported in several series, with a difference ranging from 3 to 10% [14,15]. Only 4 cases of tubular carcinoma were reported in this series, 2 of which showed node metastasis. It has been recently reported that in tubular carcinoma, ANI occurs infrequently and when observed, rarely involves more than one axillary LN. There is little adverse effect of node positivity in tubular carcinoma [16]. The lowest rate of node positivity was observed in medullary and mucinous carcinomas (30.9% and 31.4%, respectively), both of which were of favorable histology. This is supported by the work of De Laurentiis et al. [7] who identified these 2 tumor types as being low risk with respect to node metastasis. Yet, the outcome of medullary carcinoma associated with more than 3 metastatic axillary LNs was reported to be poor or not different from that of common ductal carcinoma [13]. In other studies, less than 10% of medullary carcinoma presented with node metastasis [17]. In pure mucinous carcinoma, 3-5% metastasized to LNs compared to 33-46% of the mixed variant [18].

Tumor grade appeared to play an important role in predicting LN positivity rate. Grade 1 tumors showed a node positivity rate of 49.3% compared to 86% of grade 2 and 3 tumors.These results are in concordance with the results of Olivotto et al. [8], Recht & Houlihan [19] and Chua et al. [9].

In this study, tumor size exerted its effect on node positivity despite tumor histology or

grade. Node positivity increased progressively from 62.3 to 85% with the progression of stage from T1 to T3. These results agreed with the findings of Cutuli et al. [6], De Laurentiis et al. [7] and Olivotto et al. [8].

In the present study, the number of tumors also played a role in predicting node positivity. Patients with multicentric tumors appeared to be at a higher risk of developing node metastasis compared to those with a single tumor. The same results were previously reported by De Laurentiis et al. [7]. Chua et al. [9] stated that multicentricity is an independent predictor of node metastasis in breast cancer. The same finding was recently reconfirmed by the study of Andea et al. [20].

Since constitutional delay of menopause is prevalent in our country, a cutoff value of 50 years was used to identify pre and post menopausal populations in this work as actual data regarding menopausal status were dominantly deficient in NCI records. Using this cutoff value, node positivity was almost equal in both groups. This was in contrast to the findings of Olivotto et al. [8] who found statistical significant difference between the two groups, in favor of the post menopausal status. In other studies [6], a slight decrease in the incidence of node metastasis was observed with advancement of age using 40 and 60 years as stratification lines. However, Bonnier et al. [21] supported our finding that menopausal status is not a determinant of ANI. In the latter study done on 1266 patients, 37 and 70 years were used as age stratification lines and the difference of node positivity in the 3 groups despite showing a slight progressive decrease with advancement of age, was not statistically significant.

The fascinating finding in this study was the relation of tumor laterality to node positivity. Left side breast cancer was less prone to give node metastasis in comparison to right side breast cancer. It could be explained by the relative excess movement of the right arm with pumping action of tumor cells to the axillary lymphatics.

Tumor histology appeared not only to predict node positivity, but, also to affect the extent of node involvement. Unfavorable breast cancer histology was associated with a heavier axillary LN metastatic burden compared to favorable histology and carcinoma in situ groups. To the best of our knowledge, this association was not explored in previously published studies. A similar association was observed between tumor size and nodal metastatic burden. A weaker association which was close to, but not reaching the significance level was observed between tumor histopathologic grade and tumor multiplicity. However, Rosen et al. [22] stated that tumor histologic grade was not significantly associated with number of positive LN in their study on 644 patients with N0 and N1 breast cancer.

The present study comprised the largest series of breast cancer cases from the principle cancer care institution in Egypt. It emphasized the low incidence of early detected breast cancer cases as 1.1% were carcinoma in situ, 14.3% were T1 stage and 4.1% were T1 with negative nodes. The unfortunate high tumor burden at presentation was reflected in average tumor size (median of 3 cm) as well as high average number of positive nodes per case (70%). The previous findings put breast cancer as a priority problem which necessitates early detection and public education.

In conclusion, breast cancer patients with age younger than 40 years and with tumor size greater than 2 cm are at more risk of having lymph node metastasis. The burden of metastasis becomes higher if she had a tumor size > 5 cm and if it is of unfavorable histologic type. The above mentioned risk factors could serve as useful guidlines in the management of patients with breast cancer.

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