Distribution of axillary lymph node metastases in different levels and groups in breast cancer, a pathological study

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KEYWORDS
Extensive axillary lymph node dissection (ALND); Breast cancer; Pathology

Abstract  Background: It was observed during dissection of heavy deposits of axillary lymph nodes (LNs) in breast cancer that there were grossly positive LNs outside the confines of classical axillary dissection.

Aim of study: To know the extent of LN metastases in these new basins by dissecting and labeling them separately, for pathological examination and proper staging of those patients.

Patients and methods: From 2005 to 2009, 59 private patients with breast cancer who had positive axillary LNs were subjected to axillary dissection with accurate leveling according to its relation to pectoralis minor. In addition to the classical three levels, the brachial, thoracoacromial, humeral, scapular and Rotter’s lymph nodes were dissected.

Results: Levels I, II and III axillary LNs were involved in 91.5%, 62.7%, and 52.5%, respectively. Skip metastases (without the involvement of level one) were found in 5/59 patients (8.4%). Brachial, acromiothoracic, humeral and Rotter’s LNs were involved in 10.1%, 15.2%, 5% and 1.7%, respectively, with no metastatic deposits encountered in scapular LNs. In our patients, lymphedema of the ipsilateral upper limb was nearly of the same incidence as after classical axillary dissection.

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Conclusion: In addition to the classic complete axillary lymph node dissection (ALND) indicated in patients with breast cancer with axillary LNs metastases, dissection of the brachial, acromiothoracic, humeral, Rotter’s and scapular LNs, is recommended for proper staging.

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Introduction

Carcinoma of the breast is the most common malignant tumor and is the most common cause of death from carcinoma in females [1,2]. In the West, widespread use of mammography has resulted in a marked increase in early detection of this carcinoma, when it is still microscopic or localized and small in size. This, however, unfortunately is not the case for developing countries where breast cancer mortality is still rising [3].

In the late 19th century, breast cancer was considered a fatal disease. This began to change in the 1880s when Halsted described radical mastectomy as the way to treat patients with breast cancer [4]. This aggressive surgical treatment in which the breast, axillary LNs, and chest muscles are all removed, remained the standard of care throughout much of the 20th century; as late as the early 1970s, so that nearly half (48%) of breast cancer patients were treated with radical mastectomy. During the 1970s, however, the Halsted radical mastectomy was largely abandoned for a less-disfiguring muscle-sparing technique called the modified radical mastectomy; so that by 1981, only 3% of the patients underwent the Halsted mastectomy [5]. The 1980s heralded even more minimally invasive techniques with the advent of breast conservation therapy, in which an incision is made over the tumor and the tumor is completely removed with negative margins, leaving behind the normal breast tissue. During the 1990s, surgical invasiveness was further minimized with the emergence of sentinel LN excision [5].

The positivity of axillary LNs for metastases is one of the most important prognostic parameters in carcinoma of the breast with sharp differences in survival rates between those with negative and positive nodes. In addition, the absolute number of nodes involved, the presence or absence of extranodal spread, capsular invasion, and the amount of carcinoma in the positive nodes (measured by the microscopic size of the largest nodal metastases) are also prognostically important with survival rates falling with increased number of nodes involved (less than 4 versus 4 or more), presence of extranodal spread and increased amount of tumor in positive nodes [6,7]. Carter and co-workers, in a study on 24,700 patients reported that the extent of axillary LN involvement in breast cancer is the dominant prognostic indicator for the development of a later systemic disease [8].

Complete and detailed axillary dissection in patients with positive axillary LNs will provide proper staging, accurate prognosis and optimum loco-regional control [8]. It was observed during dissection of heavy deposits of axillary LNs in breast cancer that there were grossly positive LNs outside the confines of the classical axillary lymph node dissection (ALND). Those nodes were found anterior to the brachial plexus (brachial LNs), around thoracoacromial vessels (thoracoacromial LNs), humeral LNs, just lateral to the origin of thoracodorsal artery, scapular LNs (inter-nerve LNs between nerve to lattismus dorsi and long thoracic nerve) in addition to Rotter’s LNs. The aim of the present study is to determine the extent of LN metastases in these new basins by dissecting and labeling them separately, for pathological examination and hence a proper staging of those patients.

Patients and methods

The study population consisted of patients with operable breast cancer who underwent surgery for invasive breast cancer between January 2005 and December 2009. According to the international TNM staging system by the American Joint

Figure 1  Lt brachial LN.

Figure 2  Lt thoracoacromial LN.
Committee on Cancer (AJCC) published in 2005 [9], all patients with operable T1, T2, T3, with positive LN on final pathological examination, breast cancer were included in the study. Patients with locally advanced stage III breast cancer who received pre-operative (neo-adjuvant) chemotherapy were included in the study whenever down staged.

This prospective study was conducted on 59 private female patients for whom surgical treatment of the primary tumor was done according to the standard criteria. Thirty four out of 59 patients (57.6%) underwent conservative breast surgery, 12 patients (20.3%) underwent modified radical mastectomy and 13 patients underwent radical mastectomy (22%).

Complete axillary clearance (levels I, II and III) was done and each of the three levels was separately marked and submitted for pathological examination. Five separately studied LN groups were also dissected, namely:

1. Brachial LNs (Infraclavicular) this is the pad of fat containing LNs anterior and above the cords of brachial plexus, under the insertion of pectoralis minor muscle and medial to the coracobrachialis muscle; this pad of fat which was taken separately was carefully examined to detect the presence of metastases (Fig. 1).
2. Thoraco-acromial LNs (surrounding thoraco-acromial vessels) (Fig. 2).
3. Humeral LNs (lateral to thoracodorsal vessels) (Fig. 3).
4. Inter-Pectoral LNs (Rotter’s).
5. Inter-nerve LNs (scapular).

Pathological analysis of each LN with staining with Hema-toxin and Eosin was done. Correlation of each of the five separately dissected groups of nodes was done with each level of standard axillary LNs. Results of this study may show the indication, benefits and sequelae of the dissection of these additional groups of nodes. Routine postoperative care was adopted and all patients had an uneventful course. Follow-up period ranged between 1 and 65 months with special attention to seroma and arm lymphedema. Lymphedema is defined as volume difference between the treated and untreated arm of more than 200 ml, or more than 2 cm difference in the circumference of both arms.

<table>
<thead>
<tr>
<th>Nodal status (n = 59)</th>
<th>Number of patients</th>
<th>Percentage (%)</th>
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<tbody>
<tr>
<td>Patients with positive classical axillary groups</td>
<td></td>
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<tr>
<td>Metastases in level I axillary LN</td>
<td>54</td>
<td>91.5</td>
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<tr>
<td>Metastases in level II axillary LN</td>
<td>37</td>
<td>62.7</td>
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<tr>
<td>Metastases in level III axillary LN</td>
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<td>50.8</td>
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<tr>
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<td>18.6</td>
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<tr>
<td>Skip metastases</td>
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<td>8.4</td>
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<tr>
<td>Patients with positive new axillary groups</td>
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<tr>
<td>Positive Rotter’s LN</td>
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<td>Positive acromiothoracic LN</td>
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<tr>
<td>Positive humeral LN</td>
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<td>5.08</td>
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<tr>
<td>Positive scapular LN</td>
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Figure 3  Lt humeral LN.

Table 1  Distribution of LN metastases in different levels and groups of axillary LNs in 59 breast cancer patients under study.

Figure 4  Relation between the number of positive LN in the three levels of axillary LNs to that of the positive LNs in the newly dissected LN groups.

Results

The patients’ age ranged between 24 and 77 years (mean 52.9 ± 13 years). Thirty four patients (57.6%) had breast conserving surgery (BCS), 12 patients (20.3%) had undergone modified radical mastectomy (MRM) and 13 patients (22%) had radical mastectomy.

Pathological analysis revealed that of the 59 patients, 48 patients had infiltrating duct carcinoma (IDC), eight patients had invasive lobular carcinoma, two patients had tubular carcinoma and a single patient had mucinous carcinoma. Among the 59 patients, two patients (3.4%) were of grade 1, 47 patients (79.9%) were grade of 2, and 10 patients (16.9%) were grade 3.

According to the tumor size; 11 patients (18.6%) had T1 tumor, 40 (67.8%) had T2 tumor and 6 (10.2%) had T3 tumor. Two patients had T4 tumor (3.4%). All patients had N1
disease and the metastatic work-up (chest X-ray, Abdominal and pelvic ultrasound, Bone scan) was free of metastases.

When the axillary dissection materials were reviewed, the mean number of dissected LNs from the 59 patients was 24.1 ± 8.7, and the mean number of metastatic LNs was 9.9 ± 9.1. Among the 59 patients with positive LNs: Twenty patients were pN1a (metastasis in 1–3 axillary LNs), 19 patients (32.2%) were pN2a (metastasis in 4–9 axillary LNs); and 19 patients (33.9%) were pN3 (metastasis in 10 or more axillary LNs) (32.2%). Extra nodal spread was present in 20 patients (33.9%).

Level I axillary LNs were involved in 54 of the 59 patients (91.5%); level two LNs were involved in 37 of the 59 patients (62.7%), while level three LNs were involved in 31 of the 59 patients (52.5%) (Table 1). Fourteen patients (23.7%) had metastatic deposits in either Rotter’s, brachial, acromiothoracic, or humeral LNs (Table 1).

When level III harbored metastases, 10/31 of patients (32.3%) had metastatic disease in either brachial, acromiothoracic or humeral LNs. When level II harbors metastases (with negative level III), only 1/11 patients (9%) had metastases in brachial LNs. While LN metastases were restricted to level I (with negative level II and level III) 3/18 patients (16.6%) had metastases in either the brachial, acromiothoracic or humeral LNs. There was a statistically significant relation between LN metastases in the newly dissected groups and more than 10 LNs metastases (Fig. 4). Also, a border line significance was found between metastases in new groups and involvement of level III (Fig. 5).

Eight (13.5%) of our patients had lymphedema of the ipsilateral upper limb. Two (3.4%) more patients presented with local recurrence after breast conserving surgery for which salvage mastectomy was performed.

Discussion

Green and co-workers (2002), revised the sixth edition of the American Joint Committee on Cancer staging manual in 2002 and introduced new prognostic factors and a new stage III C in which a new pN3 was introduced. In the revised staging system, the level of axillary involvement and the number of metastatic LNs have been accepted as prognostic factors. In this staging system pN1 = 1–3 positive nodes, pN2 = 4–9 positive nodes and pN3 ≥ 10 positive axillary nodes and any positive LN at the apex of the axilla or infraclavicular node is pN3 [10,11].

Axillary dissection still offers the most efficient local control in node-positive patients. It is of no doubt that surgical therapy still contributes to cure early-breast-cancer patients and seems to be curative for certain patients with stage-I carcinoma [12].

It is reasonable to perform a complete axillary node dissection including level III as we have found that 31 of the 59 patients (52.5%) had metastatic deposits in that level. This goes with the study done by Ouyang and associates who found metastases at level III LNs in 18 patients (20.7%) among 87 patients [13].

In another study by Veronesi and associates done on 539 patients with breast cancer, they reported involvement of level 3 in 16.9% of T1 breast cancer patients. Veronesi and associates stated that the likelihood of involvement of either level II or III is related to the number of LNs containing metastases in level I, so when only one node in level I contained metastases only 8% of patients had involvement of the upper levels of the axilla. Whereas when level I was involved with two nodes, 25.3% of patients had higher level metastases, and this ratio rises to 65.8% if level I had four or more LN metastases [14,15].

In our study, skip metastases (i.e. without level I involvement) was found in five of the 59 patients (8.4%). All the five negative level I patients exhibited skip metastases, two patients skip to level II only, one patient at level III and two patients at levels II and III and this was much higher than the study done by Veronesi et al. on 539 patients and Rosenet and associates on 1228 patients with breast cancer who reported 0.4% and 0.2% incidence of skip metastases, respectively. The discrepancy between the two previous studies and the present study can be explained by the fact that both studies were applied only to early breast cancer [14,16]. A higher number of skip metastases was found in the study conducted by Zhong and Zhi (2008) who found skip metastases in 119/814 patients (14.6%) with positive axilae [17].

The risk of axillary failure appears to be inversely related to the number of LNs removed as reported by Graverson and his colleagues in their study done on risk of axillary recurrence following limited axillary dissection, where the risk of axillary failure was 5–21% when <5 LNs were removed whereas it decreased to 5% if more than five LNs were dissected [15].

Kiricuta and Tausch constructed a mathematical method to predict the number of nodes that must be removed, based on the data from 1446 axillary dissections performed at the Milan NCI on T1 tumors; they stated that at least 10 negative LNs predicted that the remainder of the axilla did not contain metastases with 90% certainty [18].

Among women undergoing mastectomy for breast cancer, 10–15% will have a recurrence of cancer in the chest wall or axillary LNs within 10 years [19]. Similarly, among women undergoing breast conservation therapy plus radiation therapy, 10–15% will have in-breast cancer recurrence or recurrence in axillary LNs within 10 years [19]. Axillary failure rates are low, however there is a 21% risk of developing axillary recurrence in patients not undergoing treatment of the axilla. For this reason, the levels I and II axillary LN dissection has been considered the standard of care in early-stage, node-negative cancer [20,21]. In the present study which was done on 59 patients, after a follow up period of 1–65 months.
Survival rates in a series of 1277 patients [22]. Infraclavicular patients with breast carcinoma and was associated with poor failures. (median 30.6 months) there were no patients with axillary failures.

Kuru et al. reported that apical (Infraclavicular) metastasis was an independent predictor of survival in node-positive patients with breast carcinoma and was associated with poor survival rates in a series of 1277 patients [22]. Infraclavicular LN metastasis causes migration to stage IIIC, even in early stage patients with T1 tumors, and shifts these patients to a locally advanced stage. In the study done by Güven et al. (2007), among 44 patients who were treated with mastectomy, 11 patients (25%) were reclassified as stage IIIC because of the infraclavicular LN metastasis. Seven of these patients (63.6%) were in stage I or II, according to the previous staging system but became locally advanced according to the latest system [23]. In the present study brachial LNs were involved in six patients (10.1%).

Although there is some controversy regarding the percentage of patients that may develop metastases to interpectoral nodes, as many as 14% of the patients of operable breast cancer have positive interpectoral nodes at the time of operation [13,24,25]. In the present study only one patient had involvement of the interpectoral LN (1.7%). In the study conducted by Komenaka et al. (2004), four patients (0.1%) had recurrence at the interpectoral nodes among 4097 patients who underwent surgical management for breast cancer. They also concluded that recurrence at the interpectoral nodes can be the initial site of surgical failure. These nodes may represent the site of primary drainage in a percentage of patients [26].

We found in this study that capsular infiltration is present in 20 of the 59 patients (33.9%). In the literature, extracapsular spread (ECS) is documented in the range of 24-60% of breast cancer patients. However, it is not clear that ECS was significantly associated with supraclavicular, local or axillary recurrence [27].

The yield of axillary LN metastases in groups outside the three levels may increase with step sectioning of axillary LNs and/or the use of cytokeratin to examine the negative LNs pathologically. Querzoli and colleagues demonstrated minimal LN deposits in 13% of pN0 patients. Occult metastases can indeed be identified in up to 30% of patients previously classified as pN0 [28]. Studies based on these procedures have shown that axillary LN microinvasion is a prognostic factor for breast cancer patients, and is associated with poorer disease-free and overall survival. As a consequence, micrometastasis (0.21–2 mm in diameter) has been identified as a relevant risk factor and its detection has been introduced in TNM staging procedures (2003 TNM edition). Following these guidelines, isolated tumor cells or cell deposits smaller than 0.2 mm are currently required to be classified as pN0 [11].

It is of great importance to notice that breast cancer patients in Egypt show a much higher lymph node positivity status than their western homologues. Nouh et al. (2004), published a study on 3755 Egyptian breast cancer patients, in one, if not the largest, published breast cancer pathological studies from Egypt. He found that LN metastasis was evident in 2646 (70.6%) of the total cases, while 1101 cases (29.4%) were free of metastasis [29]. This is in comparison to the node positive patients, who constitute 25-40% of the cases in the west [30,31]. This explains the need to extend the territory of the axillary lymph node dissection to the adjacent LN groups described in this study.

The most controversial aspect of axillary dissection is its impact on survival [27]. There are two potential mechanisms by which residual tumor in the axilla could act as a source of distant metastases, thereby affecting survival. First, uncontrolled loco-regional tumor is a potential source of metastases and this hypothesis is supported by the work of Arrigada and colleagues who studied 960 node positive breast cancer patients treated with modified radical mastectomy and irradiation, second, uncontrolled axillary disease can act as a source of tumor reseeding [32]. Other studies were done by Overgaard and colleagues on 210 breast cancer patients treated with modified radical mastectomy versus 241 patients treated with simple mastectomy and axillary biopsy. They reported a 10 year survival of 58.8% in the axillary dissection group versus 42.3% for those who had axillary LN biopsy. Conversely, inadequate treatment of the axilla has been associated with decreased survival [33].

In the present study, no major complications of axillary dissection occurred, and complications such as thrombosis or injury of the axillary vein/artery, damage to the motor nerves of the axilla were not reported. Regarding the morbidity of the proposed technique of dissecting additional nodal basins compared retrospectively to similar stages of breast cancer patients who underwent standard axillary dissection, the rates of both were similar. The incidence of lymphedema in this study was (10.1%) which goes with that reported in the literature (between 6% and 30%) depending upon the methods to define it and the adequacy of follow-up. Lymphedema remains a significant problem even in patients treated with a level I and II ALND as reported by Lin and colleagues [34].

It was recognized that the rates of lymphedema are very low if the adventitia of the axillary vein is not violated. So if the surgeon dissects the brachial pad of fat above the axillary vein in order to dissect the brachial LN basin, care should be taken to not violate the adventitia surrounding the vein [35].

Conclusion
Complete ALND is recommended in the presence of axillary LNs metastases, including the three classical levels, brachial, acromiothoracic, humeral, Rotter’s and scapular LNs in patients with breast cancer, for proper staging and optimum regional control. It may result in a better long term survival. In these new groups, metastatic deposits were found in 14 patients (23.7%) out of the 59 patients with N1 disease. Underestimation of the number of positive nodes examined will result in errors in the assessment of individual risk for loco-regional control, survival and will adversely impact further treatment.

References