How much is the axillary nodal status in breast cancer affected by neoadjuvant chemotherapy? An Alexandria medical research institute hospital experience

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Received 13 December 2014
Accepted 31 January 2015

The Egyptian Journal of Surgery
2015, 34:94–98

Background
The multidisciplinary approach, including surgery, chemotherapy, endocrine therapy, and radiation therapy, has become the standard treatment for primary breast cancer patients. The status of axillary lymph nodes (AxLNs) remains the most important prognostic factor. The number of lymph nodes retrieved in axillary lymph node dissection (ALND) varies considerably. Removal of at least 10 AxLNs is generally considered as an adequate ALND for reliable lymph node staging. Several authors have reported a significantly lower AxLN count in patients undergoing ALND after the completion of neoadjuvant chemotherapy (NAC) compared with patients who underwent surgical resection first.

Objective
Our aim was to evaluate the effect of NAC on the axillary nodal status in breast cancer patients regarding the number of AxLNs retrieved at ALND and to compare the degree of response to NAC relative to the primary tumor's nodal status in the both studied groups.

Patients and methods
In this retrospective study, we reviewed the records of all patients with invasive breast cancer who were admitted to the Department of Surgery, Medical Research Institute hospital, Alexandria, during the period between August 2013 and July 2014 and were scheduled for ALND. Cases were categorized into two groups: group I included patients who received NAC and were then subjected to surgery, whereas group II included patients who were subjected to surgery without NAC. Data collected from both groups included patient demographics and clinicopathological characteristics.

Results
The study included 237 female patients who were allocated to one of the two groups: group I (GI) included 93 patients (39.2%), whereas group II (GII) included 144 patients (60.8%). There was no statistically significant difference between the two groups regarding the age, the tumor grade, and the tumor type. However, significant differences were seen in a variety of baseline criteria between the two groups; patients who received NAC had larger tumors (T) ($P = 0.001$), a higher lymph node (*N*) classification ($P = 0.002$), and a higher overall disease stage ($P = 0.0001$) compared with patients who underwent surgical resection first. After NAC in GI, AxLNs were significantly more responsive to NAC relative to the primary tumor ($P = 0.003$). The number of AxLNs harvested during ALND revealed a significantly lower LNY in patients who underwent NAC in comparison with patients who did not, with a median total number of nine nodes in GI compared with 14 axillary nodes in GII ($P = 0.0001$). The number of positive AxLNs was higher in patients who underwent surgical resection first, with a statistically significant difference ($P = 0.006$).

Conclusion
NAC is a significant independent parameter for a reduced AxLN number retrieved by ALND. Also, we can conclude that AxLNs are significantly more responsive to NAC relative to the primary tumor either clinically or pathologically.

Keywords:
axillary lymph node, axillary lymph nodes dissection, breast cancer, lymph node status, neoadjuvant chemotherapy

Egyptian J Surgery 34:94–98

1110-1121

Introduction

Breast cancer is the most frequent malignant tumor in women worldwide. The incidence and mortality rates among women vary among countries, but are steadily increasing worldwide [1]. In Egypt, breast cancer is the most common cancer among women, representing 33.5% of the total number of cases, with 18660 new cases diagnosed in 2012. It is also the leading cause of cancer-related mortality, accounting for 29.1% of the total with 6546 deaths [2]. These estimates are confirmed in many regional Egyptian cancer registries [3,4]. The axillary nodal status remains the most important prognostic factor for patients with breast cancer. Clinical assessment and imaging

 DOI: 10.4103/1110-1121.155718

modalities are not always reliable. Axillary lymph node dissection (ALND) is routinely performed for patients with lymph node-positive breast cancer for purposes of staging and regional control. However, the optimal management of the axilla remains uncertain [5]. The number of nodes retrieved during axillary dissection has been demonstrated to have a significant impact not only on regional nodal failure, but also on local failure [6]. Current guidelines suggest that at least 10 nodes should be examined for reliable lymph node staging [7]. The role of the percent of positive lymph nodes in predicting distant metastasis and survival was recently demonstrated in several institutional series. These studies showed consistently that the percentage of positive lymph nodes is a significant independent prognostic indicator of survival in women with lymph node-positive breast carcinoma [8–10]. The multidisciplinary approach, including surgery, chemotherapy, endocrine therapy, and radiation therapy, has become the standard treatment for primary breast cancer patients [11]. When it first emerged in the late 1970s, the use of neoadjuvant chemotherapy (NAC) was limited primarily to women with inoperable locally advanced breast cancer to enable surgical resection [12]. Many other trials followed in the past two decades studying the role of induction chemotherapy [13]. Currently, NAC followed by surgery is the treatment of choice for patients with inflammatory breast cancer or locally advanced breast cancer [14,15]. Recently, this approach was also recommended for primary operable breast cancer [16]. NAC has been compared with standard, postoperative adjuvant chemotherapy, with the dual goals of improving survival and facilitating local therapies. Large randomized trials proved that preoperative chemotherapy has at least the same survival benefit as postoperative chemotherapy [17]. Several authors have reported a significantly lower AxLN count in patients who underwent ALND after the completion of NAC compared with patients who underwent surgical resection first without any prior chemotherapy [18,19]. In this study, we aimed to evaluate the effect of NAC on the axillary nodal status in breast cancer regarding the number of AxLNs retrieved at ALND and the degree of response to NAC relative to the primary tumor.

Patients and methods

This retrospective review was conducted on all patients with pathologically proven nonmetastatic invasive breast cancer, who were admitted to the department of Surgery, the hospital of Medical Research Institute, University of Alexandria, during the period between August 2013 and July 2014. These patients were scheduled for ALND as a part of modified radical mastectomy or conservative breast surgery with or without reconstruction. Patients who underwent sentinel lymph node biopsy, who had bilateral breast cancer, who had primary inflammatory carcinoma, who were operated upon by a surgeon lower than senior residents, and patients with level III ALND were excluded. Cases were categorized into two groups: GI included patients who received NAC and were then subjected to surgery, whereas GII included patients who were subjected to surgery without NAC. Patients were examined by a multidisciplinary team to confirm the diagnosis of breast cancer and to evaluate the clinical stage of the disease at presentation (GI, GII) and the response after four cycles of chemotherapy (GI). The tumor size and the nodal status before and after NAC were measured routinely by ultrasound. Data collected from both groups included patients' characteristics, diagnostic methods, the type of surgery, tumor characteristics such as the histological subtype, the tumor grade, the total number of AxLNs identified in pathologic specimens, the number of positive AxLNs, lymphovascular invasion, estrogen and progesterone receptors, the human epidermal growth factor receptor 2 (Her-2) status, and treatment details. Patients in the former group were treated as per the institutional protocols during that time, which included anthracycline-based therapy with or without the addition of taxanes. After four cycles of NAC in GI, only responding patients underwent surgery, whereas patients with a partial response, no response, or progressive disease underwent additional cycles of non-cross-resistant chemotherapy. The standard surgical technique at our institution is to perform level I and II ALND. Pathologic processing of ALND specimens at our institution has been consistent throughout the study period and is comprised of sharp dissection of all lymph node tissue from the surrounding fat. No fat-dissolving techniques are used. All lymph node tissues are then examined histologically.

Statistical analysis

Data were analyzed using the statistical package for social sciences (SPSS ver.20; SPSS Inc., Chicago, Illinois, USA). Quantitative data were described using the mean and SD, whereas qualitative data were described using the number and percent. For comparing quantitative variables between the two groups, we used the independent sample t-test. We used the Monte Carlo significance test if $>2 \times 2$ categories and more than 20% of the cells had an expected cell count less than 5. In all statistical tests, a level of significance of 0.05 was used; statistical significance was set at P less than 0.05.

Results

This study included 237 female patients who were allocated to one of the two groups: GI received NAC and was then subjected to surgery and included 93 patients (39.2%), whereas GII was subjected to surgery without NAC and included 144 patients (60.8%). On comparing the two groups, there was no statistically significant difference between them regarding patients' age (P = 0.196). In contrast, there was a statistically significant difference in the other standard prognostic factors between the two groups. As treatment decisions regarding NAC are routinely based on the tumor size, clinical nodal involvement, and the overall disease stage, patients who received NAC had larger tumors (T) (P = 0.001), a higher lymph node (N) classification (P = 0.002), and a higher overall disease stage (P = 0.0001) than patients who underwent surgical resection first (GII). The distribution of the studied patients according to age and intial tumor characteristics are summarized in Table 1.

After NAC in GI, we registered both the tumor stage and the nodal stage to assess the degree of response of AxLNs (the nodal stage) and the primary tumor (the tumor stage) to NAC, which revealed that axillary AxLNs (the nodal stage) were significantly more responsive to NAC relative to the primary tumor (the tumor stage) (P = 0.003) as shown in Table 2.

Regarding the data collected from postoperative pathological reports, there were no statistically significant differences between the two groups regarding the tumor grade and the tumor histological subtype. In contrast, the number of AxLNs harvested during ALND revealed a significantly lower LNY in patients who underwent NAC in comparison with patients who did not receive NAC. The median total number of nodes was 9 in GI compared with 14 axillary nodes in GII; these results were highly statistically significant (P = 0.0001). The number of positive AxLNs was higher in patients who underwent surgical resection first, with a statistically significant difference (P = 0.006) as shown in Table 3.

Discussion

In our practice, we have noticed that NAC in breast cancer can downstage AxLNs more than the primary tumor, and also, the number of retrieved lymph nodes in ALND in patients who received NAC is usually lower than that in patients who underwent surgical resection first, but both former points were just observations and the literatures showed debates about them.

According to Erbes *et al.* [20], NAC reduces the number of AxLNs retrieved by ALND significantly, whereas Boughey *et al.* [21] concluded that the number of AxLNs recovered at ALND does not appear to be affected by NAC and may even be higher than in patients who underwent surgical resection first. Also Sinn *et al.* [22] concluded that NAC could result in a downstaging of positive AxLNs, but the potential

Table 1 Distribution of the studied patients according to age and tumor characteristics before neoadjuvant chemotherapy in group I and before surgery in group II

Item	Group I (N = 93)	Group II (N = 144)	P
Age (years)			0.196**
Range	32–53	30–50	
Mean ± SD	43.250 ± 7.46835	40.4500 ± 5.89804	
Tumor stage [N (%)]			
T0	0 (0)	20 (13.9)	0.001*
T1	6 (6.5)	38 (26.4)	
T2	28 (30)	68 (47.2)	
T3	42 (45.2)	18 (12.5)	
T4	17 (18.3)	0 (0)	
Nodal stage [N (%)]			
N0	8 (8.6)	19 (13.2)	0.002*
N1	16 (17.2)	76 (52.8)	
N2	45 (48.4)	38 (26.4)	
N3	24 (25.8)	11 (7.6)	
Overall disease stage			0.0001*
Stage I	0 (0%)	7 (5%)	
Stage II	23 (24.7%)	88 (61%)	
IIA	12	59	
IIB	11	29	
Stage III	66 (71%)	49 (34%)	
IIIA	47	25	
IIIB	4	6	
IIIC	15	18	
Stage IV	4 (4.3%)	0 (0%)	

*The Monte Carlo test; **The t-test.

Table 2 Distribution of patients in group I according to the degree of response of the axillary lymphadenopathy (nodal stage) to neoadjuvant chemotherapy relative to the primary tumor (tumor stage)

Item	Group I (before NAC) (N = 93) [N (%)]	Group I (after NAC) (N = 93) [N (%)]
Tumor stage		
T0	0 (0)	5 (5.4)
T1	6 (6.5)	17 (18.3)
T2	28 (30)	29 (31.2)
T3	42 (45.2)	31 (33.3)
T4	17 (18.3)	11 (11.8)
Nodal stage		
N0	8 (8.6)	23 (24.8)
N1	16 (17.2)	39 (41.9)
N2	45 (48.4)	22 (23.6)
N3	24 (25.8)	9 (9.7)
P	0.003*	

NAC, neoadjuvant chemotherapy; *The t-test.

Table 3 Distribution of postoperative pathological parameters in the two studied groups

Item	Group I (N = 93) [N (%)]	Group II (N = 144) [N (%)]	P
Tumor grade			
1	27 (29)	24 (16.7)	0.165*
2	45 (48.4)	72 (50)	
3	21 (22.6)	48 (33.3)	
Tumor histological subtype			
Invasive ductal	58 (62.4)	96 (66.7)	1.000*
Invasive lobular	21 (22.6)	29 (20.1)	
Other	14 (15)	19 (13.2)	
Number of AxLNs			
Median	9	14	0.0001**
Positive			
<4	29 (31.8)	26 (18)	0.006**
≥4	64 (68.2)	118 (82)	

AxLNs, axillary lymph nodes; *The Monte Carlo test; **The Pearson χ^2-test.

influence of chemotherapy on the LNY and their morphology and detectability is still unclear.

To resolve this conflict, we conducted this research work. We retrospectively reviewed all patients with breast cancers who were admitted to the Department of Surgery, Alexandria Medical Research Institute Hospital, during the period between August 2013 and July 2014 and were scheduled for ALND. Patients who underwent sentinel lymph node biopsies, who were operated upon by surgeons lower than senior residents, and patients with level III ALND, who had bilateral or inflammatory breast cancer, were excluded to avoid selection bias. Cases were categorized into two groups: GI included patients who received NAC and were then subjected to surgery, whereas GII included patients who were subjected to surgery without NAC. We examined 237 patients who were allocated to one of the two groups: GI included 93 patients (39.2%), whereas GII included 144 patients (60.8%).

The findings of this study demonstrated that the number of AxLNs recovered after completion of NAC was lower than in patients who underwent surgical resection first, which is similar to the results of Belanger *et al.* [18] and Neuman *et al.* [19], but in contrast to the results of Boughey *et al.* [21], Straver *et al.* [23], Petrick *et al.* [24], Patel *et al.* [25], and Cil *et al.* [26] who concluded that the number of AxLNs recovered at ALND does not appear to be affected by NAC and may even be higher than in patients who underwent surgical resection. Boughey *et al.* [21] explained the slightly higher average number of lymph nodes found after the completion of NAC by a subconscious decision to perform a more aggressive surgical approach in these locally advanced cases, a subconscious effort to conduct a more comprehensive search for lymph nodes in the resected specimen by the pathologists, or due to a statistically higher lymph node stage and a higher number of positive lymph nodes in the neoadjuvant group.

In contrast, Belanger *et al.* [18] suggested that the lower number of AxLNs after NAC may be secondary to the fibrosis of lymphatics caused by NAC; this explanation is similar to the findings of recently published studies that also reported chemotherapy-induced changes in lymph nodes, including lymphoid depletion [27–29], and this may affect the pathologist's ability to find AxLNs within the dissection specimen as NAC could cause fibrosis of lymphatics, resulting in smaller atrophic AxLNs that are more challenging to identify macroscopically [26]. Results of the current study support this theory.

In our study; the number of positive lymph nodes was lower in the patients undergoing NAC, and this may support our findings regarding the downstaging effect of NAC on AxLNs not only clinically (as shown in our results in Table 2) but also pathologically. this finding is still in contrast to the results of Boughey *et al.* [21], who concluded that the number of positive lymph nodes was higher in the patients who underwent NAC, reflecting the more advanced stage of disease in these patients. Regarding surgeons' training as a factor, some reports concluded that the surgeon's level of training appears to impact the number of AxLNs resected [24,30]. To avoid this bias, patients who were operated upon by surgeons lower than senior residents were excluded from the study to fulfill a satisfactory level of training for adequate axillary dissection.

Some previous studies have indicated that the number of AxLNs found correlates inversely with the patient's age, with younger patients having more lymph nodes excised than older patients [24,26,31], whereas other studies have not found this association [11]. We did not notice this as there was no statistically significant difference between the two groups regarding age (P = 0.196), and this supports our results of NAC as the strongest independent variable for a diminished lymph node number.

Conclusion and recommendations

Our study identified NAC as a significant independent parameter for a reduced LNY number retrieved by ALND.

Existing recommendations for a minimum removal of 10 lymph nodes by ALND are clearly compromised by the clinically already established concept of NAC. Consequently, the lymph node count of less than 10 by ALND after NAC is not indicative of insufficient axillary staging.

Our study concluded that axillary AxLNs (nodal stage) are significantly more responsive to NAC relative to the primary tumor (tumor stage) both clinically (TNM staging) and pathologically (the number of positive LNYs). Therefore, guideline recommendations for the future should consider these points.

Because of the short period of the study and the low number of patients studied, larger scale, longer period, and multicentric surveys for the documentation of our finding are needed.

One of the major limitations of this study is that this study is retrospective in design, and therefore, it is potentially biased by which patients underwent NAC and which patients underwent surgical resection first. In addition, the pathologic processing of ALND specimens varied between pathologists, and so we recommend conducting prospective studies to unify the inclusion and exclusion criteria and the surgical, pathological, and oncological parameters.

Acknowledgements
Conflicts of interest
None declared.

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