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RESEARCH ARTICLE/ARAŞTIRMA YAZISI

CLINICAL AND PATHOLOGIC FEATURES ASSOCIATED WITH REMOVAL OF FEWER THAN 10 LYMPH NODES IN AXILLARY LYMPH NODE DISSECTION FOR BREAST CANCER

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MEME KANSERİ TEDAVİSİNDE AKSİLLADA 10 LENF NODUNUN ALTINDA LENF NODU ÇIKARILMASI İLE İLİŞKİLİ KLİNİK VE PATOLOJİK ÖZELLİKLER

ÖZET

Amaç: Meme kanseri tedavisinde hastalığın doğru patolojik evrelendirilmesi ve adjuvan tedavi kararı için aksilla diseksiyonununda minumun 10 lenf nodu çıkarılması önerilmektedir. Bu çalışmanın amacı sentinel lenf nodu (SLN) metastazı sonrası tamamayıcı aksilla diseksiyon (TAD) yapılan hastalarda 10 ve altında lenf nodu çıkarılmasını etkileyen klinik ve patolojik faktörleri saptamaktır.

Gereç ve Yöntem: UPMC Magee-Womens Hastanesinde SLN biyopsisi ve ardından TAD yapılan meme kanserli hastaların kayıtları incelendi. Hastalar toplam diseke edilen lenf nodu sayısına göre iki gruba ayrıldı. Gruplardan biri 10 ve üstünde, diğeri ise 10'un altında lenf nodu diseke edilen hastalardan oluşuyordu. Çıkarılan lenf nodu sayısını etkileyen klinik ve patolojik faktörler değerlendirildi. Analiz edilen değişkenler, hastanın yaşı, aksiller cerrahinin zamanlaması, neoadjuvan kemoterapi (NCT), tumor ve SLN özelliklerinden oluşuyordu.

Bulgular: SLN biyopsisinde metastaz saptanan 373 hasta erken veya geç dönemde seviye I-II TAD geçirmişti. Ortalama yaş 53 idi (29-84). 54 hasta NCT görmüştü. SLN nun patolojik incelenmesi sonrasında hastaların %35.4' üne aynı seansta, %53.9'una ise geç (ikinci seansta) TAD uygulandı. Tek değişkenli analizde 10'un altında lenf nodu çıkarılmasını etkileyen faktörler: NCT, tumor çapı, gecikmiş TAD ve SLN da mikrometastaz idi ($p<0.05$). Çok değişkenli analizde, NCT ve SLN mikrometastazı 10'un altında lenf nodu çıkarılması ile anlamlı düzeyde ilişkili idi.

Sonuç: SLN metastazı saptanması sonrasında TAD yapılan hastalarda NCT ve SLN mikrometastazının 10'un altında lenf nodu çıkarılması ile ilişkili olduğunu saptadık.

Anahtar sözcükler: meme kanseri, sentinel nod, aksiller lenf nodu sayısı

ABSTRACT

Background: Current guidelines suggest that when performing axillary lymph node dissection for treatment of breast cancer, a minimum of 10 lymph nodes should be removed to allow for accurate pathologic staging to guide the treatment decision regarding the adjuvant treatment. The purpose of this study is to identify clinical and pathologic factors associated with retrieval of fewer than 10 lymph nodes in completion axillary lymph node dissection (CALND) performed for patients with breast cancer who had sentinel lymph node (SLN) metastasis.

Materials and Methods: Patients with breast cancer who underwent SLN mapping and subsequent CALND at UPMC Magee-Womens Hospital were identified using the tumor registry database. Patients were divided into two groups according to the total number of nodes dissected. One group was comprised of patients in who had 10 or more lymph node dissection after SLN positivity while the other group comprised of the patients with fewer than 10 nodes dissected. We evaluated a number of clinical and pathological variables with their association with number of lymph nodes retrieved. These variables included patient age, timing of axillary surgery, neoadjuvant chemotherapy (NCT), tumor characteristics and SLN characteristics.

Results: Three hundred seventy three patients underwent immediate or delayed completion level I-II axillary lymph node dissection after SLN biopsy demonstrated metastasis. The mean age of the patients was 53 (range 29-84) years. Fifty-four patients underwent NCT. Following SLN pathologic examination, immediate CALND was performed for 35.4% of patients and delayed CALND for 53.9% of all patients. By univariate analysis, following factors had significant association with dissection of fewer than 10 lymph nodes: NCT, tumor size, delayed CALND, and SLN micrometastases ($p<0.05$). By multivariate analysis, NCT and SLN micrometastases were significantly associated with retrieval of fewer than 10 lymph nodes.

Conclusion: In patients who have undergone CALND after identification of SLN metastasis, we found NCT and SLN micrometastases were associated with dissection of fewer than 10 axillary lymph nodes.

Key words: breast cancer, sentinel node, axillary lymph node number

Introduction

Axillary lymph node dissection (ALND) is the gold standard for assessing the status of axillary lymph nodes in patients with breast cancer. This procedure decreases loco-regional recurrence and provides accurate staging by guiding therapeutic decisions (1, 2). The axillary lymph node status is one of the most important independent prognostic factors for disease free and overall survival of patients with breast cancer (3, 4). The standard of care prior to

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February 2011 for patients with sentinel lymph node (SLN) metastasis is completion level I and II ALND completion axillary lymph node dissection (CALND). CALND can be performed immediately or delayed after positive SLNB (5). Current guidelines suggest that a minimum total of 10 lymph nodes be removed in an axillary lymph node dissection specimen to provide for accurate pathologic staging (3, 6). Retrieval of 10 axillary lymph nodes was determined as the cutoff value to achieve 90% specificity for ALND (7). Several factors have been reported to be associated with the number of lymph nodes dissected. These factors include neoadjuvant chemotherapy (NCT), lymphovascular invasion (LVI), increased number of involved SLNs, size of SLN metastasis, lobular histology, patient age, clinical nodal status, and tumor size (8,9,10). In this study, we examined the association between various clinical and pathologic variables and numbers of axillary lymph nodes dissected in patients with breast cancer and lymph node metastasis. We reviewed our institutional data to verify our clinical observations that NCT lowers axillary lymph node count, and also to assess whether other clinical and pathologic variables are significantly associated with a lower lymph node count during CALND.

Materials and methods

Using the tumor registry database, all patients who underwent SLN mapping for breast cancer at Magee-Womens Hospital during the time period 1999-2007 were identified. We then identified the subset of these patients who had sentinel node metastases and subsequently underwent immediate or delayed CALND. We retrospectively reviewed the records of the patients in this subset. Patients were divided into two groups based on the total number of axillary nodes dissected during both the SLN dissection and the CALND. One group consisted of patients with fewer than 10 nodes dissected, while the other group consisted of those patients with 10 or more nodes dissected in the CALND. The clinical and pathologic factors examined for correlation between the number of lymph nodes dissected are listed in Table 1 and includes patient age, timing of surgery (immediate vs. delayed), SLN and tumor characteristics, and administration of NCT. Of this group of patients, 319 patients underwent primary surgery and 54 underwent NCT. All patients were clinically node negative. Initial histopathologic diagnosis of primary tumor was made by core-needle biopsy or excisional biopsy.

Surgeries were performed by four surgical oncologists who participated in the Magee-Womens Hospital Breast Cancer Program. SLN mapping was done using blue dye, radioactive colloid, or both. Each SLN was sectioned at 2-mm intervals perpendicular to the long axis. Surgeons intraoperatively, examined each node for suspicious lesions. Touch prep and frozen sections were performed if there were grossly suspicious areas. All lymph node sections were ultimately fixed in formalin and submitted for histologic evaluation. The sections were stained with hematoxylin and eosin. After processing, the lymph node sections were embedded in paraffin and a single 4µm section was stained with hematoxylin and eosin (HE) and was evaluated by a breast pathologist. In cases of primary invasive lobular carcinoma, additional immunohistochemical (IHC)

Table 1. Descriptive characteristics of study group (n=373)

Characteristics of the patients'	*n (%)*
Age (year)	
<60	273 (73.6)
≥60	100 (26.4)
Pathologic tumor size (cm)	
≤2	185 (49.6)
2-5	149 (39.9)
≥5	39 (10.5)
Tumor type	
IDC	312 (83.6)
ILC	61 (16.4)
Nuclear Grade	
1	60 (16.1)
2	173 (46.4)
3	140 (37.5)
Lympho-vascular invasion	
Yes	184 (50.7)
No	189 (49.3)
Estrogen Receptor status	
Positive	321 (86.1)
Negative	52 (13.9)
Progesteron Receptor status	
Positive	207 (55.5)
Negative	61 (16.4)
Unknown	105 (28.2)
Her2/neu	
Positive	48 (12.9)
Negative	266 (71.3)
Unknown	59 (15.8)
Multifocality	
Yes	123 (33.0)
No	250 (67.0)
Micrometastasis	
Yes	94 (25.2)
No	279 (74.8)
ECE	
Positive	113 (30.3)
Negative	260 (69.7)
NCT	
Yes	54 (14.5)
No	319 (85.5)
Timing	
Delayed	201 (53.9)
Immediate	132 (35.4)
Total SLN number	
1	67(18)
2	106 (28.4)
≥3	200 (53.6)
Number of positive SLN	
1	249 (66.8)
2	92 (24.7)
≥3	32 (8.6)
Number of negative SLN	
0	113 (30.3)
1	117 (31.4)
2	67 (18.0)
≥3	76 (20.4)
Size of largest SLN metastasis	
≤2.0 mm	80 (21.4)
2.1-4.0 mm	47 (12.7)
4.1-10.0 mm	88 (23.6)
>10.0 mm	131 (35.1)
Unknown	27 (7.2)
Number of lymph node in AD	
<10	61 (16.4)
≥10	312 (83.6)

IDC: Infiltrative ductal carcinoma, **ILC:** Infiltrative lobular carcinoma, **SLN:** Sentinel lymph node, **ECE:** Extracapsular extension, **NCT:** Neoadjuvant chemotherapy, **AD:** Axillary dissection

staining for cytokeratin AE 1/3 was performed. Appropriate positive and negative controls were run for IHC stains. Non- SLNs from axillary dissection were also submitted in their entirety for routine histologic examination. Larger lymph nodes were generally sectioned parallel to the long axis to be submitted in tissue blocks. Estrogen receptor status (ER) and progesterone receptor (PR) status was determined by IHC staining. A positive HER-2/neu was defined by either 3+ IHC staining or gene amplification noted on fluorescence in situ hybridization. A standardized pathology reporting form was used at Magee-Womens Hospital during this period. This form addressed the histology, size of the lesion, nuclear grade, lymphovascular invasion (LVI), number of nodes involved, number of nodes examined, overall metastasis size of the largest nodal metastasis (OMS), method of nodal metastasis detection, extracapsular extension (ECE), multifocality, and ER, PR, and HER-2/neu status, among other factors.

Statistics

X^2 test was used to assess the significance of the association between clinical and pathologic factors and the number of nodes dissected (<10 or ≥10). The factors evaluated with univariate analysis were age, Nottingham grade, pathologic tumor type, ER status, PR status, Her 2 neu status, tumor size, ECE, number of SLNs, number of positive SLNs, number of negative SLNs, OMS, LVI, multifocality, micrometastasis, NCT, and the timing of surgery. The factors found significant on univariate analysis were evaluated by the forward stepwise logistic regression method to predict the probability of having fewer than 10 nodes. All P values were 2-tailed, and a P value of ≤ 0.05 was considered to be significant.

Results

Three hundred seventy three patients had sentinel node metastasis and underwent immediate or delayed completion level I-II ALND. Patient and tumor characteristics are listed in Table 1. The median patient age was 53 years (range 29–84 years). Fifty four patients (14.4%) were treated with NCT. The mean tumor size was 2.54±1.6 (range 0.2 –9.5) cm. One hundred twenty three patients (33%) had multifocal breast cancer. The tumor histology was invasive ductal carcinoma for 312 patients (83.6%) and invasive lobular carcinoma for 6 patients (16.4%). The rates of ER, PR, and HER2/neu positivity were 86.1%, 55.5%, and 12.9% respectively. Nottingham grade was I in 60 tumors (16.1%), II in 173 tumors (46.4%), and III in 140 tumors (37.5%). The mean total number of SLN's per SLN biopsy was 2.9±1.5 (range 1-11). The mean numbers of SLNs with and without metastasis were 1.48±0.9 (range 1-9), and 1.42±1.4, respectively. Metastases to SLNs were detected by frozen section (37.3%), H&E staining on serial sections (58.4%), and immunohistochemistry (IHC) (26.8%). The mean OMS of the SLN was 9.5±7.5 (range 0.5-35) mm. The rate of macrometastasis (≥2mm) was 74.8% (n=279). ECE in the involved SLN was 30.3% (n=113), and 50.7% (n=184) had LVI. In 132 (35.4%) patients, CALND was done immediately after intraoperative detection of SLN metastasis. Two hundred one (53.9%) of the patients had delayed CALND after the detection of SLN positivity. Information regarding timing of CALND was not available for 40 patients.

Three hundred twelve (83.6%) patients had 10 or more axillary lymph nodes dissected. The mean numbers of total lymph nodes and lymph nodes containing metastasis in axillary dissection specimens were 15.5 ± 6.8 (range 1-50) and 2.05 ± 4.17 (range 0-47) respectively. On univariate analysis, factors significantly associated with fewer than 10 dissected nodes were NCT (OR= 0.28, P<0.0001), tumor size (OR=1.06, P=0.0087), timing of axillary surgery (OR=2.26, P= 0.02), and presence of SLN micrometastasis (OR=0.41, P=0.0023; Table 2). The other factors evaluated on univariate analysis, including age, Nottingham grade, histology, ER, PR and HER-2/neu status, tumor type, ECE, number of total SLN, OMS, number of positive SLNs, number of negative SLNs, LVI, and multifocality were found insignificant (p>0.05).

On multivariate analysis, presence of micrometastasis (P=0.004) and NCT (P= 0.011) remained significant (Table 3).

For the patients treated with NCT, the mean number of lymph nodes retrieved by CALND was 15.2±6 compared with 19.2±6 in the primary surgery group (p<0.001) (Table 4). A significantly greater percentage of patients in the NCT group (31.1%) had fewer than 10 lymph nodes dissected than in the primary surgery group (68.9%) (p<0.0001, Table 2). Similarly, the mean number of lymph nodes dissected was fewer and the percentage of patients with fewer than 10 lymph nodes recovered by CALND was greater in patients with micrometastatic SLN (Table 2, 4).

We also evaluated the prediction probabilities of obtaining fewer than 10 nodes based on combinations of the factors identified on multivariate analysis (Table 5). For example, the group who received NCT and had micrometastases in SLN had a probability of 51 % of having fewer than 10 nodes dissected. In contrast, this probability was only 11% in the group who underwent primary surgery without NCT and had macrometastases in SLN.

Discussion

We examined whether factors which are predictive of axillary disease have a significant association with total number of lymph nodes dissected. Factors which have been reported to have an association with the presence of 4 or more involved lymph nodes in SLN positive patients include: increased size of the primary tumor, LVI of the primary tumor, the size of SLN metastases, the number of involved SLNs, decreased number of negative sentinel nodes, and ECE in involved SLNs (2, 8). In the present study, there was no significant correlation between most of these factors and dissection of 10 or more nodes in CALND specimens. We found that the number of lymph nodes harvested in CALND specimen increases if the involved nodes had macrometastases in comparison to micrometastasis. A rate of 10 or more lymph nodes was higher in the macrometastases group compared with that of the micrometastatic group. One possible explanation about this situation is that, the surgeon who performed SLNB might have approached more aggressively during immediate CALND by removing more lymph nodes in the presence of gross metastases of SLN. It may also be due to immediate CALND itself.

Table 2. Fewer than 10 or more retrieved nodes with regard to patient, tumor, and treatment characteristics.

Characteristics of' the patients	*≥10 nodes n (%)*	*<10 nodes n (%)*	*P*
Age (year)			
<60	227 (72.7)	46 (75.4)	NS
≥60	85 (27.3)	15 (24.6)	
Pathologic tumor size (cm)			
≤2	165 (52.9)	20 (32.8)	0.0087
2-5	119 (38.1)	30 (49.2)	
≥5	28 (9)	11 (18)	
Tumor type			
IDC	263 (84.3)	49 (80.3)	NS
ILC	49 (15.7)	12 (19.7)	
Nuclear Grade			
1	52 (16.7)	7 (11.5)	NS
2	143 (45.8)	29 (47.5)	
3	114 (37.5)	25 (41)	
Lympho-vascular invasion			
Yes	153 (49)	31 (50.8)	NS
No	159 (51)	30 (49.2)	
Estrogen Receptor status			
Positive	272 (87.2)	49 (80.3)	NS
Negative	40 (12.8)	12 (19.7)	
Progesteron Receptor status			
Positive	179 (77.8)	28 (73.7)	NS
Negative	51 (22.2)	10 (26.3)	
Her2/neu			
Positive	41 (15.6)	7 (13.5)	NS
Negative	221 (84.4)	45 (86.5)	
Multifocality			
Yes	104 (33.4)	19 (31.1)	NS
No	207 (66.6)	42 (68.9)	
Macrometastasis in SLN			
Yes	243 (77.9)	36 (59)	0.0023
No	69 (22.1)	25 (41)	
ECE			
Positive	96 (30.8)	17 (27.9)	
NS			
Negative	216 (69.2)	44 (72.1)	
NCT			
Yes	35 (11.2)	19 (31.1)	<0.0001
No	277 (88.8)	42 (68.9)	
Timing			
Delayed	164 (57.7)	37 (75.5)	0.0213
Immediate	120 (42)	12 (24.5)	
Data not available for 40 patients			
Total SLN Number			NS
1	61 (91)	6 (9)	
2	89 (84)	17 (16)	
≥3	162 (81)	38 (19)	
Number of positive SLN			NS
1	209 (83.9)	40 (16.1)	
2	77 (83.7)	15 (16.3)	
≥3	26 (81.3)	6 (18.8)	
Number of negative SLN			NS
0	99 (87.6)	14(12.4)	
1	101 (86.3)	16 (13.7)	
2	54 (80.6)	13 (19.4)	
≥3	58 (6.3)	18 (23.7)	

IDC: Infiltrative ductal carcinoma, **ILC:** Infiltrative lobular carcinoma, **SLN:** Sentinel lymph node, **ECE:** Extracapsular extension, **NCT:** Neoadjuvant chemotherapy, **AD:** Axillary dissection

Table 3. Univariate and multivariate analysis of factors found significantly associated with dissection of fewer than 10 axillary nodes for patients with SLN metastasis.

Varieble	*Odds Ratio*	*95% Confidence Interval*	*p Value*
Univariate Analysis			
Pathologic tumor size (cm)	1.06	1.02-1.11	0.0087
Micrometastasis	0.41	0.23-0.73	<0.0023
NCT	0.28	0.15-0.53	<0.0001
Timing	2.26	1.13-4.51	0.0213
Multivariate Analysis			
Micrometastasis	0.004	0.23-0.73	<0.0023
NCT	0.011	0.15-0.53	<0.0001

SLN: Sentinel lymph node, **NCT:** Neoadjuvant chemotherapy

NCT has become the treatment of choice for patients with locally advanced breast cancer. During the past several years, the use of NCT has increased in order to facilitate breast conservation surgery and to provide improved local control (11,12). NCT can shrink the primary tumor as well as axillary nodal disease (4,11). Axillary nodal status and perhaps the number of axillary nodes involving the disease can be altered by NCT. Several studies demonstrated that NCT alters the lymphatic drainage pathways of the breast (13,14). When the primary tumor has a partial or complete response to NCT, similar changes also occur in the lymph nodes. It is well known that after NCT, microscopic examination of lymph nodes may reveal accumulations of histiocytes and display considerable lymphoid depletion, fibrosis, hyalinization, and obliteration of tumor metastases in lymph nodes (15-18). Neuman et al. reported that the rate of fewer than 10 lymph nodes retrieval in axillary dissections for patients with breast cancer treated with NCT was 13%, compared with 3% for patients who underwent primary surgery (10). Similarly Belanger J et al found that fewer lymph nodes were found in axillary dissection specimens of patients treated by NCT compared with those treated by primary surgery. They also hypothesized that this fibrotic replacement in the axilla may cause changes in axillary architecture, leading to greater technical difficulty in performing an adequate axillary dissection causing less number of lymph nodes retrieval (9). Our results support the current literature. We observed that both the mean number of lymph nodes harvested and the ratio of patients who had fewer than 10 axillary lymph nodes were significantly greater in the NCT group. In conclusion NCT is strongly associated with both a decreased median lymph node count and dissection of fewer than 10 lymph nodes in CALND. Therefore, fewer than 10 lymph nodes in CALND specimens in patients treated by NCT may not necessarily mean inadequate nodal staging if a level I and II ALND is performed.

Table 4. Association of mean numbers of lymph nodes dissected with micrometastasis and NCT

Varieble	*Mean lymph count number±SD*	*p Value*
Micrometastasis		0.047
No	19.07±6	
Yes	17.4±6	
NCT		
No	19.2±6	<0.001
Yes	15.2±6	

SLN: Sentinel lymph node, **NCT:** Neoadjuvant chemotherapy, **Sd:** Standard deviation

Table 5. Prediction Probabilities of dissection of fewer than 10 Nodes for Patients with Combinations of the Significant Factors Identified on Multivariate Analysis.

Logit (prob of lymph nodes <10) = 2.17 - 1.287 (NCT) - 0.907(micromet).

Combinations of the Significant	*Prediction Probabilities (%)*
Factors on Multivariate Analysis	
NCT +, micrometastasis +	51
NCT +, micrometastasis -	30
NCT -, micrometastasis +	23
NCT -, micrometastasis -	11

NCT: Neoadjuvant chemotherapy

The number of total lymph nodes retrieved from axillary dissection decreases with advanced age (19- 22). It was reported that with older age, some lymph nodes may regress spontaneously. In addition, more fat tissue may be present in the axilla challenging to palpate lymph nodes. In our study, there was no difference between patients who were 60 years and older when retrieved lymph node counts were compared. Similarly there was no significant correlation between the harvested lymph node count and tumor type, grade, ER, PR and HER-2 receptor status. But there was a negative correlation on univariate analysis between tumor size and more than 10 nodes retrieval in CALND specimens. However, this was not significant on multivariate analysis. Interestingly we found that retrieving 10 or more lymph nodes is more frequent if the primary tumor size is smaller than 2cm. But the mean number of total lymph count was found to be similar in small and larger tumors. This may be due to the frequent use of NCT in patients with large sized tumor; 43.6% of patients with tumor size of more than 5 cm received NCT. Pertik D. W. et al showed that the number of nodes excised was not associated with any tumor factors or with the breast operation performed (22). These results are similar to our findings. The relationship between the number of lymph nodes excised and the academic affiliation of the four surgeons and the pathologists were not examined in the present study. All four are experienced surgeons who perform breast surgery with the same academic affiliation with large volume of BC patients per year, and they all performed standard technique of CALND including level 1 and 2 for all patients in the study group. All surgical axillary specimens were analyzed in a similar manner by a pathologist from the same hospital.

We have also searched for other factors which may affect the lymph node retrieval, such as the timing of CALND. Goyal A et al (23) showed their mean lymph node counts in the one stage vs. two stage axillary surgeries as 6.4 and 6.2, respectively. But they did not evaluate the relationship between one or two stage surgeries and fewer than 10 axillary lymph nodes rates in BC patients with positive SLN. Similarly to Goyal's study the mean retrieved lymph count in CALND was 18.8 and 18.9 in the immediate and delayed axillary surgery in our study. But interestingly we found that removal of less than 10 lymph nodes was more common in patients who underwent delayed CALND. This may result from the fact that the patients who underwent immediate CALND have a higher macrometases rate that more commonly leads to a decision of immediate CALND as compared to delayed CALND. Macrometastases was associated with increased lymph node retrieval by both univariate and multivariate analysis in the present study. It may reflect that the patient with macrometastatic lymph node disease undergoes a more extended lymph node dissection. In addition, previous dissection for SLNB may challenge the surgical technique and lead to a lower number of lymph nodes removed due to the fibrosis caused by the cicatrisation (9).

In conclusion, NCT and the presence of micrometastases in the SLN affect both the median number of lymph nodes removed and the possibility that fewer than 10 lymph nodes will be retrieved in the CALND specimen. The other possible factors, such as timing of CALND and tumor size affect the harvested lymph count. More data is required to evaluate the real effect of these factors and also the importance of the effect on local recurrence and survival.

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