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ORIGINAL ARTICLES / ORİJİNAL MAKALELER

EVALUATION OF SAFETY AND EFFICACY OF THE SENTINEL LYMPH NODE BIOPSY IN PATIENTS WITH EARLY-STAGE BREAST CANCER WITHOUT AXILLARY INVOLVEMENT

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AKSİLLA TUTULUMU OLMAYAN ERKEN EVRE MEME KANSERLİ HASTALARDA, SENTİNEL LENF NODU BİYOPSİSİNİN GÜVENİLİRLİĞİ VE ETKİNLİĞİNİN DEĞERLENDİRİLMESİ

ÖZET

Amaç: Bu çalışmada klinik olarak aksilla negatif erken evre meme kanserli hastalarda sentinel lenf nodu biyopsisinin etkinliği araştırıldı. Yöntemin sentinel lenf nodunu bulma ve yanlış negatiflik oranları hesaplanarak erken evre meme kanserli hastalarda aksillanın değerlendirilmesinde sentinel lenf nodu biyopsisinin yerinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Bu prospektif çalışma, erken evre meme kanseri tanısıyla Mart 2006 – Mart 2009 tarihleri arasında Çukurova Üniversitesi Tıp Fakültesi Genel Cerrahi Anabilim Dalı'nda tedavi edilen 57 hastada yapıldı. Hastalar iki farklı gruba ayrıldı. Grup I'de 35 hastada mavi boya tekniği, Grup II'de 22 hastada kombine teknik uygulandı. İnvaziv kanser saptanan 46 hastaya sentinel lenf nodu biyopsisi sonrası aksiller lenf nodu diseksiyonu yapıldı.

Bulgular: Grup I'de 2 hastada, Grup II'de 1 hastada olmak üzere toplam 3 hastada sentinel lenf nodu saptanamadı. Sentinel lenf nodu bulma oranı tüm hastalar için %94,7 olup bu oran Grup I'de %94,2 , Grup II'de %95,4 idi. Yanlış negatiflik oranı Grup I'de %22,2 , Grup II'de %30 olup tüm hastalar için %26,3 idi. Tekniği öğrenme sürecindeki ilk 15 olgu değerlendirme dışı bırakıldığında tüm grupta sentinel lenf nodu bulma oranı %96,8'e yükselirken yanlış negatiflik oranı %0'a geriledi.

Sonuç-Yorum: Bu çalışmada erken evre meme kanserli hastalarda aksillanın evrelemesinde sentinel lenf nodu biyopsisinin etkin ve güvenli bir yöntem olduğu belirlendi. Her merkezin yeterli deneyim kazanıncaya kadar, sentinel lenf nodu biyopsisi ile aksiller lenf nodu diseksiyonunu beraber yapmasının daha güvenli olacağı düşünüldü.

Anahtar sözcükler: meme kanseri, sentinel lenf nodu biyopsisi, yanlış negatiflik oranı

ABSTRACT

Purpose: In this study, sentinel lymph node identification and false negative rates were calculated and determination of the place of sentinel lymph node biopsy in the evaluation of axilla in patients with early stage breast cancer was aimed.

Materials and Methods: This prospective study was performed on 57 patients with early stage breast cancer who were treated at the Department of Surgery in Medical Faculty of Çukurova University between 2006-2009. Blue dye technique was performed in 35 (Group I) and the combined technique was performed in 22 patients (Group II). Axillary lymph node dissection was performed after sentinel lymph node biopsy on 46 patients who have invasive breast cancer.

Results: Sentinel lymph node was not detected in two patients in Group I and one in Group II. Sentinel lymph node identification rate was 94.7% for all patients, and it was 94.2% in Group I and 95.4% in Group II. False negative rate was 26.3% for all patients which was 22.2% in Group I and 30.0% in Group II. Sentinel lymph node identification rate was increased to 96.8% and false negative rate decreased to 0% when the first 15 patients within the learning period was excluded from the statistical analysis.

Conclusion: Sentinel lymph node biopsy is a safe and effective technique on staging of axilla in patients with early stage breast cancer. Nevertheless, every medical center should perform sentinel lymph node biopsy and axillary lymph node dissection together untill getting experienced.

Keywords: Breast cancer, sentinel lymph node biopsy, false negative rate

Axillary lymph node dissection (ALND) an integral part of the treatment of breast cancer, providing information about the prognosis and to plan the further therapy (1,2). However, it is also the most important cause of morbidity. As a result of the developments in the treatment of breast cancer, along with the transition to less invasive surgery, similar studies have been initiated for the axillary surgery, and as a result, the sentinel lymph node biopsy (SLNB) in breast cancer has been implemented.

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In this study, safety and efficacy of the sentinel lymph node biopsy was investigated in patients with clinically early-stage breast cancer without axillary involvement, at Cukurova University Faculty of Medicine, Department of General Surgery.

Materials and methods

Working model

in this prospective study, 57 patients with early-stage breast cancer (clinical T1-2, N0, M0), without previous breast surgery, and without any clinical and radiological suspicion of metastatic lymph nodes in the axilla, who were treated at Cukurova University School of Medicine, Department of General Surgery, between March 2006 and March 2009. There were two separate study groups, with a different application of the SLNB method in each. The blue dye technique was applied to 35 patients in Group I, and along with blue dye, radio-colloid substance was administered (combined technique) to 22 patients in Group II. The patients were randomly selected for the groups. The demographic characteristics of the patients and the distribution according to the groups are shown in Table 1.

Table 1. The characteristic features of the patients and distribution according to the groups.

	Group I (n=29) n (%)	*Group II (n=17) n (%)*	*Total (n=46) n (%)*	*P value*
Tumor localization				
Upper lateral quadrant	17 (58,6)	5 (29,4)	22(47,8)	
Lower lateral quadrant	1 (3,4)	6 (35,3)	7 (15,2)	-
Lower medial quadrant	3 (10,3)	2 (11,8)	5 (10,9)	
Upper medial quadrant	5 (17,2)	3 (17,6)	8 (17,4)	
Retroareolar	3 (10,3)	1 (5,9)	4 (8,7)	-
Histologic type				
Invasive ductal carcinoma	24 (82,8)	16 (94,1)	40 (87,0)	
Invasive lobular carcinoma	2 (6,9)	1 (5,9)	3 (6,4)	
Mucineous carcinoma	1 (3,4)	-	1 (2,2)	
Medullary carcinoma	1 (3,4)	-	1 (2,2)	-
Tubular carcinoma	1 (3,4)	-	1 (2,2)	
Grade				
G2	20 (68,9)	13 (76,5)	33 (71,7)	0,739
G3	9(31,1)	4 (23,5)	13 (28,3)	
Tumor Focality				
Unifocal	23 (79,3)	12 (70,6)	35 (76,1)	0,722
Multifocal	6 (20,7)	5 (29,4)	11 (23,9)	
Receptor Status				
PR(+)	21(72,4)	15(88,2)	36(78,3)	0,282
PR(-)	8(27,6)	2(11,8)	10(21,7)	
Receptor Status				
ER(+)	26(89,7)	14(82,4)	40(87,0)	0,655
ER(-)	3(10,3)	3(17,6)	6(13,0)	
Tumor Size				
≤ 2 cm	21 (72,4)	10 (58,8)	31 (67,4)	0,309
>2 cm	8 (27,6)	7(41,2)	15 (32,6)	
Breast				
Right breast	10 (34,5)	13 (76,5)	23(50,0)	0,015
Left breast	19 (65,5)	4(23,5)	23(50,0)	
BiopsyType				
Tru-cut	13 (44,8)	4 (23,5)	17 (36,9)	0,259
Excisional	16 (55,2)	13 (76,5)	29 (63,1)	
Menapausal Status				
Pre-menapausal	11 (37,9)	10 (58,8)	21(45,7)	0,231
Post-menapausal	18 (62,1)	7 (41,2)	25(54,3)	
Age				
Mean±Standard deviation	53,4±11,0	46,41±6,3	50,8±10,1	0,013
Min-max	29-74	30-59	29-74	

*The patients in whom SLN could not be found and no ALND was performed are not shown in the table.

Determination of the SLN

Isosulphane blue was used as blue dye. Three to four milliliters of dye was injected to the subareolar region in patients who are diagnosed with tru-cut biopsy, and to the biopsy cavity and around the subareolar region in patients diagnosed by excisional biopsy. In the group with the combined technique, 0.5 milliliters of Tc 99 mm nanocolloid, 0.5 to 0.6 mci, was injected to around the tumor, 2 to 4 hours before the surgery. The SLN, which was identified by the lymphoscintigraphy was localized with the gamma probe, and marked.

Surgical technique

In both groups, 5-10 minutes after the injection of the blue dye, massage was performed from the breast to the armpit. In patients undergoing modified radical mastectomy, an elliptical incision including the areola; in breast-conserving surgery an incision in the breast with a separate incision in the axilla for SLNB and ALND was made. In the fatty tissue below the axillary incision, following the blue-painted lymphatic channels, the blue stained lymph node / nodes were searched (Figure 1). All the detected blue dyed lymph nodes were removed and sent for frozen section examination as the SLN. In group II, in addition to this process, with the help of the gamma probe, the uptake in the blue-painted lymph nodes were searched and the records were kept. Axilla was then re-scanned with the gamma probe in order to search for the lymph node / nodes without dye uptake but with radioactivity. The lymph node / nodes with radioactivity were also removed and sent for frozen section examination as SLN. After the last scanning with the gamma probe, when there was activity less than 10% of that of the excised SLN in the

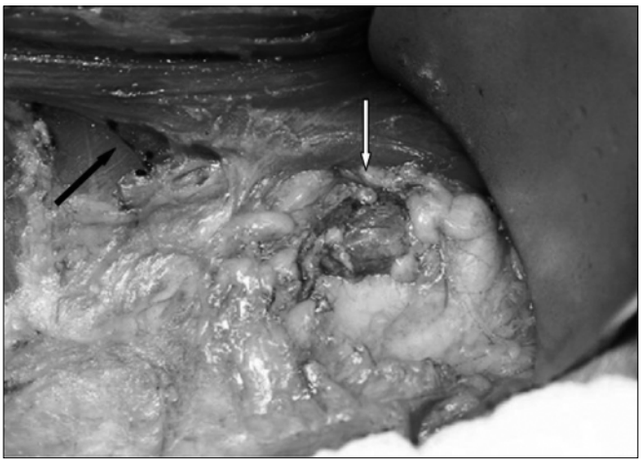

Figure 1. The black arrow shows an lymphatic duct which is draining to sentinel lymph node indicated with white arrow.

axilla, it was decided that there was no other SLN and the procedure was terminated. In all patients in both groups, who were diagnosed with invasive cancer, SLNB was followed by ALND.

Pathologic examination

For the frozen section examination, the sentinel lymph nodes were divided into two with the long axis parallel to the incision (those smaller than 5 mm in size were not divided). First the imprint examination was performed, which was followed by the frozen section. All sentinel lymph nodes were also examined in paraffin sections. For all the axillary lymph nodes other than the SLN (non-sentinel lymph nodes) underwent a routine pathological examination. In the sentinel lymph nodes in which no metastasis was detected in the paraffin sections, immunohistochemical analysis was performed retrospectively. As the immunohistochemical marker pankeratin [monoclonal mouse anti-human Cytokeratin (AE1-AE3), DAKO] was used.

Statistical analysis

The false negative, sensitivity, and negative predictive values of the method were calculated. In 8 patients with a diagnosis of ductal carcinoma in situ and a high risk of axillary metastasis (4 patients in group I and 4 in group II), no ALND was performed because no metastases were detected in the SLN. These patients were included in the calculation of statistical analysis, only in the calculation of the detection rate of the SLN. Because the SLN operation requires a learning process, the data were re-analyzed after removing the first 10 cases and the first 15 cases.

The data analysis was performed using a statistical package program, SPSS for Windows 15.0 (SPSS Inc., Chicago, IL). For the group comparisons of the variables that do not have a normal distribution, the Mann-Whitney U test was used. For the comparisons of the groups with categorical variables, the Fisher's exact and the corrected chi-square test was used. p value <0.05 was considered statistically significant. In this study, the following formulas were used in the calculation of the sensitivity, specificity, false-negative rate and the SLN detection rate:

SLN detection rate: Patients with SLN / All patients

Sensitivity: Patients with (+) SLN and (+) Axillary LN / All patients with (+) Axillary LN

Negative predictive (estimated) rate: Patients with (-) SLN and (-) Axillary LN / Patients with (-) SLN

False negative rate: Patients with (-) SLN and (+) Axillary LN / All patients with (+) Axillary LN

Results

SLN detection rate

In a total of 3 patients (2 patients in group I and in 1 patient in group II) the SLN could not be determined. SLN detection rate was 94.2% in group I, and 95.4% in group II. The mean number of extracted SLN was 2.4 (1-3), and the mean number of non-SLN issued as a result of the axillary dissection was 29.4(13-52), respectively. In group I, all the SLNs were stained with the blue dye, whereas in Group II, of the 36 SLNs 27showed involvement of both the radiocolloid substance and the blue dye. One node was only stained with the blue dye alone, and eight nodes had only the involvement of the radiocolloid substance. Of the 8 SLNs with only radiocolloid substance involvement, in 4 metastasis was found.

Pathologic evaluation of sentinel lymph nodes

all the extracted sentinel lymph nodes were sent for frozen section examination during the surgery. In 14 patients (7 patients in Group I and 7 in Group II) (30.5%) metastases were detected in the SLN. Of the 32 (69.5%) patients in whom no metastases were found in the SLNs, 5(10.8%) had metastases in the non-sentinel lymph nodes extracted during the axillary lymph node dissection (false negative cases). In the remaining 27 patients there were no metastases either in the SLNs, nor the non-SLNs. The comments made as a result of frozen section of the SLNs were confirmed with the paraffin examination. All the SLNs in which no metastasis was detected by the frozen sections and paraffin examinations underwent immunohistochemical analysis with the pankeratin. Of the 5 SLNs with positive non-SLN, 2 were stained with the pankeratin.

Predictive value of sentinel lymph node

of the forty six patients, in 14 (30.5%) metastases were detected in the SLN, whereas 27 (58.7%) patients had no metastasis either in the SLN or the non-SLNs. Five (10.9%) patients had no metastasis in the SLN, but metastases in the non-SLN (Table 2-3). SLN detection rate was 94.2% in Group I, 95.4% in Group II, and 94.7% for all patients. The

Table 2. Histopathological status of the SLN and non-SLN.

	Metastasis in the SLN	*Metastasis in the Non-SLN*	
		+	-
Group I N=29	+	3	4
	-	2	20
Group II N=17	+	6	1
	-	3	7
Total N=46	+	9	5
	-	5	27
After the learning phase			
The first 10 cases were excluded n=36	+	9	5
	-	2	20
The first 15 cases were excluded n=31	+	8	5
	-	0	18

Table 3 The real situation of the SLN and non-SLNs with respect to the learning period.

SLN	*Non-SLN*	*Total n=46*	*first 10 cases were excluded n=36*	*first 15 cases were excluded n=31*
Positive	Positive	14	14	13
Negative	Negative	27	20	18
Negative	Positive	5	2	0

Table 4. The sensitivity and accuracy rates of the SLNB method.

	SLN detection rate (%)	*Sensitivity (%)*	*False negative rate (%)*	*Negative predictive value (%)*	*Accuracy (%)*
Group I (n=29)	94,2	77,7	22,2	90,9	93,1
Group II (n=17)	95,4	70	30	70	82,3
Total (n=46)	94,7	73,6	26,3	84,3	89,1
After the learning phase					
The first 10 cases were excluded (n=36)	97,2	87,5	12,5	90,9	94,7
The first 15 cases were excluded (n=31)	96,8	100	0	100	100

sensitivity was 77.7% in Group I, 70% for Group II, and 73.6% for all patients. The false negative rate was 22.2% in Group I, 30% in Group II, and 26.3% for all patients (Table 4). The data obtained from different studies indicate that there is learning curve for SLNB and sufficient experience is acquired with an average of 10 to 20 cases. When the first 10 patients were excluded from the analysis, the SLN detection rate was 97.2%, and when the first 15 patients were excluded, it was found to be 96.8%. The false negative rate was calculated as 12.5% and 0%. When the first 15 patients were excluded from the analysis, the sensitivity, the negative predictive value and the accuracy rate of the method were calculated as 100% (Table 4).

Relationship between the tumor characteristics and the axillary metastasis

When the relationship between the variables of the primary tumor and the axillary lymph nodes examined in terms of metastasis, the presence of lymphovascular invasion was found to be the most important factor increasing the risk of the axillary metastases ($p = 0.0001$). The increase in tumor size and the presence of multi-focality were the other factors that increase the risk of tumor metastasis in axillary lymph nodes ($p < 0.05$).

Discussion

The SLNB which was previously used in the treatment of diseases such as penile carcinoma, and melanoma has been introduced in the treatment of breast cancer nowadays. As a result of the prospective randomized studies which have been conducted to determine the reliability of this method, SLNB has taken place in the standard treatment protocol of the modern breast surgery to determine the status of the axilla (3).

ALND is the most important cause of morbidity in breast surgery. Following the ALND, 50 to 70% of the patients have complaints (4). Lin et al. have shown that 40% of the patients, who underwent axillary dissection, develop acute lymphedema (5). In various studies, in which the effects of various treatment modalities in the formation of lymphedema were investigated, the incidence of lymphedema after ALND ranged from 6-30%, this proportion was even higher in case of radiotherapy (6,7). However, the low risk of axillary lymph node metastasis in small tumors, and the fact that the information obtained from the axilla in these patients does not change the decision for the adjuvant therapy, have led the researchers to the search for alternative methods to avoid these complications (8).

The NSABP B-04 (National Surgical Adjuvant Breast Project) study has shown that the axillary dissection in the treatment of breast cancer does not have any effect on the life expectancy in the long-term (9). There are also other various studies, which indicate that there is no relationship between the number of extracted lymph nodes from axilla and the prognosis (10). These data have gradually reduced the importance of the extensive axillary dissection. As a result, the question arises whether it is necessary to perform axillary dissection in patients with no clinically detectable metastatic lymph nodes in the axilla. This led to the implementation of new techniques in the axillary approach, and SLNB has been implemented for the treatment of breast cancer, in the 1990's (11,12).

To determine SLN, blue dye technique, radioisotopes or a combination of both techniques are used. Giuliano et al. have implemented SLNB using 1% isosulphane blue in their first published series of 174 patients, and have determined the SLN in 114 patients (65.5%). The same researchers have reported a rate of 94% in their other series (13). In a similar study, performed with isosulfan blue by Eser et al., detection rate of 95% was achieved (14). Albertini, who applied blue dye and radioisotope material together, has reported the detection rate of the SLN as 92% (15). In our study, the detection rate of the SLN was 94% in Group I, and 95.4% in Group II. The SLN detection rate was similar to other studies.

SLNB is considered to be an effective an easy method for staging of axilla, with a low morbidity, an accuracy of over 90%, and a false-negative rate less than 5% (16). The false negative rate of the method has been reported to vary between 0 to14% (17,18). The reasons of the high rate of false-negative results are the blockage of the lymph channels to the SLN due to the metastasis, the damage to the lymph channels by excisional lymph node biopsy, the surgeon's learning curve and the insufficient training in applying the technique (19,20). In our study, the false negative rate was 26.3%. When compared with the literature, this ratio was higher than the specified limit. The patients with false-negative results were all within the first fifteen cases. The false-negative rate in our study

was associated with the fact that these procedures were performed in the learning phase of the SLNB technique. There is a learning curve for the SLNB technique. In the first study of Giuliano et al., the false negative rate was 12%, decreasing to 0% after they gained experience (13). Other researchers, such as Cody and Morrow have also reported that the surgeons who perform SLNB frequently have higher rates of sentinel node detection and lower false-negative rates (20,21). Surgeons with sufficient experience on this technique should have a SLN detection rate above 85% and false-negative rate of less than 5%. These ratios can be achieved after an average of 10 to 20 cases. Evaluating the results of the studies of the American Society of Breast Surgeons, surgeons are advised to perform the SLNB together with ALND the first 20 cases until learning the technique (22).

In our study, the SLN detection rate was 80% at the end of the 10 patients, and rose to 87% at the end of the 15th patient. The SLN detection rate of 85% mentioned in the literature, was reached at the end of the 15th case. When these 15 cases were evaluated as the cases in the learning process, and were excluded from the statistical calculations, the SLN detection rate rose to 96.8% and the false negative rate dropped to 0%. The sensitivity of the method, the negative predictive value and accuracy rates were calculated as 100%. These results were consistent with the literature. The number of the extracted SLNs is different in most of the studies, but the false-negative rate of SLN was found to be lower when two or more SLNs are removed, compared to the studies in which only one SLN was extracted. The extraction of more than four SLNs did not affect the accuracy rates (23,24). In our study, the average number of removed SLNs was 2.4, with a range of 1 to 3 lymph nodes, which was consistent with the literature.

After the SLNB, the axillary dissection in the same session, can be decided with an accurate and reliable intra-operative examination. In this respect, the intraoperative examination of the SLN is very important. For the intraoperative examination of the SLN, imprint and scrape cytology, frozen section and rapid immunohistochemical examinations can be used. The accuracy rates of the frozen section and the cytological examination are close to each other and vary between 80% and 99% (25). False-negative rate is between 9% to 52% for frozen section, and 5% to 70% for cytological examination (26,27). Although the extremely wide range of the accuracy rate and the false-negative rate is a topic of debate all over the world, the frozen section examination is the most preferred method among the surgeons. However, the lack of detection of micrometastases of intraoperative frozen section examination is an important shortcoming (28).

In 2002, "American Joint Committee on Cancer (AJCC)" has stressed the necessity of more sensitive diagnostic tests in the staging of breast cancer by providing a separate place for the micrometastases, and this has directed the researchers to the immunohistochemical investigations. There are many studies showing the benefit of the immunohistochemical examination in determining the micrometastases (29-32). However, this method also has drawbacks, such as being time consuming and expensive. Therefore, it has been concluded that the immunohistochemical review should be implemented only in case of doubt in the H&E sections (33,34). In our study, the immunohistochemical examinations with pankeratin were done later, in 27 patients in whom no disease could be identified in the SLN, and only 2 cases were found to have micrometastasis. According to current knowledge, in the presence of undetectable micrometastases by frozen section examination, which is detected later, the axillary lymph node dissection should be performed (35).

In conclusion, SLNB was found to be an effective and a safe method for the staging of axilla in patients with early stage breast cancer, with a high accuracy and a low morbidity, as an alternative to axillary lymph node dissection. However, every surgeon should perform axillary lymph node dissection together with the sentinel lymph node biopsy until he/she acquires enough experience. The tumor characteristics, such as multifocality, tumor size and lymphovascular invasion, should be carefully considered while performing SLNB.

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