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RESEARCH ARTICLE/ARAŞTIRMA YAZISI

CLINICAL IMPORTANCE OF MICROMETASTASIS IN SENTINEL LYMPH NODE

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ABSTRACT

Introduction: The axillary lymph node status is still the most important accepted prognostic factor in the staging and treatment of breast cancer, although some controversies exist regarding tumor characteristics.

In this study, we have evaluated the incidence of micrometastasis and nonsentinel lymph node metastasis, and local and axillary recurrence rate of these patients after completed level I-II axillary lymph node dissection.

Materials and Methods: Between January 2000 and June 2008, 760 patients with early stage breast cancer underwent sentinel lymph node biopsy were evaluated and 45 patients (6.0 %) with micrometastasis (0.2-2.0 mm) in sentinel lymph node biopsy included in this study. Patients with negative SLNs determined by hematoxylin and eosin staining were evaluated further examination with cytokeratin immunohistochemistry to detect micrometastasis and isolated tumor cells. Data concerning tumor and patients' characteristics and adjuvant treatment of these patients were recorded.

Results: Median age was 46 (26-67) years, median tumor size was 20 (1-50) mm, and median number of excised sentinel lymph nodes were 2 (1-5). All patients with micrometastasis underwent further level I-II axillary lymph node dissection. In 11/45 (24.4 %) patients with micrometastasis in their sentinel lymph node biopsy had nonsentinel lymph node metastasis after an axillary lymph node dissection and the mean metastatic lymph node number was 1,2 (1-9). The factors related with nonsentinel lymph node metastasis were examined (age, tumor size, quadrant, histologic grade, lymphovascular invasion, histopathologic type, receptor status, multifocality/multicentricity, and the size of micrometastasis). There was no factor found to be related with nonsentinel lymph node metastasis. Stage migration occurred in 4 out of 45 patients (8.8%) due to the detection of micrometastasis or macrometastasis in nonsentinel lymph nodes, however, adjuvant chemotherapy regimen was not changed in these patients. The radiation therapy field was extended due to detection of 4 or more metastatic lymph nodes. The median follow up time was 19 (6-113) months and there was no axillary recurrence detected during this period.

Conclusions: The classical opinion after detection of micrometastasis in sentinel lymph nodes was further axillary dissection. However, non randomised, non prospective studies with 4-5 year follow up time showed 0.6 % of axillary recurrence without further axillary lymph node dissection. However, still we need the results of randomized, prospective studies.

Key words: Sentinel lymph node biopsy, micrometastasis, isolated tumor cells, axillary lymph node dissection, local recurrence.

SENTİNEL LENF NODUNDA MİKROMETASTAZIN KLİNİK ÖNEMİ

ÖZET

Amaç: Meme kanserinin evrelemesinde ve tedavisinde aksiller lenf nodunun durumu halen en önemli kabul gören prognostik faktördür. Bu çalışmada, sentinel lenf nodunda mikrometastaz saptanan hastalarda non sentinel lenf nodu pozitiflik oranını, level I-II aksiller diseksiyon sonrası mikrometastaz varlığının lokal ve aksiller rekürens üzerine etkilerini bulmayı amaçladık.

Hastalar ve Yöntem: Ocak 2000 ve Haziran 2008 tarihleri arasında toplam 760 hastaya erken evre meme kanseri tanısı ile sentinel lenf nodu biyopsisi yapıldı. 45 (%6) hastada sentinel lenf nodu biyopsisinde mikrometastaz (0.2-2.0 mm) tespit edildi. Hastaların ve tümörün karakteristik özellikleri retrospektif olarak kaydedildi.

Bulgular: Çalışmaya alınan 45 hastanın ortanca yaşı 46 (26-67), ortanca tümör boyutu 20 (1-50) mm ve ortanca çıkarılan sentinel lenf nodu sayısı 2 (1-5) idi. Tüm mikrometastaz saptanan hastalara tamamlayıcı seviye I-II aksiller diseksiyon yapıldı. Hastaların 11'inde non sentinel lenf nodu metastazı saptandı (11/45 - %24.4). Non sentinel lenf nodu metastazını etkileyen faktörlerden (yaş, tümör boyutu, yerleşim, histolojik grad, lenfovasküler invazyon varlığı, histolojik grad, reseptör durumu, multifokalite/multisentrisite ve mikrometastazın boyutu) hiçbiri istatistiksel olarak anlamlı bulunmadı.

Sonuç: Sentinel lenf nodunda mikrometastaz saptanması durumunda klasik bilgi tamamlayıcı seviye I-II aksiller diseksiyon yapılması yönündedir. Ancak, non randomize, prospektif olmayan bazı çalışmalar 4-5 yıllık takip sonrası aksiller rekürens oranını %0.6 olarak vermektedir. Ancak, genede prospektif, randomize klinik çalışmaların sonuçlarını beklemek gerekmektedir.

Anahtar sözcükler: Sentinel lenf nodülü biyopsisi, mikrometastaz, izole tümör hücresi, aksiller lenf nodu diseksiyonu, lokal rekürrens.

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Introduction

The advent of sentinel lymph node biopsy (SLNB) has made a significant impact on the field of surgical oncology (1,2). The sentinel lymph node (SLN) procedure is a widely accepted method for staging of patients with early breast cancer. The SLNB technique, as a staging procedure, is an extremely sensitive and specific method to predict whether breast cancer has metastasized to regional lymph nodes, and SLNB has decreased morbidity compared with axillary lymph node dissection (ALND) (3,4). In addition, lymph node status can influence management decisions regarding adjuvant local and/or systemic therapies.

Although axillary node status is one of the most important prognostic factors, about a quarter of all axillary node-negative patients with routine hematoxylin & eosin staining have relapses within 10 years (5). The methods used for detection of metastatic involvement in axillary dissected patients may be insufficient and many patients may be understaged due to missing minimal lymph node involvement (micrometastasis (MM) or isolated tumor cells (ITC)) and undertreated for that reason. The upstaging of breast cancer observed with the detailed examination of SLNs (multislice investigation and introduction of immunohistochemical examination) and the detection of more MMs (6). This has raised questions concerning treatment of the axilla with MMs positive SLN as well as questions concerning the clinical relevance of MMs in these patients.

In this study, we have evaluated the incidence of MMs in SLNs and nonsentinel lymph node metastasis, and clinical importance of micrometastatic disease, also local and axillary recurrence rate of these patients after completed level I-II axillary lymph node dissection.

Materials and Methods

Between January 2000 and June 2008, 760 patients with early stage breast cancer, underwent SLNB procedure in our Breast Unit at Istanbul University, Istanbul Medical Faculty, General Surgery Department. Forty-five (out of 760) patients (6.0 %) with MM (0.2-2.0 mm) in SLNB were included in this study. The data concerning tumor and patients' characteristics and adjuvant treatment of these patients were recorded retrospectively. This study was approved by our hospital ethics committee and all statistical analysis was performed using SPSS 15.0 (SPSS Inc, Chicago, IL) program. We used Chi-square tests to compare the relation between NSLNM rate and MMs.

The sentinel lymph nodes (SLN) were marked and identified with 99m technetium-labeled colloid and/or blue dye. Patients with negative SLNs determined by hematoxylin and eosin staining were evaluated further examination with cytokeratin immunohistochemistry (IHC) to detect MMs or ITCs.

Additional adjuvant radiotherapy, chemotherapy, and hormonal therapy was considered for each patient according to national guidelines based on conventional criteria such as SLN status, hormone receptor status, age (pre/postmenopausal), tumor size, and Scarff–Bloom–Richardson (SBR) tumor grade. Treatment of patients with breast conserving surgery was completed with radiotherapy; consisting of total breast irradiation up to a dose of 50 Gy and a boost when indicated. Patients with a sentinel node containing micrometastasis were followed-up for a median time of 19 months. Local recurrences and systemic metastasis were recorded during follow up time period.

Table 1. Patients' and tumor characteristics.

Factor	*Number*	*%*
Median age (years)	46 (26-67)	
Median tumos size (mm)	20 (1-50)	
Histopathology		
IDC	37	82.2
ILC	4	8.9
Mixed	2	4.4
DCIS	2	4.4
Unifocal	32	71.1
Multifocal and/or multicentric	13	28.9
LVI (+)	24	13.3
Median number of SLNB	2 (1-5)	
Mean number of metastatic lymph nodes	1,2±1,61 (1-9)	
Median size of metastatic SLN (mm)	1 (0.7-2.0)	

Table 2. SLNB procedure techniques.

SLNB technique	*Number*	*%*
Blue dye	35	77.8
Blue dye and 99m technetium-labeled colloid	10	22.8

Results

383/760 (50.4%) patients with early stage breast cancer had negative SLNB and 377/760 (49.6%) had positive SLNB that underwent completed ALND. Fourty-five patients (45/760, 6.0%) were diagnosed with micrometastatic disease in SLNB. The patients' and tumor characteristics of these 45 patients were shown at Table 1. SLNB procedure was performed with only blue dye in 35 patients (77.8%) and both blue dye and 99m technetium-labeled colloid in 10 patients (22.2%) (Table 2). All patients with MMs underwent further level I-II ALND. In 11/45 (24.4%) patients with MM in SLNB had nonsentinel lymph node metastasis (NSLNM) after ALND and mean metastatic lymph node number was 1,2 (1-9).

The factors related with NSLNM were examined (age, tumor size, location of tumor, histologic grade, lymphovascular invasion, histopathologic type, receptor status, multifocality/multicentric-

Table 3. The patients with stage migration.

Patient number	*After SLNB*	*After ALND*
1	T1N1	T1N2
2	T1N1	T1N2
3	T1N1	T1N2
4	T2N1	T2N2

ity, the size of MM, and the number of excised SLNs). There was no factor found to be predicted with NSLNM. On the other hand, patients with 1 excised SLN had 38.8% (7/18) NSLNM rate, with 2 excised SLN had 16.7% (2/12), and the rate of NSLNM in patients with 4 or more SLN was 0% (0/5).

Stage migration occurred in 4 out of 45 patients (8.8%), due to the detection of micrometastasis or macrometastasis in NSLNs (Table 3); however, the adjuvant chemotherapy regimen was not changed in these patients. The radiation therapy field was extended due to detection of 4 or more metastatic lymph nodes.

The median follow up time was 19 (6-113) months and there was no axillary recurrence detected during this period. Two patients (4.4%) developed distant metastasis and one patient (2.2%) died due to systemic disease recurrence during follow up.

Conclusions

Lymph node metastasis is a multifactorial event. Several variables have been described as predictors of lymph node metastasis in breast cancer. These are: the size of tumor, the size of metastasis in lymph node, the presence of lymphovascular invasion, and high histologic grade (Grade 3). In 32-66% of patients with positive SLNs, the SLN is the sole site of metastasis (7-10). Thus, it has become clear that the size of the metastasis in the SLN is generally accepted as a predictor of the NSLNM. The risk of NSLNM is high for macrometastasis (45-79%) and intermediate for MMs (13-24%) (11).

The significance of SLNs which contain MM and/or ITC in the absence of macrometastasis has been the subject of much debate. Published studies have reported divergent results regarding the significance and implications of MM in breast cancer. It is accepted procedure that positive SLNs mandate complete ALND without any randomized trial, although randomized trials are ongoing and the results are pending. What should we do about minimal SLN involvement?

Some of the earliest studies before SLNB concept comparing node negative women to those with ALN MM (not specified in diameter) found associations with poorer prognosis (12). De Mascarel et al. reported in 1992 on a group of 120 axillary dissected patients with MM (occult metastasis). On the multivariate analysis, survival for patients with MM was statistically significantly worse than that of patients with true negative ALN (13).

The study by Grabau et al. is the largest study showing population based national figures for incidence rates and the prognostic value of MMs, on multivariate analysis. In this study, of patients with three or fewer metastatic ALNs, patients with MM experienced significantly worse overall survival compared with node-negative patients (14). Although these studies belong to the SLN concept and the diameter of metastasis was not precisely described, this study shows axillary involvement is a meaningful predictor of prognosis. That is why old and new studies were not comparable. Recent studies such as oncotype show that the prognosis is more related with the tumor characteristics rather than axillary involvement (15, 16).

Recent retrospective studies of selected patients with MM without further ALND suggest that this subset of patients will not suffer from higher incidences of regional recurrence. De Mascarel et al. compared 120 women with MM to those with N0 disease, after a median follow up of 7 years, on multivariate analysis, there was no statistically different survival rate found (13). Bulte et al. showed in their prospective study including 541 breast cancer patients, patients with negative SLN had 0.6% local recurrence rate and patients with MM in their SLN without completed ALND had 11% of local recurrence rate, although this study concluded that there was no significant risk of distant disease in case of MM compared to a tumor negative SLN (17). A prospective study of 150 patients undergoing SLNB alone found no difference in the development of axillary recurrence between those with MM and those without after a median follow up of 42 months (18). The authors concluded that careful assessment of risk versus benefit of ALND should be undertaken in view of the known morbidity and effect of treatment decision (19).

The clinical and prognostic significance of the upstaging of SLN MM disease due to ALND is currently unknown. ALND will not change adjuvant chemotherapy schedules in the current practice. Because the presence of axillary involvement regardless of micro, macro, and the number of involved nodes are not used in decision making of chemotherapy regimens.

The present study also showed the total rate of NSLNM was 24.4%, however, after 3 excised SLN with one metastatic node, the patients had 13.3% of NSLNM rate, and patients with 4 or more SLNs had 0 % of NSLNM. In the study of Yi et al, the mean number of SLNs removed in the 777 lymph node-positive patients was 2.9 (range, 1-13 SLNs). They observed that removing up to 5 SLNs was sufficient to reflect the axillary satus in >99% of patients (20). These results may show that the more excised SLNs could be the marker of axillary lymph node status better than one or 2 excised nodes.

However, we still need the results of further investigations with a large number of cases as well as longer follow up, including randomized, prospective trials before we advise this concept.

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