

Histopathologic Characteristics of Sentinel Lymph Node Biopsy in Breast Carcinoma: Uludağ University Faculty of Medicine Experience

Meme Kanserinde Sentinel Lenf Nodu Biyopsisinin Histopatolojik Özellikleri: Uludağ Üniversitesi Tıp Fakültesi Deneyimi

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ABSTRACT Objective: Nowadays, sentinel lymph node (SLN) biopsy is a standard approach giving information about status of the axillary lymph nodes. Several factors affect metastasis to SLN. In our case, we aimed to indicate histopathological parameters that affect SLN and non-sentinel lymph node (n-SLN) metastasis, the importance of frozen section to determine metastasis and immunohistochemistry method for histopathological examinations. **Material and Methods:** In Uludag University Faculty of Medicine, 265 cases who had SLN biopsies were retrospectively examined. Frozen sections, permanent sections and sections with immunohistochemistry were found out from the archive. Then, preparations were re-examined by expert pathologists on breast pathology. **Results:** The mean age of the cases was 53 years. The most frequently observed tumor type was invasive ductal carcinoma. Most of the cases had nuclear grade 2. One hundred cases are diagnosed as malignant. As a result of implementation of serial sections and immunohistochemistry to 12 cases without metastasis, macro-metastasis in four cases, micro-metastasis in six cases and finally isolated tumour cells in two cases were determined. In primary breast tumor, the presence of venous/vascular invasion ($p=0.021$), lymphatic invasion ($p<0.001$), increased primary tumor diameter ($p=0.001$) and increased age ($p=0.026$) increased SLN metastasis. In primary breast tumor, the presence of perineural invasion ($p=0.033$) and lymphatic invasion ($p=0.045$), increased tumor diameter ($p=0.001$), and increased number of positive SLNs ($p=0.015$) caused an increase in n-SLN metastasis. **Conclusion:** SLN biopsy is a simple and reliable method. In our study, we found statistically significant results between SLN metastasis and age, primary tumor diameter, lymphatic invasion and venous/vascular invasion. Besides, statistically significant relationships were found between n-SLN metastasis and primary tumor diameter, perineural invasion and lymphatic invasion as well. Intraoperative analysis of SLN is very important for staging of breast carcinoma and prognosis. Moreover, accuracy of diagnosis increases with the applications of serial section and immunohistochemical method.

Key Words: Sentinel lymph node biopsy; breast neoplasms; pathology

ÖZET Amaç: Günümüzde sentinel lenf nodu (SLN) biyopsisi aksiller lenf nodlarının durumu hakkında bilgi veren standart bir yaklaşımdır. SLN metastazını çeşitli faktörler etkiler. Yazımızda, SLN ve non sentinel lenf nodu (n-SLN) metastazını etkileyen histopatolojik parametreleri, metastazı belirlemek için kullanılan frozen kesit ve histopatolojik değerlendirmede kullanılan immün boyama yönteminin önemini göstermeyi hedefledik. **Gereç ve Yöntemler:** Uludağ Üniversitesi Tıp Fakültesi'nde SLN biyopsisi yapılan 265 olgu retrospektif olarak incelendi. Frozen kesitler, kalıcı kesitler ve immünohistokimyasal kesitler arşivden bulup çıkarıldı. Daha sonra, preparatlar meme patoloji konusunda uzman patoloğlar tarafından yeniden incelendi. **Bulgular:** Olguların ortalama yaşı 53'tür. En sık gözlenen tümör tipi invaziv duktal karsinomadır. Olguların çoğu nükleer derece 2'dir. Ayrıca, 100 olgu malign olarak tanı almıştır. İlk değerlendirmede metastaz görülmeyen 12 olguya uygulanan seri kesitlerin ve immün boyama yönteminin sonucunda, dört olguda makro-metastaz, altı olguda mikrometastaz ve son olarak iki olguda izole tümör hücreleri saptandı. Primer meme tümöründe, venöz/vasküler invazyon ($p=0.021$), lenfatik invazyon ($p<0.001$) varlığı, artmış primer tümör çapı ($p=0.001$) ve ileri yaş ($p=0.026$) SLN metastazında artışla ilişkili bulundu. Primer meme tümöründe, perinöral invazyon ($p=0.033$) ve lenfatik invazyon ($p=0.045$) varlığı, artmış tümör çapı ($p=0.001$) ve artmış sayıda pozitif SLN ($p=0.015$) n-SLN metastazında artışa neden oldu. **Sonuç:** SLN basit ve güvenilir bir yöntemdir. Bizim çalışmamızda, SLN metastazı ve yaş, primer tümör çapı, lenfatik invazyon, venöz/vasküler invazyon arasında istatistiksel olarak anlamlı sonuçlar bulduk. Bunun yanı sıra, aynı istatistiksel olarak anlamlı ilişkiler n-SLN metastazı ve primer tümör çapı, perinöral invazyon, lenfatik invazyon arasında da vardır. SLN'nun ameliyat sırasında incelenmesi meme kanserini evrelemede ve prognozda çok önemlidir. Dahası, tanının doğruluğu seri kesitlerin ve immünohistokimyasal yöntemin uygulanmasıyla artar.

Anahtar Kelimeler: Sentinel lenf nod biyopsisi; meme tümörleri; patoloji

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Sentinel lymph node (SLN) biopsy in breast cancer was first introduced in the first half of the 1990s into clinical practice by Krag et al. SLN biopsy has been accepted as the standard of care for axillary evaluation in breast cancer patients with early-stage disease.¹ Nowadays, although several new prognostic factors have been defined to investigate whether axillary lymph node metastasis is the most significant prognostic factor in patients with breast cancer.² The status of the axillary lymph nodes gives information about staging, local control of disease recurrence, cure methods and survival rate.³ Breast carcinoma spreads to one or more lymph nodes through lymphatic vessels by following a theoretically organized way. Besides, SLNs are the first stations for drainage and tumor metastasis among all lymph nodes. SLN acts as a guard. Therefore, they are the most probable site of the lymphogenic metastases. The SLN is the only tumor-positive axillary lymph node in 50 to 70% of patients.⁴ If determination and investigation of the SLN are done properly, absence of tumor in this node indicates with high accuracy (95%-100%) that there are no metastases in the remaining axillary lymph nodes.⁵ Axillary lymph node dissection is considered necessary when SLN contains tumor.⁶ When the complications such as lymphedema, seroma, neuropathy, hematoma, infection, shoulder dysfunction, paraesthesia, longer duration of hospital stay are taken into consideration, it is wise to perform a SLN biopsy before axillary lymph node dissection.^{7,8} We aimed to prevent a second operation and used frozen section in our institution. In addition, adjuvant treatment can be more accurate by assessing SLN properly.

MATERIAL AND METHODS

In Uludağ University Faculty of Medicine, the use of the SLN biopsy started in 2004. A total of 265 SLN biopsies were performed between December 2004 and December 2008. All cases were included in the study. Variables such as age, grade, lymphovascular invasion, perineural invasion and primary tumor diameter were obtained from the pathology reports. Approval for the study was obtained from the ethics committee. We obtained informed consent from all patients for this study. Under general anesthesia, the

SLN biopsy was performed using both radioisotope tracer and blue dye injection. Radioactive agent was injected subdermally. After injection, lymphoscintigraphy was performed. Blue dye was injected to peritumoral area during surgery. Blue dye which flowed through lymphatics made SLN visible. SLNs are determined successfully in the 98.4% of the cases. In an ideal SLN study, both methods should be used together.⁹ The nodes that were removed during surgery were marked as hot or cold, according to their radioactive uptake status. However, the node with the highest uptake among all was not indicated. Mean number of SLN removed from per patient was 2.5 (range 1-9). Intraoperative frozen section was performed in all cases who had a SLN biopsy. Besides, imprint method with frozen sections was applied to SLNs. However, none of the diagnoses were based on imprint method. In all cases, diagnosis were done by using frozen sections. If the section was positive for metastasis, an axillary lymph node dissection was performed immediately.

According to AJCC (American Joint Committee on Cancer) staging system, lymph node metastasis were classified by the following criteria; if the tumor is larger than 2 mm, it is called as macrometastasis, if it is between 0.2 mm-2 mm or between 10-100 tumor cells, it is called as micrometastasis, if it is smaller than 0.2 mm. or not exceeding 10 tumor cells, it is called as isolated tumor cells. Besides, hormone receptor status was determined by immunohistochemistry. Estrogen and progesterone receptors which show 10% or more positivity were evaluated as positive.

While all SLNs smaller than 0.5 cm were examined as one block in frozen section, the bigger ones were examined in 2 or 3 blocks not exceeding 0.5 cm in thickness and cut parallel to long axis of the lymph node. The remaining tissues from frozen sections were embedded in paraffin blocks. One or two Hematoxylin-eosin (H&E) stained cross-sections from all paraffin blocks were examined, and metastatic ones were reported. Other lymph nodes without metastasis were examined with serial sections using immunohistochemical method. In case of micrometastases, it has been shown that 85-90% of patients do not have disease in the other non-sentinel lymph

nodes (n-SLN).⁵ Patients with micrometastases and isolated tumor cells did not undergo a second operation according to our institution's protocols. Immunohistochemical staining method, employed immune bodies, 1/200 dilution Dako cytokeratin MNF 116 clone and used application of peroxidase and antiperoxidase. In our laboratories, we have applied different serial section intervals to determine the ideal serial cross-section interval. Between 2004-2006, 4-5 serial sections were obtained from every paraffine block ensuring that initial sections have immunohistochemistry the next one was skipped and the process continued in the same way. Between 2007-2008, a section interval of 25-50 microns and a thickness of 5 micron was used. By this way, 80 sections were prepared. One of the initial sections was left for the immunohistochemical staining method and they were stained with cytokeratin. The all other sections were stained with H&E. Since April 2008, in our laboratory, serial sections have been obtained with 100 micron intervals. For every 100 micron interval, two cross-sections were stained with H&E which had 5 micron thickness, one section was used for immune staining, and after that if it is necessary, immunohistochemical staining method was applied at least one level. The lymph nodes are cut into slices through their long axis with those methods and the work load of our laboratory and our pathologist increased.

Statistical analysis was performed using SSPS version 10.0. Fisher's exact-test, Mann-Whitney U test and Pearson's-Chi-Square test were used to compare groups. P values of <0.05 were considered as statistically significant.

RESULTS

The ages of the cases were between 22 and 89 years, and the mean age was 53 years. Women constituted 98.9% of the cases. Fifty five percent of the tumors were located in the left breast. Mean diameter of tumor was 2.37/±1.60 cm and the mean diameter of the metastasis in the SLN was 18.66/±8.77 mm. The mean axillary lymph node number was found as 15.7. Studies have reported that the average number of SLNs removed at the time of SLN dissection was 3 (range 1-15).¹⁰ In our study the mean number was 2.5 (range 1-9). The most frequent tumor type was invasive ductal carcinoma (79.5%). The other types were lobular, tubulolobular, mucinous, mixt type and medullary type. Most tumors were Black's nuclear grade two. The tumor was located in the supero-external quadrant in 60.2% of the cases. Age, dimension of the tumor, estrogen (ER) and progesterone receptor (PR), lymphovascular invasion, perineural invasion, SLN metastasis, n-SLN metastases, tumor dimension in SLN and number of SLN were evaluated. There were relationships between venous/vascular invasion (p= 0.021), lymphatic invasion (p< 0.001), primary tumor diameter (p=.001), age (p= 0.026) and SLN metastasis. There were correlations between lymphatic invasion (p= 0.045), perineural invasion (p= 0.033) primary tumor diameter (p= 0.001) and n-SLN metastasis (Table 1). On the other hand, a relationship was not determined between ER, PR, SLN/ n-SLN positivity. However, there was a correlation between number of positive SLNs and number of positive n-SLNs (p= 0.015).

TABLE 1: Factors affecting SLN and n-SLN metastasis.

| Factors | (+)/(-) | n-SLN metastasis (n= 73) | | SLN metastasis (n= 265) | | p value |
|--------------------------|---------|-----------------------------|------|----------------------------|------|---------|
| | | n | % | n | % | |
| Venous/vascular invasion | (+) | 12 | 16.4 | 25 | 9.6 | 0.021 |
| | (-) | 61 | 83.6 | 240 | 90.4 | |
| Lymphatic invasion | (+) | 27 | 37 | 54 | 20.7 | 0.001 |
| | (-) | 46 | 63 | 211 | 79.3 | |
| Perineural invasion | (+) | 15 | 20.5 | 34 | 14 | 0.202 |
| | (-) | 58 | 79.5 | 231 | 86 | |

n-SLN: non-sentinel lymph node, SLN: sentinel lymph node.

In the frozen sections of 88 out of 265 (33.2%) cases, metastases were detected. Frozen section did not detect four macrometastases, six micrometastases and two isolated tumor cells. Of 177 patients who did not have SLN metastasis in intraoperative examination, 12 had SLN metastasis in permanent sections after immunohistochemistry and serial sections were applied (Figure 1, 2). Ninety nine cases out of 100 had metastasis in sections prepared from the remaining parts of the frozen (Figure 3). In one case that was reported as micrometastasis, the tumor was not observed at the permanent sections (Figure 4). Eighty eight patients whose SLNs were positive underwent an axillary dissection. In frozen section of these 88 cases, SLN biopsy was reported as malignant. In two

cases whose SLN biopsies were reported as suspicious in the frozen section, micrometastasis was determined in one and isolated tumor cells were determined in the other's permanent sections. Thirty eight out of 265 cases had received preoperative neoadjuvant chemotherapy prior to SLN mapping procedure. Metastasis was determined in the frozen sections of 12 cases who had primary chemotherapy. The metastasis was determined in 1-10 lymph nodes in the axillary dissections of those cases.

DISCUSSION

For the patients who have node negative, early stage breast cancer, SLN biopsy is a simple and highly reliable method which can be used for staging ax-



FIGURE 1: Micrometastases in sentinel lymph node stained with cytokeratin (x200).

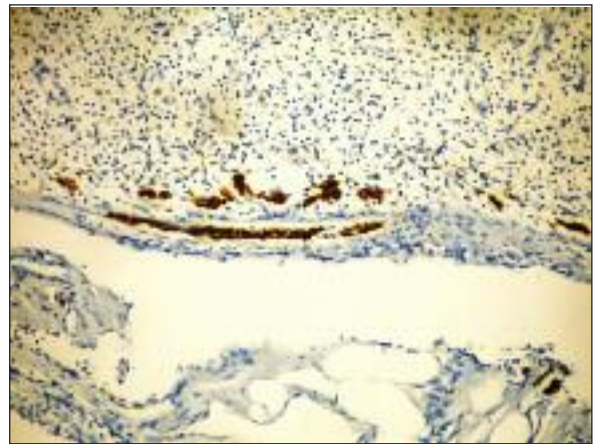


FIGURE 2: Isolated tumor cells in sentinel lymph node stained with cytokeratin (x400).

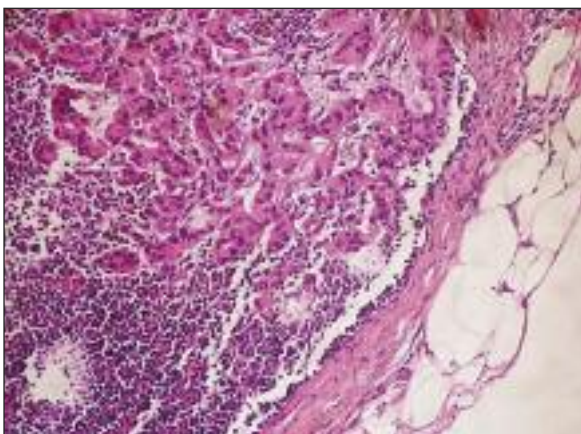


FIGURE 3: Metastatic tumor cells in sentinel lymph node in permanent section stained with H&E (x400).

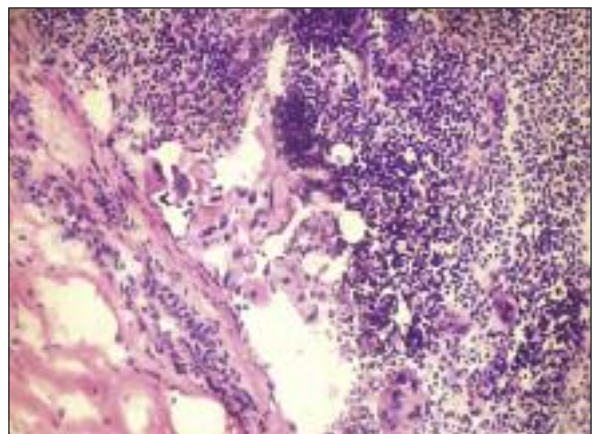


FIGURE 4: Metastatic tumor cells in sentinel lymph node in frozen sections stained with H&E (x400).

illa.¹⁰ Intraoperative frozen section examination of the SLN is a useful predictor of axillary lymph node status in breast cancer patients.² The advantage of intraoperative SLN evaluation is that SLN positive patients can have an immediate axillary lymph node dissection and thereby avoid reoperation.

For histopathologic examination, serial sections and immunohistochemical staining are very expensive and time consuming if performed for every axillary lymph node. The use of this method in the SLN biopsy is very effective to determine minimal metastasis.¹¹ In six of our cases, we determined micrometastasis by serial sections and immunohistochemical staining. Isolated tumor cells was found in two cases. Its prognostic significance is controversial.^{12,13} Patani et al reported that micrometastases in SLN increased risk of n-SLN involvement.¹⁴ In most of the studies, the ratio of the false negativity has been reported as 2-10%.^{6,15} In our study, this ratio was 2.2%. Veronesi reported n-SLN metastasis in 35-67% of the cases with SLN metastasis.¹⁶ In our study, the positivity of the axilla for metastasis was found as 50% after axillary lymph node dissection. The sensitivity of frozen section to detect sentinel lymph node macrometastases has been reported as 92-100%. We found sensitivity of SLN frozen section 95.0%.

In our study, 2.2% of metastases were missed on frozen section, and diagnosed on permanent section as micrometastases. None of false-negative cases developed of local axillary recurrence in a follow up period of 20 months (mean). It was lower than the values reported in the literature.¹⁵ It may depend on the experience of the surgeon and the pathologist, frozen section artefacts and serial section interval and thickness in permanent sections.

Tumor size, presence of lymphovascular invasion, number of positive SLNs, and size of SLN metastases were the most frequently identified independent predictors associated with n-SLN metastases.¹⁷ In our study we found the same results. Bolster et al. and Coufal et al stated that the incidence of n-SLN metastases was related to the size of the SLN metastases.^{18,19} The results of a number of studies in the literature indicate a direct relationship between SLN metastasis and age, primary tu-

mor diameter, lymphatic invasion and venous/vascular invasion.^{20,21} Turner et al. stated that primary tumor diameter indicated a high risk for SLN metastasis.²² Yip et al. stated that lymphovascular invasion was associated with higher rates of SLN involvement.³ In our study, we found that age, primary tumor diameter, lymphovascular invasion and number of metastatic n-SLNs were associated with SLN metastases. However, no relation was determined between lymph node metastasis and ER, PR, and cerbB2 status in our study. Diameter of the tumor, lymphatic invasion and perineural invasion determine n-SLN metastasis and as a consequence they determine axillary dissection.^{12,23,24} The rate of positive SLN varies between 27-45%. In our series, the positive SLN was 33.4%.

Immunohistochemical staining for cytokeratin is not routinely suggested but it is used commonly. In our laboratory, we use it to confirm the diagnosis of micrometastases and isolated tumor cells (ITCs). The clinical significance and management of patients after diagnosis of micrometastases or ITCs in the SLNs have remained a point of controversy.¹⁸ Wada et al. reported that patients with micrometastases should be given adjuvant systemic therapy.²² ITCs are now generally believed to be of limited prognostic significance and are categorized as node-negative disease and require no further treatment.¹¹ Since the SLN is the most probable location for the local metastasis, staging can be made more accurate by detailed investigation of SLN metastasis. The validation of the SLN biopsy as accurate staging procedure depends on correct localization of the SLN and scope of its histopathological examination. It is a controversial issue whether scope of the histopathological evaluation is extensive enough or not. Besides, the methods are different in several countries and different laboratories.²⁵ Therefore, every laboratory uses and applies its own methods according to its own conditions by testing different methods. Therefore, serial sections with different intervals are used in different laboratories.²⁶ More recently, molecular biology techniques have been used. Their specificity and sensitivity is higher than routine methods.²⁷

Intraoperative frozen section examination of the SLN is a useful predictor of axillary lymph node status in breast cancer patients. Using cytokeratin and applying serial sections to confirm the diagnosis of micrometastases and isolated tumor cells is important. In this study, we found that there were relationships between venous/vascular in-

vasion, lymphatic invasion, primary tumor diameter, age and SLN metastasis and there were correlations between lymphatic invasion, perineural invasion, primary tumor diameter and n-SLN metastasis. In addition, there was a correlation between number of positive SLNs and number of positive n-SLNs.

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