Review Article

Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy

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Background: We surveyed single-center and multi-center studies pertaining to sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy to compare the results with those of our current study to evaluate the feasibility and accuracy of SLNB after neoadjuvant chemotherapy.

Methods: From October 2001 to July 2003, 80 patients who had neoadjuvant chemotherapy underwent curative surgery and axillary lymph node dissection (ALND) after SLNB at the Center for Breast Cancer, National Cancer Center. A MEDLINE search was performed using the keywords breast cancer, sentinel lymph node biopsy, and neoadjuvant chemotherapy.

Results: Our results showed that 42 (52.6%) of 80 patients had downstaging of the primary tumor; 9 patients (11.3%) had pathologic complete response (pCR) and 33 (41.3%) had pathologic partial response (pPR). 26 patients (32.5%) showed complete axillary clearance after neoadjuvant chemotherapy. Among them, 5 patients (6.3%) revealed pCR of both the primary tumor and axillary metastasis. SLNB was successful in 61 of 80 patients (76.3%) and there were 3 false negatives, yielding a false negative rate (FNR) of 7.3% (3/41), a negation prediction value (NPV) of 87.0% (20/23), and an accuracy of 95.1% (58/61). Thirteen out of 16 studies retrieved by MEDLINE pertaining SLNB after neoadjuvant chemotherapy concluded its feasibility and accuracy with an identification rate of 82%-100% and a FNR of 17-100%.

Conclusion: Most studies, including ours, concluded that SLNB after neoadjuvant chemotherapy is accurate and could be an alternative to ALND.


Key words: Axillary lymph node dissection, Breast cancer, Sentinel lymph node biopsy, Neoadjuvant chemotherapy

Neoadjuvant chemotherapy has been widely accepted as a standard of care for both resectable and nonresectable locally advanced breast cancer. It has been demonstrated to make many patients good candidates for breast conserving surgery and a subset of patients with complete eradication of axillary metastasis achieve a survival benefit\(^1\). For this subset of patients, sentinel lymph node biopsy (SLNB) is emerging as a minimally invasive alternative to axillary lymph node dissection (ALND) for axillary staging after neoadjuvant chemotherapy. SLNB has been increasingly accepted as an alternative to level I and II ALND for the staging of early breast cancer. Accurate sentinel lymph node acquisition is important to appropriately stage the patients, to prevent axillary recurrence, and to potentially improve survival. However, there are still controversies regarding the feasibility and accuracy of SLNB after neoadjuvant chemotherapy. Although several investigators have demonstrated the accuracy of SLNB after neoadjuvant chemotherapy, most of the studies were small single-center studies and showed variability in the identification rate and a false negative rate (FNR). If SLNB is feasible and accurate after neoadjuvant chemotherapy, ALND might be avoided in an additional significant proportion of the patients with eradication of axillary metastasis after neoadjuvant chemotherapy.

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Abbreviations:
ALN, Axillary lymph node; ALND, Axillary lymph node dissection; SLN(s), Sentinel lymph node(s); SLNB, Sentinel lymph node biopsy; FNR, False negative rate; NPV, Negative prediction value; SUV(s), Standard uptake value(s); pCR, Pathologic complete response; pPR, Pathologic partial response; pSD, Pathologic stable disease; IHC, Immunohistochemical; RI, Radioisotope

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We reviewed single-center and multi-center studies pertaining to SLNB after neoadjuvant chemotherapy and compared the results with those of our current study to evaluate the feasibility and accuracy of SLNB after neoadjuvant chemotherapy.

Current Study at the National Cancer Center, Korea

Patients and Method

From October 2001 to July 2003, SLNB followed by curative surgery with formal ALND was undertaken for eighty patients who had received neoadjuvant chemotherapy at the Center for Breast Cancer, National Cancer Center, Korea. Patients with clinically apparent axillary node metastasis or tumor size > 3 cm were selected for neoadjuvant chemotherapy. Staging was performed according to the new 2002 American Joint Committee on Cancer staging system. Axillary node positivity was determined either by fluorine-18 fluorodeoxyglucose positron emission tomography ("18F-FDG-PET) or by histologic examination of the node. The cut-off value of positivity for axillary metastasis was a maximum SUV higher than 2.5.

Lymphatic mapping was performed using isosulfan blue dye (n = 11), radioisotope (RI)- Technetium-99m (99mTc)-antimony trisulfide colloid (n = 51), or a combination of both (n = 18). The antimony trisulfide colloid was obtained from a kit produced by Korea Atomic Energy Research Institute and labeled with 99mTc. 0.4 mCi 99mTc-antimony trisulfide colloid was diluted with 0.2 ml of saline and injected intradermally 2-4 hours before surgery (n = 23), or 4 mCi 99mTc-antimony trisulfide colloid with 4 ml of saline was injected peritumorally late in the afternoon the day before operation (n = 46). Lymphoscintigraphy was performed before surgery and sentinel lymph nodes (SLNs) were localized with a Gamma Guidance System in the operating room. When they could not be identified with lymphoscintigraphy or with the gamma probe, isosulfan blue dye was also injected (n = 18). After anesthesia, 3-4 ml of isosulfan blue dye was injected intradermally around the tumor, and the breast was massaged to facilitate lymphatic spreading. Once localized, the SLNs were removed and sent to the pathology department.

All SLNs were measured and subjected to immediate serial 2 mm step sections and frozen section analysis. After histologic evaluation of SLNs, all remaining SLN tissue was fixed in 10% formalin and processed in paraffin blocks to produce permanent sections with hematoxylin and eosin (H&E) staining. If the H&E section was negative or equivocal for metastatic disease, an immunohistochemical (IHC) stain for keratin was performed with monoclonal anti-human cytokeratin (clone AE1/AE3, DAKO, USA) and LSAB kit (DAKO).

We performed logistic regression as well as the chi-square test to evaluate the variables related to identification rates. We used the likelihood-ratio statistics based on the conditional parameter estimate (Forward: conditional) as a method for entering and removing the variables when performing the logistic regression. The identification rate is defined as the ability to successfully identify a SLN. The false negative rate is defined as the number of patients with a negative SLN, but with one or more positive non-sentinel nodes (false negative) divided by the total number of patients with a positive axillary lymph node (ALN). The negative predictive value is defined as the number of true negative SLNs divided by the sum of the true negative SLNs and false negative SLNs. Accuracy was defined as the sum of the true positive and true negative SLNs divided by the total number of patients with successful mapping. Student's t-test and ANOVA were used for continuous variables. SPSS 9.0 for windows was used for the statistical analysis. The level of significance was p < 0.05 (two-sided).

A MEDLINE search was performed using keywords breast cancer, sentinel lymph node biopsy, and neoadjuvant chemotherapy to evaluate SLNB after neoadjuvant chemotherapy.

Results

The characteristics of the patients and their responses to neoadjuvant chemotherapy are shown in Table 1. Eighty patients received neoadjuvant chemotherapy either with doxorubicin and cyclophosphamide (AC, n = 31), doxorubicin and docetaxel (AT, n = 14), AC followed by AT (AC/AT, n = 7), docetaxel and capecitabine (TX, n = 22), or other regimens (n = 6). Forty-two patients (52.6%) showed effective downstaging of the primary tumor, 9 patients (11.3%) had pathologic complete response (pCR) and 33 (41.3%) had pathologic partial response (pPR) (Table 1). Breast-conserving surgery was performed for 48 patients.