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The clinical implication of the number of lymph nodes harvested during sentinel lymph node biopsy and its effects on survival outcome in patients with node-negative breast cancer

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ABSTRACT

Background: The optimal number of sentinel lymph nodes (SLN) that need to be harvested to achieve favorable survival outcome during a SLN biopsy (SLNB) has not yet been established.
Methods: Six hundred and thirteen patients with clinically node-negative breast cancer who underwent SLNB were reviewed. Survival outcomes according to the number of total harvested lymph nodes (THLNs), defined as the sum of enumerated SLNs and non-SLNs were analyzed.
Results: Patients with only 1 THLN showed lower recurrence-free survival (RFS) as compared to those with ≥2 THLNs ($p = 0.049$). In multivariate analysis, only 1 THLN was associated with poor RFS (HR = 2.711; $p = 0.029$).
Conclusions: Removing at least 2 lymph nodes during SLNB may be acceptable. Harvesting only 1 lymph node should be undertaken cautiously because of false negative results and increasing the subsequent recurrence rate.

1. Introduction

The results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial indicated that sentinel lymph node biopsy (SLNB) is superior to axillary lymph node dissection (ALND) in terms of post-surgical morbidity outcomes in patients with clinically node-negative breast cancer.[1] Furthermore, it showed that survival outcomes, including OS (overall survival) and DFS (disease-free survival), were statistically equivalent between the SLNB and ALND groups.[2] As a result, SLNB is considered the standard method for axillary staging of breast cancer, with similarly reliable accuracy and fewer surgical complications than complete ALND.[3]

During SLNB, enlarged axillary non-SLNs located near SLNs can be identified and removed by surgeons. Consequently, ≥6 LNs that are regarded as axillary lymph nodes (LNs) according to the American Joint Committee on Cancer (AJCC) definition, including SLNs and non-SLNs, can be dissected in a subset of patients.[4] Furthermore, the prevalence of morbidity, such as patient-perceived lymphedema, increases with the number of LNs harvested.[5] Additionally, cost-effectiveness and cost-utilization studies have found that excising a high number of SLNs is associated with longer operation durations, higher pathology costs, and higher procedural costs.[6] Thus, it is important to clarify the optimal number of SLNs to be harvested to minimize morbidity and maximize cost-effectiveness.

Our prior study suggested that 4 might be the optimal number of SLNs that need to be removed[7]; the removal of more than 4 SLNs does not improve axillary staging accuracy in term of false negative rates.[7] Similarly, results from the NSABP B-32 trial indicated that removal of at least 2 LNs is important to reduce the false negative rate.[8] Nevertheless, there exists uncertainty regarding the association between increasing the accuracy of SLNB and the survival benefits of removing additional LNs. Therefore, it is necessary to establish the optimal number of SLNs to be harvested to achieve favorable oncologic outcomes during SLNB.

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2. Methods

2.1. Patient selection

The medical records of 3151 patients with clinically node-negative breast cancer who underwent SLNB and/or ALND between 2006 and 2010 at Severance Hospital, Yonsei University Health System in Seoul, Korea were reviewed. The Severance Hospital Breast Cancer Registry was used to collect clinicopathologic feature and survival outcome data. The Severance Breast Cancer Registry is a prospectively maintained database containing clinicopathological information, treatment modalities, and outcome details including disease recurrence.[9]

We excluded patients who had ductal carcinoma in situ, lobular carcinoma in situ, stage T4 or IV disease, clinically node-positive disease, inflammatory carcinoma, phyllodes, sarcoma, lymphoma, or who had received neoadjuvant chemotherapy, previous axillary surgery, or radiation. Patients without available medical records were also excluded. Patients with ≥6 total harvested LNs (THLNs) were also excluded according to the guideline for the use of the sentinel node modifier in the 7th AJCC Cancer Staging Manual. Six hundred and sixteen patients were thus enrolled into the study (Fig. 1).

We defined the number of total THLNs as the sum of SLNs and non-SLNs. SLNs were detected via the radioisotope technique as previously described.[7] Briefly, on the day of surgery or the evening before surgery (in the event that surgery was scheduled in the early morning), we injected 18.5 MBq (0.5 mCi) 99mTc phytate (Korea Atomic Energy Research Institute, Daejeon, Korea) diluted in 0.5 mL saline using the subareolar technique. A lymphoscintigraphy was performed after injection. The area with the greatest radioactive intensity as identified using a handheld probe was incised (Navigator GPS; RMD Inc., Watertown, USA). SLNs were defined as nodes with *ex vivo* radioactive counts of 10% or more than that of the origin site, which was the periareolar area of isotope injection. We also removed axillary lymph nodes that were near SLNs; we were able to identify axillary LNs via inspection or palpation, but not with gamma probe. The present study considered these LNs as non-SLNs. All SLNs and non-SLNs had intraoperative frozen sections prepared and were evaluated via permanent pathologic analyses.

Our institutional practice of adjuvant treatment was described in previous studies.[10,11] In brief, chemotherapy was administrated based on patient's clinicopathologic features and physician's preferences. Endocrine therapy was routinely recommended in patients with hormone receptor-positive breast cancer. Patients who underwent breast-conserving surgery routinely received adjuvant radiation therapy with a median boost dose of 10 Gy, which covered the whole breast, with or without the regional nodal area. Postmastectomy radiation therapy was considered for patients with locally advanced breast cancer, such as node-positive breast cancer or tumor greater than 5 cm in diameter.

We analyzed all patients according to the number of THLNs. The number of THLNs was categorized into 1 of 5 subgroups: only 1 THLN versus ≥2 THLNs, 1 to 2 THLNs versus ≥3 THLNs, 1 to 3 THLNs versus ≥4 THLNs, or 1 to 4 THLNs versus 5 THLNs (Fig. 1).

Positive for ER and progesterone receptor (PR) expression was defined as 10% or more positively nuclear-stained cells. Human epidermal growth factor receptor 2 (HER2) staining was scored by counting the number of cells positively stained on the membrane as a percent of the total number of tumor cells.[12] HER2 status was evaluated using the HercepTest™ (DAKO, Glostrup, Denmark) and was interpreted as 0, 1+, 2+, or 3+. HER2 staining was considered positive in cases with an immunohistochemistry score of 3+. Breast

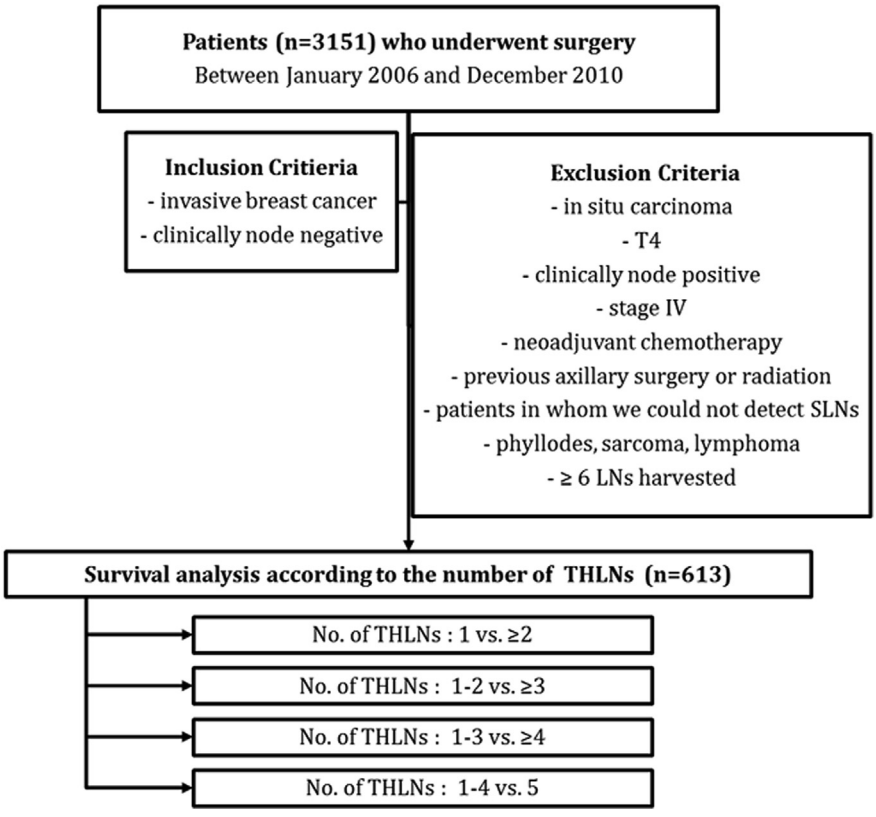

Fig. 1. Study scheme. SLN=Sentinel Lymph Node, THLN = Total Harvested Lymph Node, LN = Lymph Node.