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Original Article

Lymph node ratio as an alternative to pN staging for predicting prognosis after neoadjuvant chemotherapy in breast cancer

Dong Hui Cho [a], Soo Youn Bae [b], Ji Young You [b], Hong Kyu Kim [b], Young Woo Chang [b], Yoo Jin Choi [b], Sang Uk Woo [b], Gil Soo Son [b], Jae Bok Lee [b], Jeoung Won Bae [b], Seung Pil Jung [b,*]

[a] *Division of Breast and Endocrine Surgery, Department of Surgery, Seoul Medical Center, Seoul, Republic of Korea*
[b] *Division of Breast and Endocrine Surgery, Department of Surgery, Korea University Hospital, Korea University College of Medicine, Seoul, Republic of Korea*

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Abstract Axillary nodal status is one of the most important prognostic factors in breast cancer. The lymph node ratio (LNR) has been suggested as an independent prognostic factor because the number of dissected and involved lymph nodes might differ across institutions. Neoadjuvant chemotherapy (NAC) has been the preferred treatment method for reducing tumor mass in the breast and axillary area. However, NAC can reduce total number of excised lymph nodes compared with upfront surgery. Therefore, an emerging question is whether axillary nodal status and LNR following NAC can accurately predict prognosis. We evaluated the prognostic value of axillary nodal status and LNR after NAC. A total of 236 patients were enrolled. Patients were divided into four groups according to the following cut-off values for LNR: 0 (n = 107), 0.01–0.20 (n = 68), 0.21–0.65 (n = 50) and >0.65 (n = 11). Pathologic complete responses were observed in 16.9% of the overall cohort. In univariate analysis, pathologic N stage was a significant prognostic factor of disease free survival (DFS, $p = 0.013$) and overall survival (OS, $p = 0.004$). However, in multivariate analysis, hormone receptor status ($p = 0.043$) and LNR ($p = 0.028$) were significantly associated with DFS and LNR ($p = 0.017$) showed statistical significance for OS; however, pathologic N stage was no longer significantly associated with DFS or OS. Traditional nodal staging has been accepted as an important prognostic factor; however, our result indicated that the nodal ratio could be an alternative to pN staging as a prognostic factor after NAC in breast cancer.

Conflicts of interest: All authors declare no conflicts of interests.

* Corresponding author. Department of Surgery, Korea University College of Medicine, 126-1 Anam-dong 5-ga, Seongbuk-gu, Seoul 136-705, Republic of Korea.
E-mail address: jungspil@korea.ac.kr (S.P. Jung).

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Introduction

Axillary nodal status is one of the most important prognostic factors in breast cancer [1,2], and the number of involved axillary nodes has been incorporated into clinical decision making [3]. The number of involved lymph nodes identified depends on the number of lymph nodes removed and examined, which depends on the surgical and pathologic procedures. The extent of axillary dissection varies according to the surgeon and there is further variation in the number of reported positive nodes across different pathology laboratories [4]. More extensive axillary dissection or pathologic examination of the resected specimen results in a higher number of positive nodes [5]. Recent studies have reported the oncologic importance of the lymph node ratio (LNR), defined as the ratio of involved nodes to dissected nodes, as a predictor of prognosis in breast cancer [5–8].

Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced breast cancer and has been increasingly implemented for the treatment of patients with earlier stage operable cancer. NAC results in improvements in disease-free survival (DFS) and overall survival (OS), similar to those obtained with adjuvant chemotherapy [9,10]. NAC has been shown to down stage not only breast cancer size, but also the axillary status in approximately 30% of patients [11,12]. However, an adverse effect of NAC is anatomical alteration of the lymphatic drainage, with lymphatic vessels disrupted by the tumor, inflammation, or fibrosis or blocked by necrotic debris and/or apoptotic cells [13]. This histologic change in the lymphatic environment could result in a lower lymph node harvest [14]. Currently, axillary nodal status of breast cancer is evaluated by the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification system [15]. The current AJCC breast cancer staging system corresponds to clinical stage at the initial diagnosis and the definitive pathologic stage based on information obtained at the time of surgical removal of the tumor. Consequently, AJCC staging does not consider the effects of NAC, which is a common treatment modality for breast cancer, and no standard classification system for reporting the response to NAC currently exists.

The LNR may be a better prognostic factor than nodal staging in the neoadjuvant setting, however, few studies have considered the prognostic value of the LNR in patient who receive NAC. In this study, we evaluated the prognostic value of LNR after neoadjuvant chemotherapy for breast cancer.

Methods

Patients and treatment

This study was performed retrospectively using the records of 236 patients who received NAC for the treatment of breast cancer between January 2006 and December 2015 at Seoul Medical Center and Korea University Hospital. Patients with preoperative distant metastasis and those who did not undergo surgery were excluded. Patient demographics and clinical characteristics were collected from the hospital's electronic database. This study was approved by the Hospital Institutional Review Board (No. 2017-10-003). Written informed consent was obtained from the patient or the patient's family.

The chemotherapy regimen consisted of doxorubicin and cyclophosphamide by intravenous infusion every three weeks for four cycles in clinically node-negative patients, with an additional four cycles of a taxane-based regimen every three weeks in clinically node-positive patients. After 2013, trastuzumab was administered to HER-2 receptor-positive patients as neoadjuvant treatment.

Research methods

Patient age at diagnosis and clinical stage before NAC were evaluated. All patients underwent a core needle biopsy to evaluate histologic type, hormone receptor status, HER-2 receptor status, tumor grade, and presence of lymphovascular invasion (LVI). Tumor size prior to NAC was determined at the time of diagnosis using imaging modalities. If magnetic resonance imaging results were not available, breast ultrasonography results were utilized.

Estrogen receptor and progesterone receptor status in the primary tumor was evaluated using standard immunohistochemistry (Dako, Glostrup, Denmark), and the tumors were considered positive if more than 1% of cells exhibited nuclear staining. HER-2 status was determined in primary tumor tissues using anti-HER-2 monoclonal antibody (Lab Vision, MI, USA) and was considered positive for a staining intensity score of 3 alone or a staining intensity score of 2 combined with fluorescence *in situ* hybridization (FISH) positivity. FISH was conducted according to the Abbott PathVysion HER2 DNA Probe kit protocol (Abbott Laboratories, Abbott Park, Des Plains, IL). A minimum of 60 nuclei from invasive tumor cells were scored using an Olympus BX61-32FA1-S08 microscope with fluorescence equipment (Olympus, Tokyo, Japan). The FISH staining had been evaluated according to the algorithms of the manufacturers and the 2007 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines until 2013 [16]. Cases with a HER2/CEP17 ratio <1.8 were considered negative for HER2 gene amplification, whereas those with a HER2/CEP17 ratio >2.2 were considered positive for HER2 gene amplification. From 2014, we interpreted the FISH scoring according to the updated 2013 ASCO/CAP guideline [17]. Positive status was defined either as an average HER2 gene copy number of 6 at cases with a HER2/CEP17 ratio of less than 2 or a HER2/CEP17 ratio of 2 or more. Negative status was defined as average gene copy number of less than 4 with a HER2/CEP17 ratio of less than 2.