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Review

Ratio and log odds of positive lymph nodes in breast cancer patients with mastectomy

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ABSTRACT

Purpose: This study aimed to investigate the predictive role of lymph nodes (LNs) and assess the prognostic significance of the ratio of positive LNs (LNR) and log odds of positive LNs (LODDS) in breast cancer patients who have undergone a mastectomy.

Patients and methods: All of the breast cancer patients in the Taiwan Cancer Database during 2002–2006 were considered. We excluded patients who had inflammatory breast cancer, stage 0 and IV disease, breast conservative surgery or survival <1 month. The primary end point was overall survival (OS). A Cox hazards model was constructed and compared via Nagelkerke R^2 (R^2_N) and receiver operating characteristics (ROC).

Results: A total of 11,349 (6042 node-negative, 5307 node-positive) patients were enrolled, and 10.5% patients had a limited number of LNs harvested. In a multivariate Cox model, LNR and LODDS demonstrated prognostic significance (<0.001). For node-positive patients, a model with LNR showed the best fit ($P < 0.001$; $R^2_N = 18.2\%$) when sufficient LNs were examined. However, a model with LODDS showed the best fit in patients with a limited number of LNs harvested ($P < 0.001$; $R^2_N = 21.1\%$), even in node-negative patients ($P = 0.004$; $R^2_N = 13.5\%$). The area under the ROC curve (AUC) was highest for LODDS (AUC: 0.761), followed by LNR (AUC: 0.757). A limited LN harvest induced an AUC value for an approximate 3.6% loss (LNR) or 3.1% loss (LODDS).

Conclusion: The prognostic superiority of LNR is confounded by a limited LN harvest, thus making LODDS the most powerful and unified prognostic classifier in breast cancer patients who have had a mastectomy.

Contents

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Introduction

Lymph node (LN) assessment in breast cancer patients is widely accepted as a factor for indicating disease severity and establishing prognostic prediction and as a guide for adjuvant therapy, which has a positive influence on patient survival [1]. Traditionally, the number of positive LNs (LNP) is considered to be the most powerful prognostic predictor in breast cancer and forms the basis of the current pN category of the Tumor Node Metastasis (TNM) staging system, which provides a clear and succinct manner to predict patient survival [2,3]. In addition to this absolute number classification, other nodal expression, such as the ratio of involved LN, has been introduced as an alternative or even more powerful predictor of patient outcome. Two frequently mentioned forms of ratio-based nodal indices are the lymph node ratio (LNR) and a newer one, the log odds of involved lymph nodes (LODDS) [4]. Index LNR, defined as the number of involved LNs divided by the total number of lymph nodes (LNT) retrieved, is a powerful prognostic predictor in breast cancer [5–11]. Index LODDS, defined as the logarithm of the quotient of the number of positive LNs divided by the number of negative LNs, has also demonstrated prognostic superiority (compare to the pN or LNR classification system) in other cancer fields, such as gastric cancer [12,13] and colorectal cancer [14–17]. Unfortunately, the literature on comparing these three powerful lymph node predictors (including LNP) is still scarce in breast cancer.

Furthermore, there is evidence of a negative correlation between a low LNT harvest (often < 10) and overall survival in breast cancer patients [18]. In healthcare, researchers set a minimum requirement of harvesting ten LNs after a mastectomy as a benchmark of quality to prevent underestimating tumor stage in the case of a limited number of LNs harvested [19]. As its definition suggests, LNR is most likely subject to a fluctuation of the LNT and therefore loses its predictive value. For these reasons, some authors excluded patients who had fewer than 10 dissected LNs in their studies to have reliable LNR estimates [20]. However, the impact of a limited LN harvest on the prognostic accuracy of these nodal indices remains untested. Given the proposal of incorporating LNR into pN staging in breast cancer patients, we believe that examining which nodal category best predicts survival and exploring the influence of a limited LN harvest on prognostic significance of these nodal categories are important issues that may answer the questions that should be addressed today.

In this study, we aimed to compare the prognostic significance of the conventional LNP category and ratio-based nodal indices (LNR and LODDS) in breast cancer patients who had undergone a mastectomy. The impact of a limited LN harvest on the prognostic prediction of these nodal indices was also investigated.

Patients and methods

Study population

Candidates for the study included all of the breast cancer patients registered in the Taiwan Cancer Database (TCDB) between January 2002 and December 2006. Nationwide collaborative efforts from 32 medical centers and hospitals have contributed to the TCDB since 2002. The database covers approximately 60% (increasing annually) of Taiwanese patients with breast, colorectal, liver, lung, cervical and buccal cancer and is collated to provide data regarding tumor characteristics and treatments for academic analysis [17]. The data within the TCDB undergo a quarterly update.

Cohort analysis

We identified breast cancer patients in the TCDB according to ICD-O-3 (International Classification of Diseases for Oncology, third revision) code C50 (breast). Patients with stage 0 and IV disease (6th edition of American Joint Commission on Cancer Staging Manual) were excluded. Patients who had neo-adjuvant chemotherapy or radiotherapy, inflammatory breast cancer, a pathology report not showing infiltrating ductal carcinoma (IDC), a tumor size > 5 cm, no (modified) radical mastectomy, age <25 years or > 95 years, survival less than 1 month, and an unspecified lymph node evaluation were also excluded. According to the number of LNs examined, a limited group (number of LNs harvested between 1 and 9) and a sufficient group (number of LNs harvested $\geq$10) were designated.

Prognostic variables

Relevant clinical, pathological, and interventional data and the survival status of breast cancer patients were retrieved and linked to 2002–2009 Taiwanese Death Registries (from Ministry of the Interior) to double-check patients' survival statuses and the cause of death. Prognostic variables (confounders) included patient characteristics (age, gender), disease characteristics (tumor laterality, location, size, the grade of cell differentiation and the status of hormone receptors) and interventional factors (safe surgical margin, chemotherapy, radiotherapy and hormone therapy). Nodal categories (LNP, LNR and LODDS) were evaluated as continuous variables when a Cox proportional hazards model was performed. In order to eliminate the possible production of an infinite value in the calculation of LODDS, 0.5 was routinely added to both numerator and denominator before the quotient was calculated [27].

Study outcomes

The primary end point was overall survival (OS), referring to the percentage of patients who had still been alive for a certain period of time after receiving a mastectomy to treat breast cancer. The secondary end point was disease-specific survival (DSS), referring to the percentage of patients who had not died from breast cancer or metastasis for a certain period of time after receiving a mastectomy to treat breast cancer [17].The institutional review board at Buddhist Xindian Tzu Chi General Hospital waived informed consent and approved this study (No: 01-X07-028).

Statistical analysis

Demographic, clinical, pathological and interventional variables were reported as percentage or mean ± standard deviation. Between the limited and sufficient groups, categorical variables were compared by Chi-square test and numeric variables were compared by Mann–Whitney U test. Univariate analysis was performed for all possible confounders using the Cox model. Significant confounders