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The prognostic value of lymph node status among breast cancer subtypes

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Abstract

BACKGROUND: Breast cancer subtypes (BCSs) are predictive of responses to specific therapies and of prognostic value for clinical outcomes. This study aimed to evaluate the relative 5-year overall survival (OS) and recurrence-free survival rates (RFS) based on lymph node (LN) status among BCSs.

METHODS: Medical records of 1,399 breast cancer patients treated from 2006 to 2011 were retrospectively reviewed. Pathologic findings, type of treatment, and OS and RFS were evaluated for 5 molecular subtypes.

RESULTS: Luminal A cancers accounted for 40.9% of the total, luminal B 21.5%, luminal human epidermal growth factor receptor 2 (HER2) 24.8%, HER2 6.9%, and triple negative 5.9%, of which 30% (n = 395) were LN positive. Analysis of patient characteristics showed significant differences among BCSs in age, tumor size, LN status, chemotherapy, and endocrine therapy. Adjustments for age and tumor size revealed significant differences in OS according to the nodal status in luminal A, luminal B, and luminal HER2 subtypes, and with RFS in the luminal B and luminal HER2 subtypes.

CONCLUSION: LN status in BCS presents an important prognostic factor of OS and RFS.

Perou et al[1] identified breast cancer cells that shared gene expression patterns resembling those of luminal epithelial cells (luminal), myoepithelial (or basal) cells, and/or overexpressed cells of human epidermal growth factor receptor 2 (c-Erb-2 or HER2). The 12th St Gallen International Breast Cancer Conference (2011) established molecular subtypes for routine immunohistochemical (IHC) biomarker analysis as a surrogate for genetic analysis, which include luminal A (estrogen receptor [ER]+ and/or progesterone receptor [PR], low Ki67, and HER2−), luminal B (ER+ and/or PR+, high Ki67, and HER2−), luminal HER2+ (ER+ and/or PR+ and any Ki67 and HER2+), HER2 (ER−, PR−, and HER2+), and triple negative (TN; ER−, PR−, and HER2−) subtypes. If reliable assessment of the Ki-67 labeling index is not possible, an alternative measurement of proliferation, such as histologic grading, may be used for distinction.[2,3] The molecular heterogeneity reflects alterations in cell biology and is associated with significant differences in survival and relapse.[4–7] Lymph node (LN) status has been established as the most important prognostic factor for breast cancer.[8,9] The 5-year overall survival (OS) rate for breast cancer patients with LN metastasis is 40% lower than that of patients without

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LN metastasis.[10–12] Although breast cancer subtype (BCS) and LN status have both been independently demonstrated as prognostic factors, there is a paucity of data describing the relationship between the two.[13,14] Several authors have underscored a strong relation between BCS and LN status of patients with breast cancer[7,8,15], whereas others have suggested that BCS may not be a useful prognostic variable influencing regional management considerations.[16,17] Therefore, this study aimed to evaluate the relative proportions of the 5-year OS and recurrence-free survival (RFS) rates according to the LN status among BCSs.

Patients and Methods

Study population

After obtaining the approval of the institutional review board, we reviewed the medical records of all patients with breast cancer treated at the Tri-Service General Hospital from January 2006 to June 2011. Using hospital chart numbers, 1,399 women were consecutively selected from patients with confirmed histopathologic diagnosis of breast carcinoma. Patients were treated with either mastectomy or breast-conserving surgery. After completion of surgery, endocrine therapy, and local radiotherapy or adjuvant systemic treatments were administered as indicated on the basis of international recommendations.[18] Total incidences of recurrence or death from breast cancer were ascertained from follow-up lasting until June 31, 2013.

Eligibility criteria

Information recorded for each patient included age at diagnosis; year of diagnosis; and dates of death, relapses, and last contact. Tumor characteristics included tumor size ($\leq$2, 2 to 5, and >5 cm); tumor pathologic stage (I, II, III, IV); status of ER, PR, and HER2 (positive, negative, or unknown); and LN status (negative or positive). Treatment factors included radiotherapy, type of surgery, chemotherapy, or endocrine therapy. Tumor pathologic stage was defined by the tumor node metastasis (TNM) classification as proposed by the American Joint Committee on Cancer for grouping patients with respect to prognosis.[7,19,20] The subtypes were categorized as follows: luminal A (ER/PR+, HER2−, low grade, or intermediate-), luminal B (ER/PR+, HER2−, high grade), luminal HER2 (ER/PR+, HER2+), HER2 (ER−, PR−, HER2+), and triple negative (ER−, PR−, HER2−).[2,21,22] ER/PR positivity was determined by IHC analysis of the number of positively stained nuclei (>1%+). Tumors were considered as HER2+ when cells exhibited strong membrane staining (3+). Tumors exhibiting 0 or 1+ staining for HER2 protein overexpression were considered to be HER2−. In cases of equivocal membrane staining (score 2+) for HER2, fluorescence in situ hybridization was used to evaluate gene amplification.[3,13]

Statistical analysis

All statistical analyses were performed using the PASW statistical software (version 18.0; SPSS, Inc, Chicago, IL). The one-way analysis of variance and the Bonferroni method were used to compare BCS and patient age. The chi-square test and Fisher's exact test were used to compare the distribution of baseline characteristics among BCS and patient demographics and tumor characteristics; the endpoints studied were OS and RFS rates. Frequencies and percentages were reported for categorical variables (such as tumor size, LN status, and BCSs). Multivariate Cox proportional hazard analysis was performed to calculate adjusted mortality risks and to identify the best combination of factors for predicting OS and RFS. Statistical differences between curves were calculated using the log-rank test. P values were 2-sided and were considered statistically significant when less than .05.

Results

Clinicopathologic characteristics

The clinicopathologic BCS characteristics among the 1,399 patients included in this study are shown in Table 1. Analysis of patient characteristics showed significant differences among BCS in terms of age ($P = .019$), tumor size ($P < .001$), LN status ($P < .001$), and tumor pathologic stage ($P < .001$). In addition, 44.3% ($n = 509$) of the patients were classified as stage I, 38.3% ($n = 440$) as stage II, 15.8% ($n = 181$) as stage III, and 1.6% ($n = 18$) as stage IV. With regard to treatment, most patients (95%) underwent surgery; of these, 36.4% underwent breast conservation surgery and 58.6% underwent modified radical mastectomy. In addition, 44.4% received radiotherapy, 55.8% received chemotherapy, and 70.3% received endocrine therapy. Luminal A patients received chemotherapy less often than other patients (54.2 vs $\geq$55.7%, $P < .001$); 71.8% of TN and 79.2% of luminal B patients received chemotherapy. Most (>70%) patients with luminal-like cancer received endocrine therapy.

Survival outcomes

Of the 1,399 patients with breast cancer in the BCS group, 912 were LN negative and 395 were LN positive (the total number of cases and controls do not correspond because of missing data). Results from an exploratory analysis of crude 5-year OS and RFS rates according to the nodal status in BCS are shown in Table 2. In addition to the HER2 subtype, there were significant differences in the OS rates according to the nodal status in the distribution of luminal A, luminal B, luminal HER2, and TN subtypes (Fig. 1). In addition, there were significant differences in the 5-year outcomes for RFS in luminal B and luminal HER2 subtypes (Fig. 2). Among the LN-negative primary tumors, a higher OS rate was observed in TN (100.0%) and luminal A (99.0%) subtypes and a lower OS rate were observed among the luminal B