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# Developing and comparing two different prognostic indexes for predicting disease-free survival of nonmetastatic breast cancer patients

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**Aim:** To determine 2 different prognostic indexes (PI) for the differentiation of subgroups of nonmetastatic breast cancer patients with the Cox regression analysis and survival tree (ST) methods and the additional usage of the Kaplan-Meier estimates to investigate the predictive power of these methods.

**Materials and methods:** Prognostic factors data were collected for 410 patients. The Cox regression analysis examines the relationship of the survival distribution and covariates. The ST method is a tree-structured survival analysis based on a recursive partitioning algorithm. In this study, Harrell's concordance indexes of models for training and test sets were computed. Furthermore, survival curves were estimated by the Kaplan-Meier method. Disease-free survival (DFS) was calculated from the time of initial diagnosis (initiation of the first treatment) to the first recurrence of disease.

**Results:** After a median follow-up of 48 months, 100 (24.4%) patients have had at least 1 of the DFS events. In Cox regression analysis, we proposed the simple PI, which is a sum of axillary nodal and HER2/*neu* status. In the ST method, we identified 3 variables: HER2/*neu*, axillary nodal, and estrogen receptor status. The axillary nodal status was the most important determining factor for recurrence.

**Conclusion:** We found that the PI of the ST and Cox regression methods had similar performance levels in predicting DFS, and the error rates of the models were close to each other in the training and test sets. Furthermore, we determined that the axillary nodal status and HER2/*neu* were the most important determining factors for prediction of DFS in breast cancer patients.

**Key words:** Breast cancer, survival tree, recursive partitioning, disease-free survival, prognostic index

## Nonmetastatik meme kanserli hastalarda hastalıksız sağkalımın belirlenmesinde iki farklı prognostik indeksin geliştirilmesi ve kıyaslanması

**Amaç:** Cox regresyon analizi ve recursive partitioning analizine dayanan sağkalım ağacı (ST) ile non-metastatik meme kanserli hastaların alt gruplara ayrılmasında farklı prognostik indeksler (Pİ) belirlemek ve bu metodların tahmin güçlerini Kaplan-Meier analizi ile karşılaştırmaktır.

**Yöntem ve gereç:** Veriler, her bir prognostik faktör için 410 hastadan elde edildi. Cox regresyon analizi, ortak değişkenlere göre yaşamsal dağılımı inceleyen bir yöntemdir. ST yöntemi ise recursive partitioning algoritmasına dayanan ağaca yapılı bir sağkalım analizidir. Çalışmada, train ve test setleri için Harrell'ın uyum indeksine göre hata oranları incelendi. Ayrıca train seti için yaşam eğrileri Kaplan-Meier yöntemi ile tahmin edildi. Hastalıksız sağkalım, hastalığın ilk tanısından (ilk tedavinin başlangıcından) ilk nüksüne kadar geçen zaman olarak hesaplandı.

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**Bulgular:** 48 aylık ortanca takip sonrası 100 (% 24,4) hastada hastalıksız sağkalım açısından en az bir olay görüldü. Cox regresyon analizinde HER2/*neu* ve aksiller nodal durumuna dayanan basit bir Pİ geliştirildi. ST metodunda üç değişken belirlendi ve bunlar HER2/*neu*, aksiller nodal durum ve östrojen reseptör durumu idi. Nüksü belirleyen en önemli faktör aksiller nodal durum idi.

**Sonuç:** ST ve Cox regresyon analizi ile elde edilen Pİ'ler, hastalıksız sağkalımın tahmin edilmesinde benzer performans gösterdi. Modellerin hata oranlarının, train ve test setlerinde birbirilerine yakın olduğu belirlendi. Ayrıca HER2/*neu* ve aksiller nodal durumun, meme kanserli hastalarda hastalıksız sağkalım süresinin tahmini için en önemli faktörler olduğu belirlendi.

**Anahtar sözcükler:** Meme kanseri, prognostik indeks, sağkalım ağacı, recursive partitioning, hastalıksız sağkalım

## Introduction

In general, 5-year disease-free survival (DFS) ranges from 65% to 80% in all populations in breast cancer patients (1). Current evidence supports a clear association between some clinicopathologic factors and reduced DFS. The clinicopathologic characteristics of patients are heterogeneous, and the survival times are different in subgroups of patients. The aim of prognostic classification indexes is to define subgroups of patients with well-separated survival distributions. Combinations of prognostic factors further augment the recurrence risk, warranting the recommendation of combination chemotherapy and radiotherapy to improve survival. Several prognostic classification indexes were developed (2-5), but often these are contradictory.

The Cox regression analysis is the most common tool for investigating simultaneously the influence of several factors on the survival time of patients (6). However, it does not provide an estimate of the degree of separation of the different subgroups. Decision tree algorithms such as the survival tree (ST) method allow for nonlinear relations between predictive factors and outcomes. They also support mixed (numerical and categorical) and heterogeneous data types, isolate outliers, and incorporate a pruning process using cross-validation as an alternative to testing for unbiasedness with a second data set (7,8). They can identify prognostic subgroups that are clinically useful because they are based on simple combinations of clinical characteristics. In contrast to traditional regression methods, which compute a prognostic index as a weighted average of the patient's characteristics (i.e. an algebraic formula), decision tree algorithms construct groups based on logical combinations of patient characteristics. Thus, the prognostic subgroups are based directly rather than indirectly on the patient characteristics. Therefore, decision tree methods such as ST are more suitable than classical statistical methods. In the literature, there are several reports about the separation of patients with different prognoses for survival into subgroups (5,9-12).

The purpose of this study was to determine 2 different prognostic indexes for the differentiation of subgroups of nonmetastatic breast cancer patients and to explore the very complicated and heterogeneous survival data with the Cox regression analysis and ST methods.

## Materials and methods

### Patients

A retrospective analysis was performed in 640 breast cancer patients diagnosed between 1997 and 2006. Data for 410 nonmetastatic patients were available and formed the basis of this study. We investigated age, menopausal status, age of menarche, body mass index, hormone replacement therapy, pathology of tumor, quadrant of tumor, tumor size, estrogen and progesterone receptor status (Lab Vision, USA), histologic and nuclear grading according to Scarf-Bloom-Richardson criteria (13), axillary nodal status, lymphovascular invasion, HER2/*neu* expression (NeoMarkers, USA), adjuvant radiotherapy, chemotherapy, and hormonal therapy as prognostic factors. Surgery (modified radical mastectomy or breast-conserving surgery) was the primary local treatment. According to the American Joint Committee on Cancer staging (14), 13 (3.2%) patients had in situ, 319 (77.8%) had early stage, and 78 (19%) had locally advanced disease. Tumors were considered positive for

estrogen and progesterone receptors if more than 10% of the tumor cells showed nuclear staining (15). HER-2/*neu* staining was scored on a scale of 0, 1+, 2+, or 3+. Scores of 0 or 1+ were deemed negative for HER-2/*neu.* Positive HER-2/*neu* expression was defined by weak/moderate (2+) or moderate/strong (3+) complete membrane staining in more than 10% of the tumor cells (16). Samples with scores of 2+ were assessed further by fluorescence in situ hybridization (FISH) analysis to examine gene amplification. FISH analysis was performed using the PathVysion™ HER-2 DNA Probe Kit Package Insert (Vysis Inc., Illinois, USA) according to the manufacturer's instructions, using reagents, probes, and positive controls provided by the manufacturers (17). Adjuvant radiotherapy was given to 286 (69.8%) patients, chemotherapy was administered to 334 (81.5%) patients, and hormonal therapy was given to 313 (76.3%) patients. Chemotherapy was delivered prior to radiotherapy. Hormonal therapy was initiated after the completion of radiotherapy and typically continued for 5 years in hormone receptor-positive patients until the recurrence of disease. Follow-ups consisted of a clinical assessment every 3 months for the first 2 years, every 6 months for 3 years, and annually after 5 years.

**Statistical analysis**

Descriptive statistics of clinical and pathologic data for the entire patient population are listed in Table 1. We performed classical statistical analysis to examine the differences in the distribution of variables between patients who had a recurrence and those who did not. The Kolmogorov-Smirnov test was used to assess the normality of numeric variables. For all of the numeric variables that were nonnormally distributed, comparison between the 2 groups was made by the Mann-Whitney U-test, and results were expressed as medians and interquartile ranges (IQR). Association of recurrence with nominal variables was assessed using the chi-square test.

Before the building of the models, the data sets were randomly split into 2 subsets: 70% (n = 287) of the data for the training set and 30% (n = 123) of the data for test set. Using ST and Cox regression analysis, 2 different prognostic indexes, which were solely based on standard factors, were developed. Harrell's concordance index was computed for both the training and test sets.

Survival analysis was performed for DFS, the time from initial diagnosis (initiation of the first treatment) to the first recurrence of disease (locoregional recurrence, distant metastases, or second cancer). For the terminal nodes of the ST and the Cox model from the training data set, the difference between the curves was estimated by the Kaplan-Meier method, and the curves were evaluated with the log-rank test, also known as the Mantel-Cox test. Follow-up time for each patient was calculated in months from the last day of the initial treatment to the date of death or the date of last visit. For all statistical tests, P-values less than 0.05 were considered significant.

**Tree-structured survival analysis: recursive partitioning analysis**

The recursive partitioning analysis is used to correctly classify members of a population based on categorical or continuous dependent variables (18). It is commonly used for classification and regression problems. It is also used as an approach for extending regression trees to survival data; the prediction at each leaf is a survival distribution (19,20). The goal is to produce subsets of the data that are as homogeneous as possible with respect to survival. In our study, tree-structured survival analysis was called survival tree (ST) for recursive partitioning analysis. For analyzing survival data, deviance-based criteria that need survival distribution with just one parameter varying between nodes is used for splitting. This approach evaluates all possible dichotomous splits for all potential prognostic factors (19). In ST, the recursive partitioning procedure commonly uses exponential scaling as the splitting rule. To find a tree that is defined by characteristics of the underlying population, the tree is pruned. ST uses a complexity parameter (cp) for the control of tree-growing. Breiman et al. (18) presented a comprehensive overview of recursive partitioning methodology.

**Cox regression analysis**

Survival analysis investigates the relationship of the survival distribution to covariates. Most commonly, this examination entails the specification of a linear-like model for the log hazard. The Cox regression analysis may be written as:

$$h(t, \times) = h_0(t)e^{\beta' \times},$$

where x is the covariate vector, β is the unknown parameter vector, and $h_0(t)$ is the baseline hazard (i.e. the hazard for the respective individual when all independent variable values are equal to zero). The resultant hazard is denoted as h(t, ×), given the values of the m covariates for the respective case and the respective survival time (t).

The Cox regression analysis equation has 2 assumptions, while no assumptions are made about the shape of the underlying hazard function. The first assumption is that a multiplicative relationship between the underlying hazard function and the log-linear function of the covariates is specified. The second assumption is that there is a log-linear relationship between the independent variables and the underlying hazard function (6).

**Harrell's concordance index**

Harrell's concordance index is a measure of survival performance. It does not depend on choosing a fixed time for evaluation of the model and specifically takes into account the censoring of individuals. The error rate is computed as 1-C, where C is Harrell's concordance index. Error rates are between 0 and 1, with 0.5 corresponding to a procedure with results no better than random. A value of 0 denotes perfect accuracy (21,22).

We used Harrell's concordance index to quantify the accuracy of ST and Cox regression analysis.

**Kaplan-Meier survival analysis**

The Kaplan-Meier analysis is a nonparametric technique for estimating time-related events (23). It can be used to test the statistical significance of differences between survival curves associated with 2 different circumstances. It is applied by analyzing the distribution of patient survival times following their recruitment to a study. The analysis expresses these in terms of the proportion of patients still alive up to a given time following recruitment. In graphical terms, a plot of the proportion of patients surviving against time has a characteristic decline (often exponential), the steepness of the curve indicating the efficacy of the treatment being investigated. The more shallow the survival curve, the more effective the treatment (24).

A variety of tests may be used to compare 2 or more Kaplan-Meier curves under certain well-defined circumstances. Median remission time (the time when 50% of the cohort has reached remission), as well as quantities such as 3-, 5-, and 10-year probability of remission, can also be generated from Kaplan-Meier analysis, provided that there has been sufficient patient follow-up.

## Results

**Characteristics of study subjects**

After a median follow-up of 48 months, 100 (24.4%) patients had at least 1 DFS event. Tumor size, quadrant of tumor, nuclear and histologic grade, estrogen and progesterone receptor status, lymphovascular invasion, axillary nodal status, and HER2/*neu* were statistically significant prognostic factors for recurrence (Table 1). The median age was 50 years (mean of 51, range of 26-79), and the median tumor size was 3 cm (mean of 3.16, range of 0.1-14).

**Cox regression analysis for the prediction of DFS in breast cancer patients**

In Table 2, we give estimates of the regression coefficients in the stepwise Cox regression analysis for the training data set. In this analysis, HER2/*neu* status and axillary nodal status have significant effects as prognostic factors ($P < 0.001$ and $P < 0.01$, respectively). Interaction terms did not enter the final model. Based on these results, we propose the simple prognostic index (PI):

PI = HER2/*neu* status + axillary nodal status,

where axillary nodal status and HER2/*neu* note the indicator function taking values of 0 and 1, dependent on whether the patient is axillary nodal status = positive or HER2/*neu* status = positive, respectively. The index gives from 0 to 2 points to each patient (Table 3). PI = 0 is the group with the minimal risk, while PI = 2 is the group with the maximum risk.

The concordance error rate of this model was 0.2093 for the training set and 0.2160 for the test set (Table 4).

**ST for the prediction of DFS in breast cancer patients**

With the ST method, we identified 3 variables that play important roles in explaining recurrences:

Table 1. Clinicopathologic characteristics of the study groups.

| Independent variables | | Recurrence | | P-value |
|---|---|---|---|---|
| | | Absent | Present | |
| Age (years) median (IQR) | | 50 (15) | 51 (16) | 0.409 |
| Age of menarche (years) median (IQR) | | 13 (1) | 13 (2) | 0.707 |
| Tumor size (cm) median (IQR) | | 2.75 (2.1) | 3 (2.8) | 0.019 |
| Body mass index (kg/cm$^2$) median (IQR) | | 29 (5.9) | 30 (7.1) | 0.320 |
| | | n (%) | n (%) | |
| Hormone replacement therapy | Present<br>Absent | 53 (18.1)<br>240 (81.9) | 14 (15.1)<br>79 (84.9) | 0.606 |
| Menopausal status | Post<br>Pre | 160 (51.6)<br>150 (48.4) | 49 (49.0)<br>51 (51.0) | 0.649 |
| Quadrant of tumor | Unicentric<br>Multicentric | 288 (94.4)<br>17 (5.6) | 81 (85.3)<br>14 (14.7) | 0.007 |
| Nuclear grade | I + II<br>III | 177 (76.0)<br>56 (24.0) | 47 (58.8)<br>33 (41.3) | 0.005 |
| Histologic grade | I + II<br>III | 191 (70.0)<br>82 (30.0) | 50 (54.9)<br>41 (45.1) | 0.009 |
| Estrogen receptor status | Negative<br>Positive | 67 (22.4)<br>232 (77.6) | 40 (42.1)<br>55 (57.9) | <0.001 |
| Progesterone receptor status | Negative<br>Positive | 78 (26.0)<br>222 (74.0) | 35 (36.8)<br>60 (63.2) | 0.042 |
| Adjuvant radiotherapy | Absent<br>Present | 87 (28.1)<br>223 (71.9) | 37 (37.0)<br>63 (63.0) | 0.091 |
| Chemotherapy | Absent<br>Present | 62 (20.0)<br>248 (80.0) | 14 (14.0)<br>86 (86.0) | 0.232 |
| Lymphovascular invasion | Absent<br>Present | 154 (55.6)<br>123 (44.4) | 32 (36.8)<br>55 (63.2) | 0.002 |
| Axillary nodal status | Negative<br>Positive | 200 (64.5)<br>110 (35.5) | 40 (40.0)<br>60 (60.0) | <0.001 |
| Pathology | Ductal<br>Nonductal | 240 (77.4)<br>70 (22.6) | 81 (81.0)<br>19 (19.0) | 0.538 |
| HER2/*neu* | Negative<br>Positive | 278 (89.7)<br>32 (10.3) | 56 (56.0)<br>44 (44.0) | <0.001 |

Table 2. Estimated regression coefficients with standard error hazard ratios with 95% (CI) intervals and P-values from the stepwise Cox model with forward elimination for disease-free survival time.

| Independent variables | | β | SE | HR | 95% (CI) | p |
|---|---|---|---|---|---|---|
| Axillary nodal status | Negative (0)<br>Positive (1) | 0<br>1.763 | -<br>0.51 | 1<br>5.83 | -<br>(2.14-15.84) | <0.01 |
| HER2/*neu* | Negative (0)<br>Positive (1) | 0<br>1.572 | -<br>0.43 | 1<br>4.82 | -<br>(2.09-11.09) | <0.001 |

SE: Standard error
HR: Hazard ratio

Table 3. Subgroups for prognostic index (PI) of Cox model.

| Group | Value | Subgroup categories |
|---|---|---|
| COX-I | PI = 0 | HER2/neu (negative) + axillary nodal status (negative) |
| COX-II | PI = 1 | HER2/neu (negative) + axillary nodal status (positive)<br>HER2/neu (positive) + axillary nodal status (negative) |
| COX-III | PI = 2 | HER2/neu (positive) + axillary nodal status (positive) |

Table 4. Subgroups for prognostic index of ST.

| Group | Node | Terminal node |
|---|---|---|
| ST-I | 4 | Axillary nodal status (negative) + HER2/neu (negative) |
| ST-II | 5 | Axillary nodal status (negative) + HER2/neu (positive) |
| ST-III | 12 | Axillary nodal status (positive) + HER2/neu (negative) + estrogen receptor status (positive) |
| ST-IV | 13 | Axillary nodal status (positive) + HER2/neu (negative) + estrogen receptor status (negative) |
| ST-V | 7 | Axillary nodal status (positive) + HER2/neu (positive) |

axillary nodal status, HER2/*neu* status, and estrogen receptor status (Table 4). This indicated that the axillary nodal expression status was the most important determining factor for recurrence. This first-level split produced the 2 initial branches of the tree, negative versus positive. We could see differences in the 2 subtrees. For the axillary nodal status positive and negative subgroups, HER2/*neu* proved to be the best predicting variable. For the positive axillary nodal status and the negative HER2/*neu* branch, estrogen receptor status (negative vs. positive) was the most prominent predicting variable. The ST has 8 leaf nodes, 5 of which are terminal nodes.

The concordance error rates of this model were 0.1899 for the training set and 0.2143 for the test set (Table 5).

**Survival analysis for breast cancer patients**

In the Cox regression analysis, the 5-year DFS rate was 78.0% in the entire patient population. For the COX-I (PI = 0) subgroup, which included patients with HER2/*neu* and axillary nodal status negative,

Table 5. Harrell's concordance error rates (C index) for methods.

| Method | Training set | | Test set | |
|---|---|---|---|---|
| | C index | SD | C index | SD |
| COX | 0.2093 | 0.0758 | 0.2160 | 0.1062 |
| ST | 0.1899 | 0.0812 | 0.2143 | 0.0855 |

the 5-year DFS rate was 93.3%. Median survival was 259.0 in this subgroup. For the COX-II (PI = 1) subgroup with HER2/*neu* positive and axillary nodal status negative or HER2/*neu* negative and axillary nodal status positive, the 5-year DFS rate was 67.2%. Finally, for the COX-III (PI = 2) subgroup with HER2/*neu* positive and axillary nodal status positive, the rate was 50.0% (Table 6). Figure 1 shows the estimated DFS rates according to the Cox regression analysis. The statistical significance of the difference between the survival curves of the subgroups was tested using the log-rank test (Table 7). All of the survival curves of the subgroups were statistically different from each other. The survival distributions for the Cox regression analysis were statistically significant ($\chi^2 = 107.319$, df = 2, $P < 0.001$).

In the ST method, the 5-year DFS rate was 78.0% in the entire patient population. For the terminal node of ST-I with HER2/*neu* and axillary nodal status negative, the 5-year DFS rate was 93.3%. Median survival was 259.0 in this subgroup. For the ST-II subgroup with axillary nodal status negative and HER2/*neu* positive, it was 42.9%. For the ST-III subgroup with axillary nodal status positive, HER2/*neu* negative, and estrogen receptor status positive, it was 78.8%. For the ST-IV subgroup with axillary nodal status positive, HER2/*neu* negative, and estrogen receptor status negative, it was 45.4%. Finally, for the ST-V subgroup with axillary nodal status and HER2/*neu* positive, it was 50.0% (Table 8). Figure 2 shows the estimated DFS rates according to the ST method. The statistical significance of the difference between the survival curves of 2 terminal nodes was tested using the log-rank test (Table 9). In the ST method, ST-I was statistically different from all other subgroups. The survival curve of ST-V was statistically different from ST-I and ST-

Table 7. Pairwise comparisons by log-rank for PI obtained from Cox model.

| | COX-II | COX-III |
|---|---|---|
| COX-I | $\chi^2 = 88.116$<br>$P < 0.001$ | $\chi^2 = 81.047$<br>$P < 0.001$ |
| COX-II | | $\chi^2 = 7.631$<br>$P = 0.006$ |

Table 6. Descriptive statistics and 5-year disease-free survival (DFS) for Cox model.

| Group | Median | Mean | Standard error | Number of recurrences | n | 5-year DFS (%) |
|---|---|---|---|---|---|---|
| COX-I | 259.0 | 228.1 | 16.6 | 9 | 135 | 93.3 |
| COX-II | 47.8 | 49.5 | 4.5 | 42 | 128 | 67.2 |
| COX-III | 29.3 | 31.9 | 3.0 | 12 | 24 | 50.0 |
| Total | 139.3 | 159.2 | 14.5 | 63 | 287 | 78.0 |

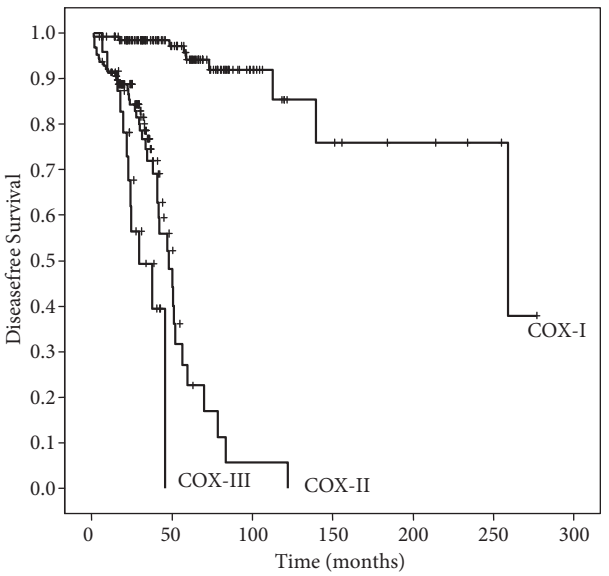


Figure 1. Kaplan-Meier survival curves of the 3 groups generated from the Cox model.

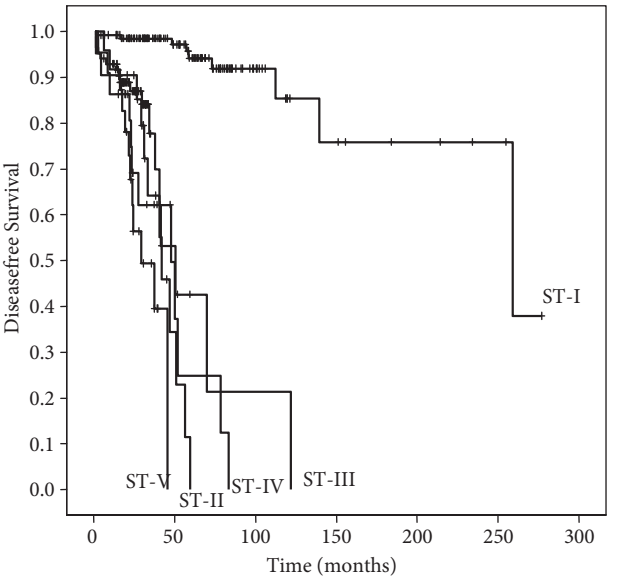


Figure 2. Kaplan-Meier survival curves of the 5 groups (terminal nodes) generated from ST.

Table 8. Descriptive statistics and 5-year disease-free survival (DFS) for each node of ST.

| Group | Median | Mean | Standard error | Number of recurrences | n | 5-year DFS (%) |
|---|---|---|---|---|---|---|
| ST-I | 259.0 | 228.1 | 16.6 | 9 | 135 | 93.3 |
| ST-II | 42.2 | 40.5 | 4.0 | 12 | 21 | 42.9 |
| ST-III | 50.7 | 60.4 | 11.3 | 18 | 85 | 78.8 |
| ST-IV | 47.8 | 45.7 | 6.9 | 12 | 22 | 45.5 |
| ST-V | 29.3 | 31.9 | 3.1 | 12 | 24 | 50.0 |
| Total | 139.3 | 159.2 | 14.5 | 63 | 287 | 78.0 |

Table 9. Pairwise comparisons by log-rank for PI obtained from ST.

| | ST-II | ST-III | ST-IV | ST-V |
|---|---|---|---|---|
| ST-I | $\chi^2 = 95.764$<br>$P < 0.001$ | $\chi^2 = 42.634$<br>$P < 0.001$ | $\chi^2 = 82.791$<br>$P < 0.001$ | $\chi^2 = 81.047$<br>$P < 0.001$ |
| ST-II | | $\chi^2 = 1.845$<br>$P = 0.174$ | $\chi^2 = 0.182$<br>$P = 0.670$ | $\chi^2 = 3.601$<br>$P = 0.058$ |
| ST-III | | | $\chi^2 = 1.522$<br>$P = 0.217$ | $\chi^2 = 7.752$<br>$P = 0.005$ |
| ST-IV | | | | $\chi^2 = 1.793$<br>$P = 0.181$ |

III. The survival distributions for the ST method were statistically significant ($\chi^2 = 116.215$, df = 4, $P < 0.001$).

According to these findings, we determined that COX-I was the group with the low risk, COX-II was the group with the intermediate risk, and COX-III was the high-risk group for DFS. For the ST groups, we determined that ST-I was the group with the low risk, ST-III and ST-IV were the groups with the intermediate risk, and ST-II and ST-V were the high-risk groups for DFS.

## Discussion

Based on the observation of 410 patients over a median follow-up of 48 months, we determined 2 different prognostic indexes for the differentiation of subgroups of breast cancer patients using ST and Cox regression analysis methods. As a result of Cox regression analysis, we proposed the simple PI, which is a sum of HER2/*neu* status and axillary nodal status. In the ST method, we identified 3 variables that played important roles in explaining recurrences: HER2/*neu* status, axillary nodal, and estrogen receptor status. We found that the PI of Cox regression analysis and ST based on recursive partitioning analysis had a similar performance for prediction of DFS in breast cancer patients.

Breast cancer is a heterogeneous disease that encompasses several distinct entities with remarkably different biological characteristics and clinical behavior. Currently, lymph node metastases, tumor grade and size, and expression of hormone receptors provide the only true prognostic and predictive factors related to clinical outcome and response to treatment, respectively. Many other potential candidates have been suggested, but due to their limited predictive power have not been widely accepted by the general oncologic community. These histopathological features do not allow us any insight into breast cancer biology, however, and these prognostic classifications are far from perfect. With the development of genetic and molecular techniques, new molecular classifications and therapeutic targets for breast cancer have been suggested (25,26). The amplification and overexpression of HER2/*neu* is an established prognostic factor in patients with breast cancer (27,28). In 81 studies considering 27,161 patients, 90% of the studies and 92% of the cases found that HER2/*neu* overexpression predicted breast cancer outcome, both in univariate and multivariate analysis (29).

For the development of different prognostic classification indexes, we used 2 different statistical approaches. The first was based on a multivariate analysis of the prognostic factors of our study with the well-known Cox regression analysis. With this approach, we identified HER2/*neu* status and axillary nodal status as relevant prognostic factors upon which the classification index is based. In primary operable breast cancer, the Nottingham Prognostic Index (NPI), based on tumor size, lymph node stage, and histological grade, can identify 3 prognostic groups with 10-year survival rates of 83%, 52%, and 13% (30). The index defined a subset with better survival than could be defined individually by each of its 3 components, but it did not succeed in defining a subset with survival similar to expectations. Therefore, additional prognostic factors are needed. In the Cox regression analysis from the present study, the 3 resulting prognostic groups show a very good separation with 5-year DFS rates of 93.3%, 67.2%, and 50.0%.

The second statistical approach makes use of the decision tree method (7,18,31), in which prognostic groups are obtained through subsequent splitting according to the most important factors. The risk groups resulting from this procedure are defined by HER2/*neu* status, axillary nodal status, and estrogen receptor status. The resulting 5 prognostic groups show a very good separation with 5-year DFS rates of 93.3%, 42.9%, 78.8%, 45.5%, and 50.0%. The longest surviving terminal node, ST-I, included HER2/*neu* and axillary nodal status negative patients. The shortest surviving terminal node, ST-V, included HER2/*neu* and axillary nodal status positive patients. HER2/*neu* expression status and axillary nodal status were the most important determining factors for recurrence. The HER2/*neu*-overexpressed subgroups had the shortest DFS of the 2 methods. The PI of the ST and Cox regression methods, which may be explained by using different prognostic indexes, had similar performances in predicting DFS, and the error rates of the models were close to each other in the training and test sets.

Both of the resulting prognostic groups of our classification methods lead to a seemingly good separation of the nonmetastatic breast cancer patients. However, validation of these results in other studies is absolutely necessary before a definitive judgment can be made. Prognostic classification indexes are based on standard prognostic factors, which are suitable for routine use in the clinic as the basis of rational treatment decisions. In the ninth St. Gallen expert consensus meeting in 2005, the panel divided patients into low-, intermediate-, and high-risk categories (32). Tumor size, axillary nodal status, age, and grade were the main features used to define risk categories. The panel also added 2 features not previously accepted as sufficiently reliable to define risk category. The first was overexpression or amplification of the HER2/*neu* oncogene and the second was peritumoral vessel invasion, especially lymphovascular invasion (33). These categories did not change at the 10th annual St. Gallen meeting (34). In our study, although lymphovascular invasion and HER2/*neu* were statistically significant prognostic factors for recurrence (Table 1), only HER2/*neu* expression status was established as a prognostic factor for recurrence in the 2 methods.

The analyses conducted in this study demonstrated that the ST method for segregating patients into groups with similar clinical features and survival consistently applied the variables reported to be important in the Cox regression analysis. The fact that each of these approaches used similar clinical variables to stratify patient survival confirms their clinical importance and supports the validity of the ST analysis. Lamborn et al. (12) evaluated several potential prognostic markers for survival of patients with glioblastoma multiforme in order to establish risk groups by using Cox regression and recursive partitioning analyses. They reported that recursive partitioning is an exploratory tool that has found favor in recent years because it provides a method of categorizing patients into risk groups. Kenneth et al. (9) reported that clinicians often experience difficulty applying standard statistical methods to assess the interactions between clinical variables, determine the cumulative effect of these variables on survival, and translate this information into appropriate management, because of the complex presentations of patients with unknown primary carcinoma (UPC). To address the problem they explored C&RT analysis, and they showed that C&RT is a simple method for dissecting complex clinical issues in UPC patients. However, before accepting this model, they advised validation studies on an independent data set.

Ture et al. (11) tried to discover the risk groups and make decision rules for the management of breast cancer by using the C&RT, CHAID, QUEST, ID3, C4.5, and C5.0 methods and Cox regression analysis. They also determined new prognostic indexes for the differentiation of subgroups of breast cancer patients with models for risk factors according to Kaplan-Meier analysis and evaluated the performance of the methods using random survival forests (35). Ture et al. (35) further analyzed different decision tree methods (C&RT, CHAID, QUEST, C4.5, and ID3) and used them in addition to the well known Kaplan-Meier estimates to investigate the predictive power of these methods. In nonmetastatic breast cancer patients, they found that the C4.5 method showed a better degree of separation for predicting survival. They recommended using decision tree methods together with Kaplan-Meier analysis in order to determine risk factors and the effect of these risk factors on survival.

The German Breast Cancer Study Group (5) validated the C&RT method with Cox regression analysis and the NPI. They reported that the C&RT method showed a better degree of separation in node negative breast cancer patients, and that a young age (≤40 years) and very high estrogen receptor values were associated with a worse prognosis. Although the 5-year survival rates demonstrate that C&RT and Cox regression analysis lead to a better separation than the NPI, they stressed that such an assessment is difficult as they used more groups (3 for Cox, 4 for C&RT) than the NPI, which resulted in smaller groups. The current study used 3 groups for Cox and 5 groups for ST.

The ST and Cox regression methods had similar performances in predicting DFS. However, validation through other independent studies is necessary before a definitive judgment can be made. Future clinical trials of patients with breast cancer should prospectively examine the ability of the prognostic information obtained from both methods to facilitate

precise clinical decision-making. Furthermore, ST is a suitable method for exploring relationships hidden within heterogeneous data sources as a result of tree-structured survival analysis. These data can be used to identify relatively homogeneous breast cancer patient populations with similar survival in order to analyze novel therapeutic interventions and tailor treatment for individual breast cancer patients.

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