Original Article

Effect of node status on breast cancer survival by subtype: a single-center retrospective cohort study

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Background: Nodal involvement and molecular subtypes were used as independent prognostic indicators in women with breast cancer. However, they did not adequately address the effect of node status by subtype in outcomes.

Methods: We performed a retrospective review of data from 2004 to 2011 from the Affiliated Union Hospital of Fujian Medical University with newly diagnosed stage I to III breast cancer to investigate the relationship between node status and 5-year disease-free survival (DFS) and breast cancer-specific survival (BCSS) by molecular subtype. The Cox proportional hazards model was used for multivariate analysis.

Results: Median follow-up time was 6.4 years. Luminal HER2 and luminal B were the subtypes with a higher percentage of nodal involvement and high-volume nodal involvement (≥4 positive lymph node) than luminal A. The effect of node status on the prognosis varied with molecular subtype. There was no difference in 5-year DFS and BCSS between stage N1 or N2 and N0 groups in patients with luminal A disease. Nodal involvement in women with the luminal B, luminal HER2, and triple-negative subtypes showed significant difference for 5-year DFS and BCSS compared to the node negative group.

Conclusions: Nodal involvement seems to be associated with worse survival in women with the luminal B, luminal HER2, and triple-negative subtypes, but not with the luminal A subtype.

Keywords: Breast cancer; nodal status; subtype; survival

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Introduction

Breast cancer is the most frequent type of carcinoma and the second most common cause of death from carcinomas in women (1-3). Prognostic variables for breast cancer have traditionally included node status, histological grade, tumor size, hormone receptor (HR) status, and human epidermal growth factor receptor 2 (HER2) expression. Numerous studies have suggested that nodal involvement is the most crucial prognostic parameter, and play a pivotal role in instructing treatment (4,5). In 2000, Perou *et al*. identified breast tumor cells that shared gene expression patterns and clustered it into four subtypes: luminal epithelial/estrogen receptor (ER) positive, normal-breast-like, basal-like, and/or cells with over-expression of the human epidermal growth factor receptor 2 (*HER2*) gene (6). Previous studies reported that molecular subtypes are associated with different risks of early disease recurrence, metastases, and survival (7-9). Although nodal involvement and molecular subtypes are both independently well-recognized prognostic indicators, it remains unclear whether there is

Table 1 Patient and tumor characteristics

Parameters	No. of patients	Percentage (%)
Age, years		
≤40	525	25.1
>40	1,564	74.9
Tumor size, cm		
≤2	862	41.3
>2	1,227	58.7
Node status		
N0	1,119	53.6
N1	521	25.0
N2	256	12.2
N3	193	9.2
Grade		
Low/moderate	1,453	69.5
High	492	23.6
Unknown	144	6.9
Ki-67		
Low	763	36.5
High	796	38.1
Unknown	530	25.4
Subtype		
Luminal A	464	22.2
Luminal B	653	31.3
Luminal HER2	294	14.1
HER-2	341	16.3
TN	337	16.1
ER		
Positive	1,400	67.0
Negative	689	33.0
PR		
Positive	1,284	61.5
Negative	805	39.5
HER2		
Positive	638	30.5
Negative	1,451	69.5

an association between these two factors (10,11). He *et al*. have reported that triple-negative breast cancer is associated with a reduced risk of nodal involvement compared to other subtypes (12). A study by Liao *et al*. revealed significant differences in overall survival (OS) according to the node status in luminal A, luminal B, and luminal HER2 subtypes, and with recurrence-free survival (RFS) in the luminal B and luminal HER2 subtypes after adjustments for age and tumor size (13). Thus, it can be seen that node status is associated with molecular subtypes in outcomes, and nodal involvement may not always be an independent risk factor for some molecular subtypes. To address this, we retrospectively investigated the effect of the node status on the 5-year disease-free survival (DFS) and breast cancer-specific survival (BCSS) with different molecular subtypes of breast cancer. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1117).

Methods

Patients

We retrospectively reviewed the medical records of breast cancer patients with stages I to III disease [American Joint Committee on Cancer (AJCC) staging, 7th edition] treated from 2004 to 2011 in the Affiliated Quanzhou First Hospital of Fujian Medical University. We excluded 49 patients who had either had a previous diagnosis of malignant tumor or who were missing follow-up information. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Affiliated Union Hospital of Fujian Medical University Ethics committee (No. 002934) and informed consent was taken from all the patients. The demographics and clinicopathological information from their medical records were regrouped and are given in *Table 1*.

Definitions

Node status was defined by TNM classification as proposed by the American Joint Committee on Cancer for grouping patients with respect to prognosis. Categorizing the number of metastatic lymph nodes into N0 (0), N1 (≤3), N2 (4 to 9), and N3 (≥10) groups, and the N0 group acted as the reference group. The ER and PR expression were

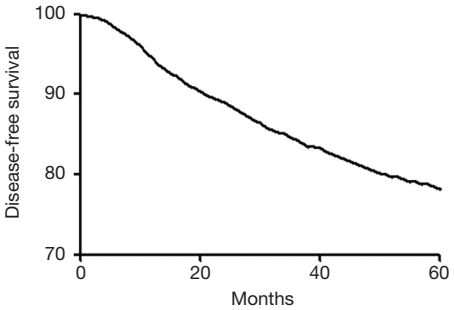

Figure 1 Kaplan-Meier curves for 5-year DFS. DFS, disease-free survival.

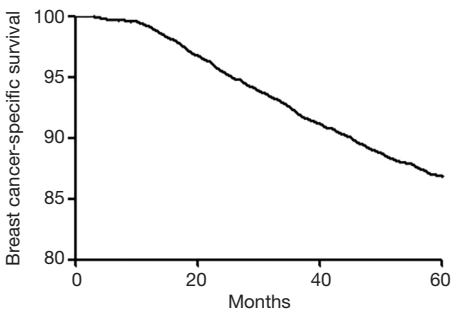

Figure 2 Kaplan-Meier curves for 5-year BCSS. BCSS, breast cancer-specific survival.

assessed using immunohistochemical (IHC) staining. An ER expression of more than 1% was considered positive, and expression of more than 20% for PR was classified as high expression. HER2 positivity was defined as a 3+ staining intensity score at IHC analysis for the HER2 protein or for *HER2* gene amplification by fluorescence in situ hybridization (FISH) (14). According to the reported from Cheang *et al*. (15), we defined expression of 14% or greater as a high Ki-67 level and less than 14% as a low level of expression. If Ki-67 results are not available, the grade can be used as a surrogate for the molecular subtypes (16). According to the St. Gallen International Breast Cancer Conference (2013 or 2015), we identified the following molecular subtypes; luminal A (ER positive and PR high, HER2 negative and Ki-67 low expression or low/intermediate grade), luminal B (ER positive and HER2 negative and either PR low or Ki-67 high or high grade), luminal HER2 (ER positive and HER2 positive), HER2 (ER negative, PR negative and HER2 positive), and triple-negative (TN; ER negative, PR negative, and HER2 negative) (17,18).

Statistics

Statistical analysis was performed using SPSS version 22.0 (IBM Corporation, New York, USA). Univariate and multivariate analyses of breast cancer survival comprising the patient's age, tumor size, histologic grade, Ki-67, and molecular subtype were performed. Furthermore, we conducted Multivariable Cox proportional hazards regression with adjustments, including age, tumor size, and histologic grade, to estimate the hazard ratios (HR) and 95% confidence interval (CI) for the relationship between node status and 5-year DFS or 5-year BCSS within each molecular subtype. The DFS was defined by the date of primary diagnosis to any case of recurrence (local-regional, contralateral breast or distant) or death. We calculated BCSS from the time of diagnose to death from breast cancer. All statistical tests were two-sided, and P values <0.05 were considered statistically significant.

Results

Clinicopathological characteristics

A total of 2,089 eligible patients with breast cancer were included in the study. The median follow-up time was 6.4 years. Patient's demographics and clinicopathological characteristics are listed in *Table 1*. Using the TNM staging system, tumors were categorized based on the number of invasive lymph nodes in N0 (n=1,119, 53.6%), N1 (n=521, 25.0%), N2 (n=256, 12.2%), and N3 (n=193, 9.2%). The percentage of molecular subtypes among the patients in the study was as follows; luminal A in 22.2%, luminal B in 31.3%, luminal HER2 in 14.1%, HER2 in 16.3%, and TNBC in 16.1%.

Survival analysis (5-year DFS and 5-year BCSS)

In the entire group the 5-year DFS and BCSS rate were 1,631/78.1% and 1,814/86.8% (*Figures 1,2*). Using univariate Cox regression, tumor size, node status, histologic grade, Ki-67, and molecular subtype were significant prognostic factors for 5-year DFS and BCSS. Age was only significant for 5-year DFS but not for 5-year BCSS (*Tables 2,3*). After adjusting for other prognostic factors, the nodal involvement (N1, N2, N3) was associated with worse 5-year DFS and 5-year BCSS compared with the node negative group.

Table 2 Univariate and multivariate analyses of DFS

Parameters	N	5-year DFS (%)	Univariate, HR (95% CI)	P value	Multivariate, HR (95% CI)	P value
Age, years						
≤40	388	73.9	1.0		1	
>40	1,243	79.5	0.8 (0.6–0.9)	0.008	0.8 (0.6–1.0)	0.084
Tumor size, cm						
≤2	757	87.8	1.0		1	
>2	874	71.2	2.6 (2.1–3.2)	0.000	1.6 (1.2–2.2)	0.001
Node status						
N0	985	88.0	1.0		1	
N1	402	77.2	2.0 (1.6–2.6)	0.000	2.1 (1.6–2.9)	0.000
N2	158	61.7	3.8 (3.0–5.0)	0.000	3.4 (2.4–4.8)	0.000
N3	86	44.6	6.6 (5.1–8.5)	0.000	6.1 (4.4–8.5)	0.000
Grade						
Low/moderate	1,164	80.1	1.0		1	
High	351	71.3	1.5 (1.3–1.9)	0.000	1.2 (0.9–1.5)	0.173
Ki-67						
Low	642	84.1	1.0		1	
High	596	74.9	1.7 (1.4–2.1)	0.000	1.0 (0.8–1.3)	0.875
Subtype						
Luminal A	426	91.8	1.0		1	
Luminal B	520	79.6	2.6 (1.8–3.7)	0.000	1.8 (1.2–2.9)	0.006
Luminal HER2	191	65.0	5.0 (3.4–7.2)	0.000	2.9 (1.8–4.6)	0.000
HER-2	241	70.7	4.2 (2.9–6.1)	0.000	1.4 (0.8–2.5)	0.180
TN	253	75.1	3.4 (2.3–5.0)	0.000	1.4 (0.8–2.5)	0.199

HR, hazard ratios; DFS, disease-free survival.

Stratification by molecular subtype

In *Table 4* we show that the luminal A and TN subtypes predict a lower incidence of nodal involvement (39.9% and 40.9%) compared with luminal HER2 and luminal B subtypes (55.1% and 52.4%). Similarly, the luminal B, luminal HER2, and HER2 subtypes present a greater percentage of high-volume nodal involvement (≥4 positive LN) compared with luminal A disease. Multivariable Cox proportional hazards regression was used to describe the association between node status and 5-year DFS or 5-year BCSS in different constructed molecular subtypes as shown in *Table 5*. After adjusting for age, tumor size, and histological grade there was no difference in 5-year DFS and 5-year BCSS between the N1 or N2 and N0 groups of patients with luminal A disease. For women with the HER2 subtype, similarly, there was no difference in 5-year DFS and 5-year BCSS between the N1 and N0 groups. However, nodal involvement (N1, N2, and N3) patients showed a significant difference for 5-year DFS and 5-year BCSS compared to the reference group (N0) with the luminal B, luminal HER2, and TN subtypes.

Discussion

Several studies have reported that nodal involvement may be an independent prognostic parameter which is associated

Table 3 Univariate and multivariate analyses of BCSS

Parameters	N	5-year BCSS (%)	Univariate, HR (95% CI)	P	Multivariate, HR (95% CI)	P
Age, years						
≤40	444	84.6	1.0		1	
>40	1,370	87.6	0.8 (0.6–1.0)	0.077	0.9 (0.6–1.2)	0.396
Tumor size, cm						
≤2	809	93.9	1.0		1	
>2	1,005	81.9	3.1 (2.3–4.2)	0.000	1.5 (1.0–2.2)	0.032
Node status						
N0	1,064	95.1	1.0		1	
N1	453	86.9	2.8 (1.9–4.0)	0.000	3.4 (2.1–5.3)	0.000
N2	188	73.4	6.1 (4.3–8.7)	0.000	6.4 (4.0–10.1)	0.000
N3	109	56.5	11.5 (8.2–16.1)	0.000	10.9 (7.0–17.2)	0.000
Grade						
Low/moderate	1,283	88.3	1.0		1	
High	403	81.9	1.6 (1.2–2.1)	0.000	1.1 (0.8–1.5)	0.578
Ki-67						
Low	700	91.7	1.0		1	
High	668	83.9	2.0 (1.5–2.7)	0.000	1.2 (0.9–1.8)	0.237
Subtype						
Luminal A	445	95.9	1.0		1	
Luminal B	591	90.5	2.4 (1.4–4.0)	0.001	1.4 (0.7–2.5)	0.307
Luminal HER2	234	78.5	5.4 (3.2–9.0)	0.000	2.5 (1.3–4.6)	0.005
HER-2	274	80.4	5.3 (3.2–8.8)	0.000	1.5 (0.7–3.1)	0.280
TN	270	80.1	5.3 (3.2–8.9)	0.000	1.8 (0.9–3.7)	0.120

Table 4 Correlation of molecular subtypes and the number of nodal involvements

Subtype	Any nodal involvement (≥1 positive LN), %	High-volume nodal involvement (≥4 positive LN), %
Luminal A	39.90	12.50
Luminal B	52.40	25.60
Luminal HER2	55.10	26.20
HER-2	41.90	25.50
TN	40.90	17.80

Table 5 Node status and 5-year DFS and 5-year BCSS by molecular subtype

Subtype/node	Patients, n (%)	5-year DFS, n (%)	HR (95% CI)*	P	5-year BCSS, n (%)	HR (95% CI)*	P
Luminal A	464	426 (91.8)			445 (95.9)		
N0	279 (60.1)	264 (94.6)	1		270 (96.8)	1	
N1	127 (27.4)	115 (90.6)	1.5 (0.7–3.4)	0.260	121 (95.3)	1.7 (0.5–5.1)	0.365
N2	41 (8.8)	36 (87.8)	2.2 (0.7–6.3)	0.162	40 (97.6)	0.8 (0.1–7.1)	0.872
N3	17 (3.7)	11 (64.7)	8.3 (3.1–22.1)	0.000	14 (82.4)	7.4 (1.8–29.3)	0.005
Luminal B	653	520 (79.6)			591 (90.5)		
N0	311 (47.6)	277 (89.1)	1		303 (97.4)	1	
N1	175 (26.8)	141 (80.6)	1.7 (1.0–2.8)	0.050	161 (92.0)	2.5 (1.0–6.3)	0.043
N2	98 (15.0)	65 (66.3)	2.8 (1.7–4.8)	0.000	79 (80.6)	6.1 (2.5–14.6)	0.000
N3	69 (10.6)	37 (53.6)	4.8 (2.8–8.1)	0.000	48 (69.5)	10.7 (4.5–25.8)	0.000
Luminal HER2	294	191 (65.0)			234 (79.6)		
N0	132 (44.9)	104 (78.8)	1		122 (92.4)	1	
N1	85 (28.9)	50 (58.8)	2.0 (1.2–3.4)	0.009	67 (78.8)	3.4 (1.5–7.7)	0.003
N2	44 (15.0)	22 (50.0)	2.7 (1.5–5.0)	0.001	27 (61.4)	5.3 (2.2–12.4)	0.000
N3	33 (11.2)	15 (45.4)	2.5 (1.3–4.8)	0.005	18 (54.5)	5.4 (2.2–12.8)	0.000
HER2	341	241 (70.7)			274 (80.4)		
N0	198 (58.1)	166 (83.8)	1		185 (93.4)	1	
N1	56 (16.4)	45 (80.4)	1.1	0.774	50 (89.3)	1.7 (0.6–4.5)	0.292
N2	39 (11.4)	16 (41.0)	4.5	0.000	21 (53.8)	8.3 (4.0–17.2)	0.000
N3	48 (14.1)	14 (29.2)	6.2	0.000	18 (37.5)	11.3 (5.6–22.9)	0.000
TN	337	253 (75.1)			270 (80.1)		
N0	199 (59.1)	174 (87.4)	1		184 (54.6)	1	
N1	78 (23.1)	51 (65.4)	3.3 (1.9–5.8)	0.000	54 (69.2)	4.7 (2.4–9.1)	0.000
N2	34 (10.1)	19 (55.9)	4.2 (2.1–8.2)	0.000	21 (61.8)	5.8 (2.7–12.6)	0.000
N3	26 (7.7)	9 (34.6)	6.9 (3.6–13.5)	0.000	11 (42.3)	10.0 (4.6–21.6)	0.000

*, adjusted for age, tumor size, histological grade.

with a poor prognosis (19-21). However, there are limited published studies on this topic that evaluate the impact of node status on prognosis by molecular subtype in women with early breast cancer. Hence, we used a large cohort of cases obtained from 2,089 women with breast cancer to conduct a retrospective study. We found that nodal involvement is an independent predictors of the 5-year DFS or 5-year BCSS in patients with breast cancer. Even when adjustments were made for patient age, tumor size, grade, Ki-67, and subtypes, a multivariate analysis showed that lymph node involvement implies a worse 5-year DFS and 5-year BCSS, which is consistent with the report by Ataseven *et al*. (19). Similarly, Liao *et al*. reported that a higher positive number of lymph nodes was associated with an inferior 5-year OS (13). On the face of it, nodal involvement and a higher number of positive nodes does increase the risk of survival (20,21).

Recent studies have suggested that some molecular subtypes are associated with the node status and an increased risk of nodal involvement (22-25). Our study indicates that the luminal A and TN subtypes predict a lower incidence of nodal involvement. However, a greater percentage of

nodal involvement and high-volume nodal involvement (≥4 positive LN) was found for women with the luminal B, luminal HER2, and HER2 subtypes. Wiechmann *et al*. have reported that after controlling for patient age, tumor size, lymphovascular invasion, and grade, that the luminal B and luminal HER2 subtype tumors were more likely to manifest nodal involvement or more metastatic lymph nodes compared with patients with luminal A (26). Our data are also consistent with a previously reported study by Crabb *et al*. that indicates that the TNBC is associated with a lower incidence of nodal involvement than other subtypes despite its poor prognosis (23). Similar results had been reported by studies from Howland *et al*. and Bhargava *et al*. (22,27). Our study supports the reports that luminal B, luminal HER2, and HER2 subtypes are associated with a higher likelihood of nodal involvement and high-volume (four or more positive lymph nodes) axillary metastasis. Furthermore, we found that the node status is associated with molecular subtype and has the prognostic value for predicting 5-year DFS and BCSS in molecular subtypes. Luminal B, luminal HER2 and TN subtypes, are more aggressive subtypes than luminal A and always considered to be associated with an unfavorable prognosis at the diagnosis of breast cancer. For the patients with these subtypes, nodal involvement had a statistically significant association with a worse 5-year DFS and 5-year BCSS compared with the N0 group. Similarly, Liao *et al*. had reported a large study with 1,399 patients to investigate the association between node status and prognosis of breast cancer by molecular subtype. Their results indicated that there were significant differences in 5-year RFS and OS according to the node status among the luminal B and TN subtypes. After adjusting for age and tumor size for OS and RFS by multivariate Cox proportional hazard analysis, a statistically significant difference remained among the luminal B and luminal HER2 subtypes (13). Among women with luminal B, luminal HER2 and TN subtypes, nodal involvement seems to remain an independent prognostic factor.

In women with luminal A subtype, our report indicated that the N1 or N2 group with luminal A disease did not have a worse 5-year DFS and 5-year BCSS compared with the N0 group. The luminal A subtype is characterized by the expression of hormone receptors and potential sensitivity to endocrine therapy. Some studies have reported than luminal A disease with nodal involvement may benefit more from adjuvant endocrine therapy or the effect of chemotherapy than do node negative patients. We hypothesize that the N1 or N2 group with a luminal A subtype benefits more from adjuvant endocrine therapy or the effect of chemotherapy than the N0 group and these treatments may help to reduce outcome disparities associated with node status among those with higher-risk luminal A tumors in particular. Nodal involvement seems not to be an independent risk factor among luminal A tumors.

For women with HER2 breast cancer, our data indicates that there was no clear decreased risk of BCSS and DFS for the N1 group compared with the N0 group when controlling for other conventional prognostic factors. Several large clinical trials have reported that 1 year of treatment with trastuzumab after adjuvant chemotherapy significantly improves DFS or overall survival among women with node-positive and high-risk node-negative HER2positive breast cancer (28,29). A randomized controlled trial reported that women with lymph node involvement benefit more from trastuzumab compared with node negative patients (30). These studies suggested that the N1 group with HER2 subtype benefit more from trastuzumab than the N0 group, and trastuzumab treatment may help to cancel out the survival difference from different degrees of lymph node involvement. Furthermore, there was a certain proportion of the N0 group who were HER2 positive who cannot accept trastuzumab for economic reasons. So, it seems that the N0 with HER2 patients who were not treated with trastuzumab had a similar prognosis to the N1 group; despite not receiving trastuzumab they did not do worse. Theoretically, nodal involvement could be an independent prognostic factor among the HER2 subtype if more N0 patients accepted treatment with trastuzumab.

Our results support that the relationship between node status and DFS or BCSS varies with molecular subtype. After controlling for other prognostic factors, we observed that there was no significant difference in survival with luminal A subtype between patients with the involvement of less than 10 lymph node and lymph node negative patients, although nodal involvement seem to be an independent predictor of a worse prognosis for patients with luminal B, luminal HER2, and triple negative subtypes. Certainly, there are several limitations to our study. First, this is a retrospective single-institution study and all patients enrolled were Chinese women and results may not apply to other ethnic population with breast cancer. The second limitation of this study was an insufficient study population and follow-up. Furthermore, the information about adjuvant therapy was lacking. However, to the best of our knowledge, this study is one of the largest similar studies reported to date.

Conclusions

The prognostic significance of node status varies with molecular subtype. Nodal involvement seems to be associated with worse survival in women with the luminal B, luminal HER2, and triple-negative subtypes, but not in the luminal A disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All methods were carried out in accordance with relevant guidelines and regulations. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Affiliated Union Hospital of Fujian Medical University Ethics committee (No. 002934) and informed consent was taken from all the patients.

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