Original Article

The number of tumor-free axillary lymph nodes removed as a prognostic parameter for node-negative breast cancer

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Abstract

Recently, there has been controversy about the relationship between the number of lymph nodes removed and survival of patients diagnosed with lymph node–negative breast cancer. To assess this relationship, 603 cases of lymph node-negative breast cancer with a median of 126 months of follow-up data were studied. Patients were stratified into two groups (Group A, 10 or fewer tumor-free lymph nodes removed; Group B, more than 10 tumor-free lymph nodes removed). The number of tumor-free lymph nodes in ipsilateral axillary resections as well as 5 other disease parameters were analyzed for prognostic value. Our results revealed that the risk of death from breast cancer was significantly associated with patient age, marital status, histologic grade, tumor size, and adjuvant therapy. The 5- and 10-year survival rates for patients with 10 or fewer tumor-free lymph nodes removed was 88.0% and 66.4%, respectively, compared with 69.2% and 51.1%, respectively, for patients with more than 10 tumor-free lymph nodes removed. For patients with 10 or fewer tumor-free lymph nodes removed, the adjusted hazard ratio (HR) for risk of death from breast cancer was 0.579 (95% confidence interval, 0.492–0.687, $P < 0.001$), independent of patient age, marital status, histologic grade, tumor size, and adjuvant therapy. Our study suggests that the number of tumor-free lymph nodes removed is an independent predictor in cases of lymph node–negative breast cancer.

Key words Number, tumor-free, axillary lymph nodes, prognostic parameter, lymph node–negative, breast cancer

With the increasing popularity of sentinel lymph node biopsy and the trend toward less aggressive axillary resections, some studies have begun to focus on the relationship between the number of tumor-free lymph nodes removed and survival of patients diagnosed with lymph node–negative breast cancer[1-4]. Camp et al.[1] first reported that, among 290 women with lymph node–negative invasive ductal breast cancer who underwent surgical resection with axillary lymph node dissection, survival was poorer for those with 20 or more nodes removed than for those with fewer than 20 nodes removed. On the contrary, Sosa et al.[2] demonstrated better survival among those with lymph node–negative invasive breast cancer who had 10 or more (up to 33) nodes removed versus fewer than 10 removed.

Moorman et al.[3] and Polednak[4] reported there was no relationship between the number of tumor-free lymph nodes removed and risk of dying from breast cancer. However, none of the above studies considered, as a possible confounding factor, adjuvant therapy after surgical resection and whether there was an association between the number of tumor-free axillary nodes removed and the outcomes for patients with lymph node–negative breast cancer. Therefore, we conducted a systematic, retrospective evaluation to examine the association between the number of tumor-free axillary lymph nodes removed and the outcomes for patients with pathologically negative nodes in a cohort of 603 patients with lymph node–negative breast cancer.

Patients and Methods

Study population

The cohort for this study consisted of 603 patients who underwent breast resection at Sun Yat-sen University Cancer Center for breast cancer between January 3, 1990 and January 6, 2005. The age at diagnosis ranged from 19 to 82 years (median, 56 years). All patients

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had axillary lymph node dissections without evidence of lymph node metastasis and all primary tumors were confined to the breast ($\leqslant 5.0$ cm). Tumor size and lymph node number were obtained from the original macroscopic and microscopic descriptions of specimens. Eighty-eight percent of the patients underwent modified radical mastectomies, and the remaining 12% underwent partial breast resections. A total of 27 surgeons performed the operations, and 18 pathologists were involved in pathologic diagnosis. The patients were stratified into two groups based on the number of tumor-free lymph nodes removed: Group A, 10 or fewer lymph nodes, and Group B, more than 10 lymph nodes. The median number of lymph nodes removed was 10. The characteristics of the patients are summarized in **Table 1**.

Follow-up

Follow-up information obtained from Sun Yat-sen University Cancer Center for each patient began at the date of surgery and ended with either the date of death or the study termination date (February 1, 2014). Patients were followed for 1–283 months, with a median follow-up time of 126 months. Surviving patients were followed for a minimum of 109 months. Death information was directly collected by the Cancer Center through active physician follow-up or direct communications with next of kin. All patients that died of causes other than breast cancer were excluded.

Statistical analysis

The association of various disease parameters and survival was analyzed using SPSS 17.0 software. Demographic data by the number of lymph nodes removed were analyzed by chi-square test. Survival analysis was performed using the Kaplan-Meier method. Cox proportional hazards regression was used to examine the independent association between the number of tumor-free lymph nodes removed and the risk of death from breast cancer. The risk of death from other (underlying) causes was also examined. Models included age (<40, 41–50, 51–60, 61–70, and 71 or more years), marital status (not married, married, or unknown), tumor size, grade, and adjuvant therapy. Tumor size was recoded as 1 cm or less (AJCC stage T1a and b), 1.1 to 2.0 cm (stage T1c), and 2.1 to 5.0 cm (stage T2). Tumor grade was classified as 1 (well differentiated), 2 (moderately differentiated), 3 (poorly differentiated), or 4 (anaplastic or undifferentiated)[5]. A P value of less than 0.05 was considered significant.

Results

In all cases, the proportion of patients with 10 or fewer tumor-

Table 1. Demographic data of patients with breast cancer stratified by the number of lymph nodes removed

Characteristic	Number of lymph nodes removed		P value (chi-square test)
	0–10	11 or more	
Age (years)			0.916
< 40	41(11.2%)	32(13.5%)	
41–50	78(21.3%)	50(21.1%)	
51–60	81(22.1%)	54(22.8%)	
61–70	101(27.6%)	60(25.3%)	
71+	65(17.8%)	41(17.3%)	
Marital status			0.659
Not married	84(23.0%)	52(21.9%)	
Married	274(74.9%)	177(74.7%)	
Unknown	8(2.2%)	8(3.4%)	
Tumor size in diameter			0.861
$\leqslant 1$ cm	123(33.6%)	76(32.1%)	
1.1–2.0 cm	139(38.0%)	89(37.6%)	
2.1–5.0 cm	104(28.4%)	72(30.4%)	
Tumor grade			0.554
1, 2	171(46.7%)	102(43.0%)	
3, 4	103(28.1%)	76(32.1%)	
Unknown	92(25.1%)	59(24.9%)	
Combined treatment			0.672
No systemic treatment	241(65.8%)	160(67.5%)	
Systemic treatment	125(34.2%)	77(32.5%)	
Total	366	237	

free lymph nodes removed was 60.7%, and the proportion with more than 10 tumor-free lymph nodes removed was 39.3%. The 5- and 10-year survival rates were higher for patients in Group A, who had 10 or fewer tumor-free lymph nodes removed, than for patients in Group B, who had more than 10 tumor-free lymph nodes removed (88.0% and 66.4% vs. 69.2% and 51.5%, respectively, $P < 0.001$; **Figure 1**).

In the multivariate Cox proportional hazards models with all patients, the adjusted hazard ratios (HRs) for risk of death from breast cancer were higher for patients with larger tumors ($P < 0.001$), patients with tumors of higher grade ($P < 0.01$), and patients who did not undergo adjuvant therapy ($P < 0.001$). It was also elevated for patients who were younger at diagnosis but was lower for married patients versus unmarried patients (**Table 2**). Compared with patients with primary tumor 1 cm or less in diameter, patients with primary tumor 1.1 to 2.0 cm in diameter and patients with primary tumor 2.1 to 5.0 cm in diameter had higher adjusted HRs for risk of death from breast carcinoma of 1.539 [95% confidence interval (CI), 1.268–1.901; $P < 0.001$] and 2.351 (95% CI, 1.796–2.889; $P < 0.001$), respectively. The adjusted HRs for risk of death from breast cancer were elevated for high or unknown tumor grade versus low tumor grade (adjusted HR = 1.288 and $P = 0.006$ for grades 3 and 4; adjusted HR = 1.795 and $P < 0.001$ for unknown grade). Compared with patients who did not undergo adjuvant therapy, patients undergoing adjuvant therapy had a lower adjusted HR for risk of death from breast cancer (adjusted HR, 0.352; 95% CI, 0.296–0.433; $P < 0.001$). The adjusted HR for patients with 10 or fewer nodes removed was significantly reduced compared with that for patients

with more than 10 nodes removed (adjusted HR, 0.579; 95% CI, 0.492–0.687; $P < 0.001$).

Discussion

In this study, we found that patients who had more than 10 tumor-free lymph nodes removed had a higher risk of death from breast cancer compared with patients who had 10 or fewer tumor-free lymph nodes removed. We chose 10 as a critical value because the median number of lymph nodes removed in this study was 10, which was similar to the value in a previous study[2]. Hence, simple pursuit of a higher number of tumor-free lymph nodes removed may be of little use for improving survival rate. Our finding of an association between the number of tumor-free lymph nodes removed and the risk of death from causes other than breast cancer suggests possible confounding with comorbidity. In other words, surgeons may not want to perform axillary dissection, or may perform less extensive dissection, on patients with comorbid conditions.

In contrast to previous reports[1-4], this study also included analysis of adjuvant therapy, which was useful for lymph node–negative patients, as a possible confounding factor; a previous report suggested adjuvant therapy had prognostic significance in patients with lymph node–negative breast cancer[6]. Thus, although Camp et al.[1] reported results similar to ours, they did not take into account of adjuvant therapy as a possible confounding factor. Our results were also in contrast to those from other studies[2-4]. Sosa et al.[2] studied 464 patients with lymph node–negative invasive breast cancer that
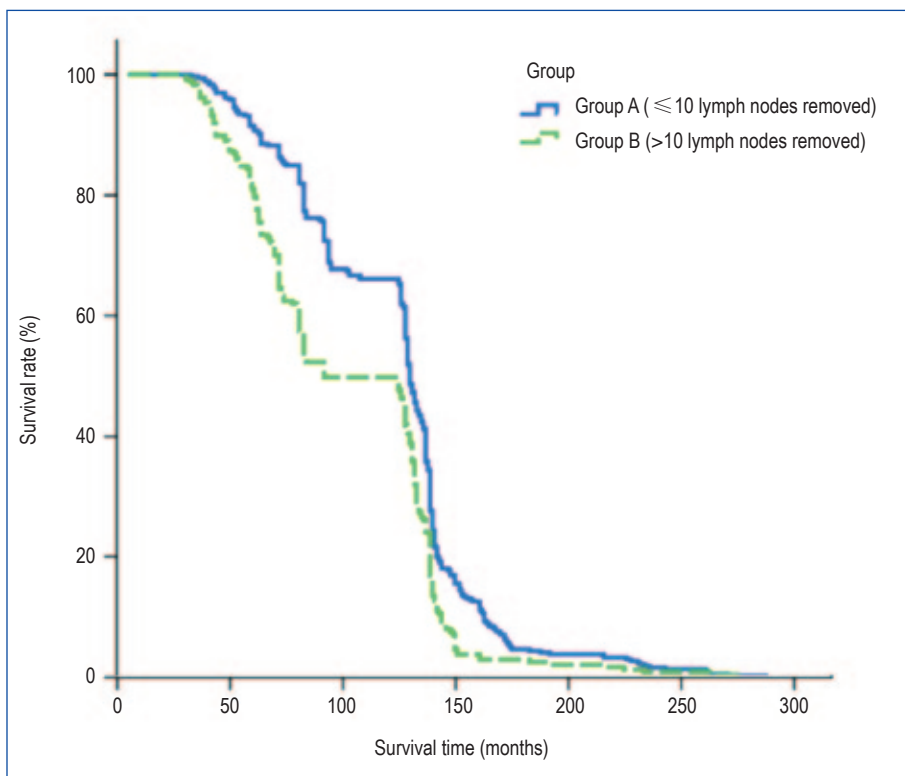

Figure 1. **Survival curves of Groups A (⩽ 10 lymph nodes removed) and B (>10 lymph nodes removed). Kaplan-Meier analysis indicated differences in survival curves between Group A and Group B ($P < 0.001$).**

Table 2. Cox proportional hazards models for risk of death from breast cancer

Covariate	No. of cases	Adjusted hazard ratio	95% confidence interval	P value
Age at diagnosis (years)				
≤ 40	73	1.000	Reference	–
41–50	128	0.865	0.759–0.958	0.023
51–60	135	0.879	0.781–0.993	0.036
61–70	161	1.004	0.749–1.352	0.978
71+	106	0.765	0.561–1.067	0.126
Marital status				
Not married	136	1.000	Reference	–
Married	451	0.874	0.786–0.994	0.035
Unknown	16	0.976	0.568–1.682	0.947
Tumor size				
≤ 1 cm	199	1.000	Reference	
1.1–2.0 cm	228	1.539	1.268–1.901	< 0.001
2.1–5.0 cm	176	2.351	1.796–2.889	< 0.001
Tumor grade				
1, 2	273	1.000	Reference	–
3, 4	179	1.288	1.092–1.587	0.006
Unknown	151	1.795	1.432–2.149	< 0.001
Adjuvant treatment				
No systemic treatment	402	1.000	Reference	–
Systemic Treatment	201	0.352	0.296–0.433	< 0.001
Lymph nodes removed				
≥ 11	237	1.000	Reference	–
0–10	366	0.579	0.492–0.687	< 0.001

was 2 cm or smaller in diameter and found better survival among those with 10 or more (up to 33) lymph nodes removed compared with those with fewer than 10 lymph nodes removed. However, their analysis did not include tumors larger than 2 cm in diameter, and the number of deaths was too small for separate analysis of mortality from breast cancer versus other causes. Moreover, the study did not demonstrate compelling prognostic significance. Similarly, studies by Moorman et al.[3] and Polednak[4] are limited by misclassifications (as indicated by reabstracting and recoding audits of stage and disease extent), the number of lymph nodes removed, and tumor size[7]. Other factors associated with the risk of death from breast cancer including age at diagnosis, marital status, tumor size, tumor grade, and adjuvant treatment were consistent with those reported in the literature[1,4,8–10].

The observation that women with more tumor-free lymph nodes removed had a higher risk of death from metastatic breast cancer may be explained by the lack of host immune responses or defense by lymph nodes[1]. Under this hypothesis, removal of more functional lymph nodes lowers defense against tumor metastasis. Other studies have focused on the prognostic benefit of host immune responses to tumor—in particular, peritumoral lymphocytic infiltrates and alterations in the architecture of tumor-draining lymph nodes such as sinus histiocytosis[11-13]. Recent studies have begun to define the cytokines underlying lymph node genesis and hyperplasia[14-17]. Hyperplasia after lymph node genesis can occur as a downstream

reaction to inflammation and/or tumor[18]. In another study, 25% of the breast carcinomas examined expressed mRNA for vascular endothelial growth factor-C (VEGF-C), which specifically induces lymphangiogenesis[19,20]. However, further exploration is needed for the role of lymphangiogenic and lymph node development factors, especially in the context of tumor size and grade, as these factors may play a role in tumor metastasis for lymph node-negative breast cancer.

Our study had limitations. A large proportion of patients underwent resection for breast cancer before 1998, when advances in adjuvant therapy were slim in China. This may explain why many patients did not undergo adjuvant therapy. Notably, whether adjuvant therapy should be used after dissection in patients with lymph node–negative breast cancer remains to be determined. Even if removal of more nodes did not, in itself, improve survival[21], which is a controversial issue[2], adjuvant therapy may be withheld from some node-negative patients[22], including a subgroup misclassified as node-negative. Weir et al.[6] demonstrated the recovery of a small number of negative lymph nodes at axillary dissection likely understages patients and leads to undertreatment, resulting in an increased regional relapse rate and poorer survival. The implication of a small number of nodes removed is that it reduces the prognostic value of the negative nodal status. For a variety of reasons, positive nodes have likely been missed in some of these patients, resulting in more regional relapses and poorer survival. This effect seemed to be largely overcome by

the addition of systemic therapy.

The temporal trend was toward less use of axillary dissection in the present study. Thus, increases would occur in both the proportion of lymph node-positive cases with extensive nodal involvement (easily detected clinically or by removal of only a few nodes) and the proportion of false-negatives among lymph node-negative cases. The 5-year and 10-year survival rates of lymph node-negative patients would ostensibly decrease over time, but overall survival of all breast cancer patients would not decline unless either removal of nodes had a direct therapeutic effect or changes occurred in the use of adjuvant therapies that improve survival[4]. Another trend may be toward the use of a combination of pathologic and biologic tumor characteristics

as predictors of axillary node status, at least for small tumors and especially for cases in which adjuvant therapy decisions do not rest fully on confirmation of nodal status[23-25].

Acknowledgment

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