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Lymph node status in inflammatory breast cancer

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Abstract

Positive lymph node status in breast cancer is known to be an adverse prognostic factor, but the effect of lymph node (LN) status in inflammatory breast cancer (IBC) has not been evaluated. This study was designed to investigate the association between lymph node status and overall survival (OS) in individuals with IBC. Using the Surveillance, Epidemiology, and End Results (SEER) 18 registry, we collected data on 761 patients diagnosed with non-metastatic IBC from 2004 to 2008. Survival analysis was performed using the Kaplan–Meier method. Cox proportional hazard regression was performed to evaluate univariate and multivariate associations between estrogen and progesterone receptor (ER/PR) status, treatment, and OS. Positive nodal status was associated with a significant decrease in OS ($p < 0.001$). Five-year survival for LN-positive and LN-negative patients was 49 and 66 %, respectively. In node-positive patients, ER or PR positivity was associated with improved OS, ($p = 0.025$, $p = 0.007$). In node-positive patients, the combination of surgery and radiation therapy improved OS when compared with surgery alone ($p = 0.002$). Nearly 80 % of the patients in this study had nodal metastasis. Positive nodal status was found to be an adverse prognostic factor. ER/PR positivity and treatment with surgery and radiation in node-positive patients was found to improve outcomes. Further studies are required to characterize the biology of IBC and guide the optimal treatment of this disease.

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Keywords

Inflammatory breast cancer; IBC; SEER; Lymph node; Estrogen receptor; Progesterone receptor; Overall survival

Background

Inflammatory breast cancer (IBC) is a rare, aggressive disease conferring a 43 % higher risk of mortality versus locally advanced (stage IIIB/C) non-IBC [1]. The diagnosis of IBC includes the following: the rapid onset of breast erythema and edema; peau d'orange occupying at least one-third of the breast (with or without an underlying mass); duration of symptoms of no more than 6 months; and biopsy-proven pathologic confirmation of breast cancer [2]. In black versus white women, IBC may have a higher incidence, present at a younger age, and have a higher incidence of nodal involvement [3]. Distant metastasis at presentation is common (about 36 % of patients) [4], and HER2/Neu positivity and ER/PR negativity are more common in IBC than non-IBC [3–5].

Studies of the epidemiology of IBC have been challenging due to the rarity of the disease and the prior lack of consistent case definitions [6]. IBC comprises 0.5–2.5 % of invasive breast cancers diagnosed in the United States, and there has been evidence that the diagnosis of IBC is increasing [3]. Chang et al. showed that the incidence of IBC doubled from 1975–1977 to 1990–1992 and that survival for IBC was significantly worse than for non-IBC patients [7]. However, a recent study querying the SEER database from 1992 to 2009 found the incidence of IBC to be essentially stable during this time period [8]. Previous data have shown that despite diagnostic and treatment advances [9], the prognosis of IBC has not changed over the last 30 years [10]. However, a recent large, population-based study showed a significant improvement in survival for non-metastatic IBC over time, suggesting a positive impact of treatment advances [11].

Management of IBC utilizes a multimodality approach. The National Comprehensive Cancer Network recommends neoadjuvant chemotherapy, modified radical mastectomy (MRM), comprehensive external beam radiation therapy, and anti-estrogen and/or anti-HER2/Neu therapy for those whose cancers are estrogen receptor or HER2/Neu-positive [6]. Anthracycline- and taxane-based therapies have shown the highest rates of pathological complete response to treatment (pCR) [6, 12] and are considered the mainstays of induction chemotherapy.

Breast cancers with positive lymph node (LN) status are associated with poorer outcomes than those with negative nodes. Although various factors have been found to influence survival [8], the effect of LN status on outcomes in IBC has not been specifically evaluated in the non-metastatic population. This study was designed to investigate the importance of LN status on overall survival (OS) in IBC to determine if LN status has prognostic significance. The secondary goal was to evaluate the effect of treatment modality (surgery alone, surgery, and radiation therapy) and ER/PR status on OS.

Materials and methods

Data source and inclusion criteria

The Surveillance, Epidemiology, and End Results (SEER) 18 database is a prospectively maintained population-based registry that includes 27.8 % of cancer patients treated annually in the United States [13]. The SEER*Stat program (available at <http://www.seer.cancer.gov>) version 8.1.2 was used to identify cases. Adult patients diagnosed with IBC between 2004 and 2008 were compiled within the SEER*Stat program using the International Classification of Diseases for Oncology (ICD-O-3) morphology code 8530. This represents a stringent definition of IBC that likely underestimates the true population-level incidence and avoids misclassifying extensive non-inflammatory locally advanced breast cancer (LABC) as IBC [3]. Only patients whose pathologic nodal status was known were included. All patients with distant metastatic disease at time of diagnosis were excluded. Patients who did not receive any surgery as part of their local therapy were also excluded to minimize the likelihood of inadvertently including patients with metastatic disease at or shortly after diagnosis. Patients were also excluded if the local treatment was unknown or if they received surgical treatment other than MRM. This study was approved by the University of Southern California institutional review board.

Study variables

The case listing function of the SEER*Stat software was used to extract raw data. Using this function, data for IBC were stratified by age, race, origin (Hispanic versus non-Hispanic), survival time (months), vital status, tumor size, regional node status (positive versus negative), and ER/PR status. ER/PR status was defined as positive, negative, borderline (undetermined), none (not performed), or unknown. HER2/Neu status was not available for most of the patients in our study and was not reported.

Patients were recorded as LN-positive if they were found to be node-positive at any time (either before neoadjuvant chemotherapy based on biopsy or after surgery based on definitive surgical pathology). SEER did not track which patients received their node-positive designation prior to systemic therapy, or how that designation was made (for example, by axillary ultrasound with needle biopsy). Patients designated as LN-negative in SEER were node-negative at the time of MRM and without positive nodes prior to neoadjuvant therapy.

Although SEER did not collect information on systemic therapy, information on receipt of radiation and surgery was available. Survival was compared between groups that received surgery alone and groups that received surgery with radiation. The survival analysis was stratified into LN-negative and LN-positive groups who received surgery with or without radiation.

Statistical methods

The association between LN status, ER/PR status, treatment, and demographic characteristics was tested by the Fisher's exact test. For each subject, survival times were computed from diagnosis to death from any cause OS or death specific to breast cancer

diagnosis. Living subjects were censored at their last follow-up; for breast cancer-specific survival, subjects dying of a non-breast cancer cause were censored at the date of death. The Kaplan–Meier life table approach was used to estimate and plot cumulative survival curves for the two survival outcomes, OS and breast cancer-specific survival. Unadjusted survival comparisons by LN status used the log rank test. Cox proportional hazards regression was used to assess the association of LN status, treatment, ER/PR status, and demographic characteristics with OS and breast cancer-specific survival. For each survival outcome, multivariate Cox proportional hazard regression was performed to evaluate associations between LN status, ER/PR status, treatment and OS while controlling for other variables. Independent variables for multivariate modeling included those variables that were significant by univariate analysis. Indicator variables for SEER registry and region were also modeled as possible confounders. As the addition of these variables did not substantially alter the estimated hazard rate ratios for other independent variables, registry and region were not included in the final multivariate models. Univariate and multivariate associations were also stratified by node status. Due to small numbers of node-negative subjects and low statistical power, interaction analyses were not performed. Therefore, stratified analyses were considered largely descriptive. All analyses were done using STATA Version 13 (College, Station, TX), reporting 2-sided p values, with level of significance for $p < 0.05$.

Results

Patient characteristics

A total of 761 patients with IBC met our inclusion criteria. (Table 1). The mean age at diagnosis was 57.1 years. The majority of the patients were node-positive [607 of 761 (79.8 %)], with roughly equal numbers of ER-positive [343 of 761 (45.1 %)] and ER-negative [357 of 761 (46.9 %)] tumors. However, more patients had PR-negative [433 of 760 (56.9 %)] than PR-positive [257 of 760 (33.8 %)] tumors at diagnosis. The majority of the patients [456 of 761 (59.9 %)] received a combination of surgery plus radiation as treatment for IBC.

Stratified by nodal status, there was no significant difference in mean age at diagnosis, ethnic distribution, or treatment modality between node-positive and node-negative cases (Table 2). Those with LN-positive disease were more likely to be ER-positive and PR-negative [$p = 0.008$, $p = 0.049$, respectively, (Table 2)].

Effect of node status on OS and BCSS

On Kaplan–Meier analysis of the entire patient cohort, five-year OS was 52 % and five-year breast cancer-specific survival (BCSS) was 59 %. Five-year OS for patients with LN-positive and LN-negative disease was 49 and 66 %, respectively, ($p < 0.0001$, Fig. 1a). Five-year BCSS was 56 % for patients with LN-positive disease and 71 % for patients with LN-negative disease. ($p < 0.0001$, Fig. 1b).

Positive LN status was associated with a significant decrease in both OS and BCSS on univariate analysis (OS: $p < 0.001$; BCSS: $p < 0.001$). On multivariate analysis positive LN status was associated with significantly worse OS (HR 2.13, $p < 0.001$, 95 % CI 1.55–2.94) (Table 3) and BCSS (HR 2.20, $p < 0.001$, 95 % CI 1.55–3.14) (Table 4).

Effect of node status and treatment on OS and BCSS

The median survival time for all patients treated with surgery and radiation was 70 months; for node-positive patients, median survival with surgery and radiation was 65 months. For all patients, treatment with surgery and radiation was associated with improved OS compared to surgery alone on multivariable modeling [HR 0.72, $p = 0.004$, CI 95 % (0.58–0.90) (Table 3)].

Among LN-positive patients, Kaplan–Meier analysis demonstrated that treatment with both surgery and radiation was associated with improved OS [$p = 0.0006$ (Fig. 2a)] and BCSS [$p = 0.019$ (Fig. 2b)], compared to surgery alone. However, there was no such association in LN-negative cases for either OS (Fig. 2c) or BCSS (Fig. 2d).

On multivariable modeling of LN-positive cases, treatment with surgery and radiation was associated with improved OS when compared with surgery alone [HR 0.70, $p = 0.002$, 95 % CI (0.55–0.88) (Table 3)]. This association was also seen in breast cancer-specific survival [HR 0.73, $p = 0.016$, 95 % CI (0.56–0.94) (Table 4)].

On multivariable modeling of LN-negative cases, there was no statistically significant OS difference between the surgery versus surgery plus radiation groups [HR 0.81, $p = 0.54$, 95 % CI (0.40–1.62)] (Table 3). Similarly, there was no BCSS advantage to the combination of surgery and radiation in LN-negative cases [HR 0.52, $p = 0.10$, 95 % CI (0.24–1.14) (Table 4)].

Effects of ER and PR status on OS and BCSS

For the entire cohort, patients who were ER- or PR-positive had increased OS when compared with ER- or PR-negative patients [HR 0.66, $p = 0.005$, 95 % CI (0.49–0.88); HR 0.67, $p = 0.014$, 95 % CI (0.49–0.92), respectively, (Table 3)]. Stratified by nodal status, ER/PR positivity was associated with improved OS in LN-positive cases [HR 0.70, $p = 0.025$, 95 % CI (0.52–0.96); HR 0.63, $p = 0.007$, 95 % CI (0.45–0.88), respectively, (Table 3)]. Among LN-negative cases, ER-positivity was strongly associated with lower breast cancer death [HR 0.32, $p = 0.04$, 95 % CI (0.11–0.95)] (Table 4), and marginally associated with a lower hazard for death from any cause [HR 0.38, $p = 0.51$, 95 % CI (0.15–1.00)] (Table 3).

Discussion

Systematic analysis of IBC is challenging, due to the rarity of the disease. This study evaluated LN and ER/PR status as potential prognostic indicators and examined the effect of locoregional treatment regimens on patient survival in LN-positive and LN-negative disease.

The findings of this study suggested that LN-positivity and ER/PR negativity in IBC were associated with a worse prognosis and that treatment with surgery and radiation may improve outcomes over those achieved with surgery alone. Of note, in the SEER database, LN status refers to pathologic nodal status at either the time of initial diagnosis or after receipt of neoadjuvant systemic therapy and surgery. Thus, one limitation of our study is that it is unknown how many patients converted from positive to negative LN status after

treatment. Previous studies have shown that clinically positive axillary LNs have been converted to pathologically negative in 12–38 % of patients with LABC [14–17].

We did not find a statistically significant survival benefit for treatment with surgery and radiation versus surgery alone in patients with LN-negative tumors. However, the sample size of node-negative patients was small and the confidence interval included 1.0 for the multivariate analysis assessing OS in node-negative patients treated with both surgery and radiation. Furthermore, meta-analysis demonstrates that postmastectomy radiotherapy confers a survival benefit only in node-positive patients; it is possible that even in inflammatory breast cancers, a pathologic complete response in the LNs disrupts the link between local–regional control and survival, rendering PMRT useful only for the local control benefit. [18, 19] Nonetheless, radiation almost certainly remains important in this patient population to reduce local recurrence rates, an endpoint that cannot be assessed in a study of this kind since SEER does not record local outcomes.

In the cohort evaluated in this study, LN-positivity at any time negatively impacted OS. Li et al. showed a similar relationship between positive LN status and decreased OS [20]. This study recapitulated that LN status is a predictor of distant metastasis for IBC [18]. Our study used a large population-based registry to confirm that both LN status and ER/PR status were independent prognostic factors in IBC. Supporting these findings is a study by Hance et al., which showed that patients with ER-negative IBC had poorer survival than those with ER-positive disease ($p < 0.001$) [3].

Standard treatment for IBC involves a multimodal approach involving neoadjuvant chemotherapy, MRM, and adjuvant radiation therapy. Adjuvant endocrine therapy is recommended for all ER-positive IBC [21, 22]. Despite multimodality treatment for IBC, outcomes remain poor with 5-year OS rates of 40–51 % [23]. Our study showed a five-year OS rate of 52 % and five-year breast cancer-specific survival of 59 %. Tailoring treatment regimens based upon the pathologic and prognostic factors of each patient's disease may be the most effective way to improve outcomes. Our study showed that for the subset of patients with LN-positive disease, the combination of surgery and radiation was associated with improved OS. In support of our findings, Bristol et al. found that women treated with chemotherapy, surgery, and radiation had better OS than those treated with single or dual-modality therapy (51 vs. 24 %, respectively) [24].

There are limitations to the present analysis. Information regarding systemic therapy was not available. However, chemotherapy and HER2/Neu targeted therapy, if indicated, is an important part of treatment and is recommended for all patients with IBC [25]. Despite the absence of information in the SEER database, we thus assume that chemotherapy was given equally to both the LN-positive and LN-negative patients in our population. Another limitation is the lack of data in SEER regarding locoregional recurrence. In addition, HER2/Neu status was not recorded in the database during this timeframe. The HER2/Neu gene is expressed in roughly 40 % of IBC cases [5], and the use of trastuzumab has significantly improved outcomes in IBC [26]. Furthermore, we reported OS at 5 years, and there may be some deaths from disease after 5 years in the ER-positive group, whereas there will likely be few deaths from disease after 5 years in the ER-negative group. Finally, as the

pCR rate was not known in our study population, the finding that positive LN status negatively affects survival may at least in part be due to a lack of LN response to neoadjuvant chemotherapy.

Conclusion

Our findings improve the understanding of the characteristics of IBC, and highlight the need for further study of the prognostic significance and treatment implications of LN and ER/PR status in IBC. Nearly 80 % of IBC patients had nodal metastasis, reflecting the aggressive biology of the disease. Patients with positive LNs as well as those with ER/PR-negative tumors had worse OS when compared with LN-negative and ER/PR-positive patients. The use of radiation and surgery in patients with LN-positive tumors was associated with improved OS, but the effect of adjuvant radiation in LN-negative patients was less definitive. Although our study included 761 IBC patients, LN-negative IBC is uncommon, and perhaps with longer follow-up a more significant benefit for radiation may be seen.

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Fig. 1. Demonstrates the association between lymph node status and **a** OS and **b** breast cancer-specific survival using a Kaplan–Meier curve, highlighting the reduction in overall survival in patients with nodal metastasis

Fig. 2.

Demonstrates the association between treatment modality (surgery alone versus surgery and radiation) and OS and BCSS using a Kaplan–Meier curve in patients with LN-positive (**a, b**) and LN-negative (**c, d**) patients

Table 1Patient demographics and clinicopathologic/treatment characteristics ($n = 761$)

Characteristic	Patients n (%)
<i>Age</i>	
20–29 years	8 (1.05)
30–39 years	62 (8.15)
40–49 years	157 (20.63)
50–59 years	232 (30.49)
60–69 years	160 (21.02)
70–79 years	91 (11.96)
80 years	51 (6.70)
<i>Ethnicity</i>	
American Indian	6 (0.79)
Asian	34 (4.47)
Black	97 (12.75)
Caucasian	512 (67.28)
Hispanic	109 (14.32)
Unknown	3 (0.39)
<i>Nodes</i>	
Positive	607 (79.76)
Negative	154 (20.24)
<i>ER</i>	
Positive	343 (45.07)
Negative	357 (46.91)
Borderline	4 (0.53)
Unknown	57 (7.49)
None (not tested)	0 (0)
<i>PR</i> *	
Positive	257 (33.77)
Negative	433 (56.90)
Borderline	7 (0.92)
Unknown	63 (8.28)
None (not tested)	0 (0)
<i>Treatment with surgery or radiation</i>	
Surgery (S)	305 (40.08)
Surgery and radiation (SR)	456 (59.92)

*
 $n = 760$

Table 2Analysis of node status ($n = 761$)

Characteristics	N (%)		p value
	Node- ($n = 154$)	Node+ ($n = 607$)	
Age			
20–29 years	1 (0.65)	7 (1.15)	
30–39 years	10 (6.49)	52 (8.57)	
40–49 years	34 (22.08)	123 (20.26)	
50–59 years	53 (34.42)	179 (29.49)	0.21
60–69 years	38 (24.68)	122 (20.10)	
70–79 years	12 (7.79)	79 (13.01)	
80 years	6 (3.90)	45 (7.41)	
Ethnicity			
American Indian	1 (0.65)	5 (0.82)	
Asian	8 (5.19)	26 (4.28)	
Black	15 (9.74)	82 (13.51)	0.12
Caucasian	99 (64.29)	413 (68.04)	
Hispanic	29 (18.83)	80 (13.18)	
Unknown	2 (1.30)	1 (0.16)	
ER [*]			
Positive	53 (38.69)	290 (51.51)	
Negative	84 (61.31)	273 (48.49)	0.008
PR [*]			
Positive	41 (29.93)	216 (39.06)	
Negative	96 (70.07)	337 (60.94)	0.049
Treatment with surgery or radiation			
Surgery (S)	56 (36.36)	249 (41.02)	
Surgery and radiation (SR)	98 (63.64)	358 (58.98)	0.31

Node-positive/negative groups compared by 2-sided Fisher's exact test

^{*} Excludes subjects with borderline or unknown receptor status

Table 3Overall survival and tumor characteristics/treatment: multivariate models ($n = 761$)

	All ($n = 761$)		Node- ($n = 154$)		Node+ ($n = 607$)	
	Adjusted HR (95 % CI)	<i>p</i> value	Adjusted HR (95 % CI)	<i>p</i> value	Adjusted HR (95 % CI)	<i>p</i> value
Positive nodes	2.13 (1.55, 2.94)	<0.001				
Ethnicity						
White	1.0	<0.001	1.0	0.048	1.0	0.003
Black	1.83 (1.37, 2.44)		3.34 (1.42, 7.86)		1.75 (1.28, 2.38)	
Hispanic	1.14 (0.82, 1.59)		1.63 (0.73, 3.65)		1.07 (0.74, 1.55)	
Other	0.90 (0.55, 1.46)		1.35 (0.38, 4.72)		0.84 (0.49, 1.44)	
ER status						
Positive	0.66 (0.49, 0.88)	0.005	0.38 (0.15, 1.00)	0.051	0.70 (0.52, 0.96)	0.025
PR status						
Positive	0.67 (0.49, 0.92)	0.014	1.29 (0.48, 3.51)	0.62	0.63 (0.45, 0.88)	0.007
Treatment						
Surgery and radiation	0.72 (0.58, 0.90)	0.004	0.81 (0.40, 1.62)	0.54	0.70 (0.55, 0.88)	0.002

341 deaths (44 node-, 297 node+)

Models also adjusted for age in categories (20–39, 40–49, 50–59, 60–69, and 70+)

Table 4Breast cancer survival and tumor characteristics/treatment: multivariate models ($n = 761$)

	All ($n = 761$)			Node- ($n = 154$)			Node+ ($n = 607$)		
	Adjusted HR	(95 % CI)	<i>p</i> value	Adjusted HR	(95 % CI)	<i>p</i> value	Adjusted HR	(95 % CI)	<i>p</i> value
Positive nodes	2.20	(1.55, 3.14)	<0.001						
Ethnicity									
White	1.0		<0.001	1.0		0.008	1.0		0.008
Black	1.91	(1.40, 2.62)		4.81	(1.94, 11.91)		1.76	(1.25, 2.47)	
Hispanic	1.15	(0.80, 1.66)		1.39	(0.52, 3.70)		1.13	(0.76, 1.68)	
Other	0.93	(0.54, 1.58)		1.92	(0.53, 6.91)		0.83	(0.45, 1.50)	
ER status									
Positive	0.63	(0.46, 0.86)	0.004	0.32	(0.11, 0.95)	0.04	0.66	(0.47, 0.93)	0.016
PR status									
Positive	0.57	(0.40, 0.82)	0.002	1.39	(0.45, 4.29)	0.57	0.53	(0.37, 0.78)	0.001
Treatment									
Surgery and radiation	0.73	(0.57, 0.92)	0.009	0.52	(0.24, 1.14)	0.10	0.73	(0.56, 0.94)	0.016

278 deaths (36 node-, 242 node+)

Models also adjusted for age in categories (20–39, 40–49, 50–59, 60–69, 70+)