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Breast Cancer

Triple-Negative Subtype Predicts Poor Overall Survival and High Locoregional Relapse in Inflammatory Breast Cancer

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ABSTRACT

Background. **Numerous studies have demonstrated that expression of estrogen/progesterone receptor (ER/PR) and human epidermal growth factor receptor (HER)-2 is important for predicting overall survival (OS), distant relapse (DR), and locoregional relapse (LRR) in early and advanced breast cancer patients. However, these findings have not been confirmed for inflammatory breast cancer (IBC), which has different biological features than non-IBC.**

Methods. **We retrospectively analyzed the records of 316 women who presented to MD Anderson Cancer Center in 1989–2008 with newly diagnosed IBC without distant metastases. Most patients received neoadjuvant chemotherapy, mastectomy, and postmastectomy radiation. Patients were grouped according to receptor status: ER^+ (ER^+/PR^+ and HER-2−; $n = 105$), $ER^+HER\text{-}2^+$ (ER^+/PR^+ and $HER\text{-}2^+$; $n = 37$), $HER\text{-}2^+$ (ER^-/PR^- and $HER\text{-}2^+$; $n = 83$), or triple-negative (TN) ($ER^-PR^-HER\text{-}2^-$; $n = 91$). Kaplan–Meier and Cox proportional hazards methods were used to assess LRR, DR, and OS rates and their associations with prognostic factors.**

Results. **The median age was 50 years (range, 24–83 years). The median follow-up time and median OS time for all patients were both 33 months. The 5-year actuarial OS rates were 58.7% for the entire cohort, 69.7% for ER^+ patients, 73.5% for $ER^+HER\text{-}2^+$ patients, 54.0% for $HER=2^+$ patients, and 42.7% for TN patients ($p < .0001$); 5-year LRR rates were 20.3%, 8.0%, 12.6%, 22.6%, and 38.6%, respectively, for the four subgroups ($p < .0001$); and 5-year DR rates were 45.5%, 28.8%, 50.1%, 52.1%, and 56.7%, respectively ($p < .001$). OS and LRR rates were worse for TN patients than for any other subgroup ($p < .0001$–$.03$).**

Conclusions. **TN disease is associated with worse OS, DR, and LRR outcomes in IBC patients, indicating the need for developing new locoregional and systemic treatment strategies for patients with this aggressive subtype.** ***The Oncologist*** 2011;16:1675–1683

INTRODUCTION

Breast cancer is increasingly recognized as a heterogeneous disease in which various subsets have distinctly different responses to treatment and outcomes [1]. Gene expression profiling has led to the discovery of four molecular subtypes of breast cancer [2–6]. Technical limitations associated with mi-

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croarray analysis of paraffin-embedded tissue samples led to the use of estrogen or progesterone receptor (ER/PR) status and human epidermal growth factor receptor (HER)-2 expression as surrogates to define four subtypes of breast cancer: ER^+ (ER^+/PR^+ and $HER\text{-}2^-$), $ER^+HER\text{-}2^+$ (ER^+/PR^+ and $HER\text{-}2^+$), $HER\text{-}2^+$ (ER^-/PR^- and $HER\text{-}2^+$), and triple negative (TN) ($ER^-PR^-HER\text{-}2^-$) [7]. The prognostic value of this surrogate subtyping has been confirmed for patients with locally advanced noninflammatory breast cancer [8] and for those with early-stage disease [9, 10]. However, this subtyping approach has not been evaluated in patients with inflammatory breast cancer (IBC). Although IBC is considered one of the most aggressive forms of breast cancer, subcategories of IBC can be distinguished by the same molecular subtypes defined for non-IBC [11, 12]. Information on the influence of ER/PR and HER-2 status and breast cancer subtype on clinical outcome in IBC would aid in management decision making and counseling patients about anticipated outcomes.

Although most studies of patients with non-IBC receiving systemic treatment tend to focus on endpoints such as distant relapse (DR) and overall survival (OS), several reports have demonstrated that ER/PR and HER-2 status can also predict locoregional recurrence (LRR). For example, data from the Danish 82b trial revealed that ER/PR negativity and HER-2 positivity were associated with a higher LRR rate after postmastectomy radiation [8]. Studies from The University of Texas MD Anderson Cancer Center (hereafter, MD Anderson) and Harvard Massachusetts General Hospital of patients with early-stage breast cancer showed that HER-2 positivity and ER/PR negativity were predictive of a higher LRR rate after breast-conserving therapy [9, 13]. However, the potential influence of ER/PR and HER-2 status on locoregional control has not been evaluated in patients with IBC. Including locoregional control as an endpoint is important because it may help identify patients who would benefit from new locoregional treatments such as accelerated hyperfractionation or radiosensitizers.

We retrospectively analyzed the impact of breast cancer subtypes, defined by ER/PR and HER-2 status, on the outcomes of 316 women treated at MD Anderson for newly diagnosed, nonmetastatic IBC. The primary endpoints were the 5-year LRR, DR, and OS rates.

Materials and Methods

Patients

This retrospective chart review was approved by the institutional review board of MD Anderson. Chart review of patients presenting to MD Anderson in January 1974 through December 2008 identified 433 patients with IBC whose ER, PR, and HER-2 status was available and who had no distant metastases at the time of diagnosis (stage IIIB–IIIC). These included two consecutive cohorts of patients, with the first one presenting before April 2005 [14]. All the pathologic specimens from those patients were prospectively reviewed at MD Anderson by pathologists specializing in breast cancer [14]. The second cohort came from an institutional registry of patients diagnosed in May 2005 through December 2008. Patients who had recurrent disease at their first presentation to MD Anderson were excluded, leaving 316 patients diagnosed in June 1989 to December 2008 for the present study. For all patients, the diagnosis of IBC was made by a multidisciplinary team.

Pathology Methods

All cancer diagnoses were confirmed by core biopsy. ER/PR status was obtained by immunohistochemical staining of paraffin-embedded tissues with monoclonal antibodies (6F11 for ER and 1A6 for PR; Novacastra Laboratories Ltd., Newcastle Upon Tyne, U.K.). Nuclear staining of $\geq$10% of invasive cells was considered positive. Before 1993, ER and PR status were determined by a dextran-coated charcoal ligand-binding method. HER-2 status was evaluated by immunohistochemical staining or fluorescence in situ hybridization. HER-2 positivity was defined as 3+ receptor overexpression (strong membranous staining in $\geq$30% of cells) or gene amplification (a gene copy ratio of *HER-2/CEP-17* $>$2.0).

Treatment and Follow-Up

The evolution of treatment for nonmetastatic IBC at MD Anderson over the past four decades has been described elsewhere [15]. Most patients received neoadjuvant chemotherapy, modified radical mastectomy, and postmastectomy radiation to the chest wall and draining lymphatics. Neoadjuvant chemotherapy consisted of 5-fluorouracil, doxorubicin, and cyclophosphamide, with taxanes introduced in 1994. Tamoxifen or aromatase inhibitors were used for patients with hormone receptor–positive disease, and HER-2–directed therapy (trastuzumab or lapatinib) was used since 1999 for $HER\text{-}2^+$ cancer. Regarding radiation, most patients received 51 Gy in 1.5-Gy fractions delivered twice daily to the chest wall and draining lymphatics, followed by a 15-Gy boost, also in 1.5-Gy fractions delivered twice daily, bringing the total dose to 66 Gy. Many patients also received adjuvant chemotherapy.

Patients were followed on a regular basis after completion of treatment (every 6 months for 5 years and then yearly). From 1989 to mid-2006, follow-up studies included physical examination, biopsy, sonography, computed tomography (CT) scan, bone scan, and (after October 2006) positron emission tomography imaging for the diagnosis of LRR. Tests used for suspected distant metastasis (DM) included CT scanning, bone scanning, liver function tests, and alkaline phosphatase level measurements.

Statistical Analysis

The primary endpoints in this study were the LRR, DR, and OS rates. LRR was defined as any recurrence within the ipsilateral chest wall or regional lymphatics including axillary, supraclavicular, and internal mammary nodes. Recurrences in the contralateral breast were considered distant if contralateral nodes were involved; otherwise locoregional was distinguished from distant recurrence based on the clinical history and distribution of disease according to physical examinations and medical photography. Time to recurrence was computed from the date of diagnosis to the date of first local or distant disease recur-

rence. Patients without recurrence were censored at the last follow-up date. Patients who died without experiencing disease recurrence were censored at the date of death, except for the OS endpoint.

χ^2 tests were used to compare the distribution of baseline characteristics among the four subgroups. Time to recurrence or death was estimated by the Kaplan–Meier method [16, 17] and compared between groups with log-rank tests. Univariate and multivariate analyses of time to event were performed using a Cox proportional hazards model. Only variables with a p-value $<.25$ on univariate analysis, except for hormone receptor status and hormone therapy because of their high linear correlation with molecular subtypes, were entered into the multivariate analysis model, and backward sequencing was used [18]. The variables analyzed were age at diagnosis (<45 years versus ≥45 years), menopausal status (premenopausal versus perimenopausal versus postmenopausal), lymphovascular invasion (present or absent), tumor nuclear grade (grade 3 versus grade 1–2), hormone receptor expression (positive or negative), HER-2 expression (positive or negative), percentage of positive nodes (≥20% versus <20%), extracapsular extension (ECE) (present or absent), margin status (close or positive versus negative), pathologic complete response (pCR) (yes versus no), neoadjuvant chemotherapy (yes versus no), taxane (yes versus no), hormone therapy (yes versus no), HER-2–directed therapy as initial treatment (yes versus no), and radiation (yes versus no). An identical method was used for time to OS, LRR, and DR. All statistical tests were two-sided, with p-values $<.05$ considered significant. All calculations were performed using Stata/MP 11.1 statistical software (StataCorp, College Station, TX).

Results

Patient Characteristics

As shown in Table 1, 105 patients (33%) had ER^+ disease, 37 (12%) had $ER^+HER\text{-}2^+$ disease, 83 (26%) had $HER\text{-}2^+$ disease, and 91 (29%) had TN disease. The median age was 50 years (range, 24–83 years). Three quarters of the patients were white and roughly half were premenopausal. The four subgroups did not differ in age, race, or menopausal status. As for tumor-related factors, 54% of the tumors showed lymphovascular invasion (LVI) and 90% of the patients had clinically node-positive disease; these characteristics were well balanced among the four subgroups. Subgroups did differ in nuclear grade, hormone receptor positivity, and HER-2 positivity.

Nearly all patients received neoadjuvant chemotherapy and most (96%) received a taxane. More than 80% of patients with hormone receptor–positive disease received hormone therapy, and those who did not were either unable to complete the therapy or had disease progression before completing definitive treatment. In $HER\text{-}2^+$ patients, 62% received trastuzumab or lapatinib under a clinical trial as part of their initial systemic therapy (46% for $ER^+HER\text{-}2^+$ disease and 67% for $HER\text{-}2^+$ disease). Those who did not receive HER-2–directed therapy did not because the treatment was unavailable at the time their disease was diagnosed. About 87% of patients received radiation therapy with curative intent, and two thirds of these received twice-daily treatment.

The pCR rate to neoadjuvant systemic therapy was 18%, and was highest in the $HER\text{-}2^+$ group (33% overall, 37% for those who received HER-2–directed therapy, and 16% for those who did not). Overall, 7% of patients had close or positive surgical margins, and 24% had ECE. About 43% of the patients had disease in >20% of the removed lymph nodes. The $HER\text{-}2^+$ subgroup was least likely to have positive margins, ECE, or nodal disease, probably because of a favorable response to neoadjuvant treatment.

After a median follow-up time of 38 months for living patients (range, 2–164 months) and 33 months for all patients (range, 2–185 months), 55 patients had had an LRR, 129 had had a DR, and 116 had died. Thirty-eight patients experienced both an LRR and a DR (19 synchronously and seven within a month of one another; eight patients had DM after LRR [interval, 4–14 months] and four patients had DM before LRR [interval, 3–18 months]). Six of those patients had an LRR after a previous DR.

OS

The median OS times were 33 months for the entire cohort (range, 2–185 months), 38 months for the ER^+ subgroup, 40 months for the $ER^+HER\text{-}2^+$ subgroup, 29 months for the $HER\text{-}2^+$ subgroup, and 24 months for the TN subgroup. The 5-year actuarial survival rates (Fig. 1) were as follows: for the entire study cohort, 58.7% (95% confidence interval [CI], 51.8%–64.9%); for the ER^+ subgroup, 69.7% (95% CI, 57.0%–79.3%); for the $ER^+HER\text{-}2^+$ subgroup, 73.5% (95% CI, 53.3%–86.1%); for the $HER\text{-}2^+$ subgroup, 54.0% (95% CI, 39.4%–66.5%); and for the TN subgroup, 42.7% (95% CI, 30.9%–54.1%) ($p < .0001$, log-rank tests). Pairwise comparisons showed that survival was worse for the TN subgroup than for the other three subgroups ($p < .0001$-.03). Survival in the $HER\text{-}2^+$ subgroup was different from that in the ER^+ subgroup ($p = .03$). No difference in survival was observed between the ER^+ and $ER^+HER\text{-}2^+$ subgroups ($p = .961$).

On univariate analysis, using TN as the baseline (Table 2), all three of the other subtypes were associated with a better survival outcome, with unadjusted hazard ratios (HRs) of 0.35 for ER^+ patients ($p < .001$), 0.39 for $ER^+HER\text{-}2^+$ patients ($p = .004$), and 0.62 for $HER\text{-}2^+$ patients ($p = .04$). When the $ER^+HER\text{-}2^+$ subgroup was used the baseline, ER^+ patients did not have a statistically different survival outcome from that of $ER^+HER\text{-}2^+$ patients. Other factors prognostic for a poor OS outcome included having LVI, nuclear grade 3, no hormone receptor expression, no hormone therapy, no pCR, ECE, ≥20% of nodes positive, and no or low-dose radiation.

On multivariate analysis after adjusting for prognostic factors, the TN subgroup was found to have a worse survival outcome than the other three subtypes: adjusted hazard ratios (AHRs) for death were 0.25 for ER^+ patients ($p < .001$); 0.32 for $ER^+HER\text{-}2^+$ patients ($p = .009$), and 0.51 for $HER\text{-}2^+$ patients ($p = .033$). When the non-TN subtypes (ER^+, $ER^+HER\text{-}2^+$, and $HER\text{-}2^+$ combined) were compared with the TN subgroup, patients with the non-TN subtypes had a bet-

Table 1. Patient, tumor, and treatment characteristics

Characteristic	All patients ($n = 316$)	ER^+ ($n = 105$)	$ER^+HER\text{-}2^+$ ($n = 37$)	$HER\text{-}2^+$ ($n = 83$)	TN ($n = 91$)	p-value
Patient factors						
Median age, yrs	50	50	48	51	50	.62
Race, %						.06
African American	10	7	11	13	11	
Hispanic	12	8	16	14	13	
White	76	83	73	70	74	
Other	2	3	0	2	2	
Premenopausal, %	52	53	46	54	49	.62
Tumor factors, %						
Lymphovascular invasion	54	54	57	49	58	.72
Grade 3	75	54	76	86	89	<.001
Clinically node positive	90	90	65	90	89	.68
Hormone receptor positive	45	100	100	0	0	<.001
$HER\text{-}2^+$	62	100	0	0	100	<.001
Treatment factors, %						
Neoadjuvant chemotherapy	99	98	100	100	99	.534
Taxane received	96	97	95	98	95	.385
Hormone therapy	37	75	84	5	3	<.001
Trastuzumab therapy (initial)	24	2	46	67	1	<.001
Trastuzumab therapy (all)	31	2	65	86	2	<.001
pCR	18	10	16	33	14	.001
Surgical margin <2 mm	7	6	8	4	11	.232
Extracapsular extension	24	30	19	14	27	.074
>20% nodes positive	43	50	46	31	44	.097
>10 nodes removed	72	73	70	72	71	.528
Radiation received	87	92	78	87	86	.16
Radiation BID	53	54	38	59	52	.303

Abbreviations: BID, twice a day; HER-2, human epidermal growth factor receptor 2; pCR, pathologic complete response.

ter survival outcome (AHR, 0.38; $p < .001$). In the final model, the percentage of positive lymph nodes (<20% versus ≥20%) after neoadjuvant chemotherapy and radiation dose remained prognostic for survival (Table 3).

LRR

At a median follow-up time of 33 months (range, 2–184 months) for the 316 patients, 55 had had an LRR, and 38 of those patients had also experienced a DR. The median time to LRR was 36 months for the ER^+ subgroup, 35 months for the $ER^+HER\text{-}2^+$ subgroup, 26 months for the $HER\text{-}2^+$ subgroup, and 19 months for the TN subgroup. The 5-year LRR rates (Fig. 2) were 20.3% (95% CI, 15.7%–26.1%) for all patients, 8.0% (95% CI, 3.8%–16.1%) for ER^+ patients, 12.6% (95% CI, 4.9%–30.1%) for $ER^+HER\text{-}2^+$ patients, 22.6% (95% CI, 13.5%–36.5%) for $HER\text{-}2^+$ patients, and 38.6% (95% CI, 27.3%–52.6%) for the TN subgroup ($p < .0001$, log-rank test). Pairwise comparisons showed a higher LRR rate in the TN subgroup than in the other three subgroups ($p < .0001$–.023), but the LRR rate was no different in the ER^+ and $ER^+HER\text{-}2^+$ subgroups ($p = .393$).

On Cox univariate analysis using TN disease as the baseline (Table 2), the ER^+, $ER^+HER\text{-}2^+$, and $HER\text{-}2^+$ subtypes were associated with a lower LRR rate (unadjusted HRs of 0.18 [$p < .001$], 0.30 [$p = .01$], and 0.42 [$p = .02$], respectively). When the $ER^+HER\text{-}2^+$ subgroup was used as the baseline, the LRR rate of ER^+ patients was not statistically different from that of $ER^+HER\text{-}2^+$ patients. Other factors prognostic of a higher LRR rate included premenopausal status, having LVI, nuclear grade 3, no hormone receptor expression or hormone therapy, no taxane or radiation, no pCR, a positive surgical margin, ≥20% of nodes positive, and ECE.

Multivariate analysis after adjusting for prognostic factors also showed the TN subgroup to have the highest LRR rate (AHR, 0.09 for the ER^+ subgroup, 0.20 for the $ER^+HER\text{-}2^+$ subgroup, and 0.39 for the $HER\text{-}2^+$ subgroup). When non-TN

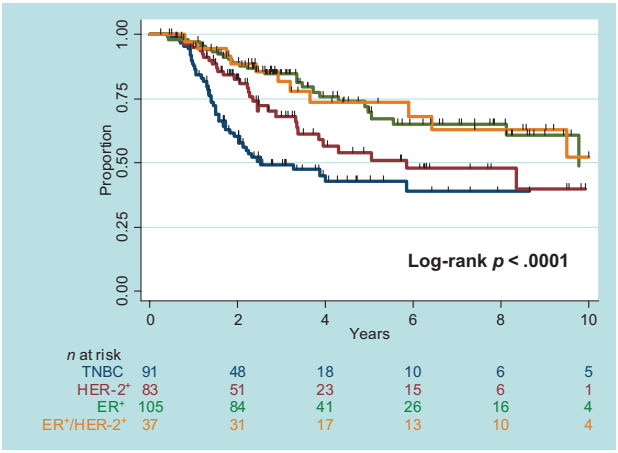

Figure 1. Overall survival according to breast cancer subtype.

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

(ER^+, $ER^+HER\text{-}2^+$, and $HER\text{-}2^+$ combined) patients were compared with the TN subgroup, patients with non-TN subtypes had a lower LRR rate (AHR, 0.19; $p < .001$). In the final model, LVI and ≥20% of nodes positive were prognostic for a worse LRR outcome (Table 3).

DR

Distant failure occurred in 129 of the 316 patients. The median time to DR was 26 months for the entire cohort, 34 months for the ER^+ subgroup, 31 months for the $ER^+HER\text{-}2^+$ subgroup, 22 months for the $HER\text{-}2^+$ subgroup, and 19 months for the TN subgroup. The 5-year DR rates were 45.5% (95% CI, 39.4%–52%) for the whole cohort, 28.9% (95% CI, 20.4%–39.6%) for the ER^+ subgroup, 50.1% (95% CI, 33.5%–69.4%) for the $ER^+HER\text{-}2^+$ subgroup, 52.1% (95% CI, 39.9%–65.5%) for the $HER\text{-}2^+$ subgroup, and 56.7% (95% CI, 45.6%–68.3%) for the TN subgroup ($p < .001$, log-rank test) (Fig. 3). Pairwise comparisons showed a higher DR rate for the TN subgroup than for the ER^+ subgroup ($p < .0001$) but no differences between the TN subgroup and the other two subgroups or between the ER^+ subgroup and the $ER^+HER\text{-}2^+$ subgroup ($p = .11$).

On Cox univariate analysis using the TN subtype as the baseline, having ER^+ disease was associated with a lower DR rate, with an unadjusted HR of 0.39 ($p < .001$). Although the DR rate seemed lower in the $ER^+HER\text{-}2^+$ and $HER\text{-}2^+$ subgroups (HR, 0.75 and 0.65, respectively), this was not significant. However, the DR rate for non-TN patients (combined ER^+, $ER^+HER\text{-}2^+$, and $HER\text{-}2^+$) was significantly lower than that for TN patients (HR, 0.55; $p = .001$). When the $ER^+HER\text{-}2^+$ subtype was used as the baseline, the DR rate was not different for the ER^+ and $ER^+HER\text{-}2^+$ subgroups. Other factors prognostic of a higher DR risk included nuclear grade 3, LVI, no hormone receptor expression or hormone therapy, no radiation, no pCR, and ≥20% of nodes positive (Table 2).

On multivariate analysis after adjusting for prognostic factors, the DR risk was higher for patients with the TN subtype than for those with the ER^+ subtype (AHR, 0.31; $p < .001$). The DR risk was no different between the TN and $ER^+HER\text{-}2^+$ or $HER\text{-}2^+$ subgroups. However, having non-TN (ER^+, $ER^+HER\text{-}2^+$, or $HER\text{-}2^+$) disease was associated with a lower DR risk (AHR, 0.44; $p = .001$). In the final model, anti–HER-2 therapy, percent nodes positive, and radiation dose were predictive for DR.

Discussion

The predictive and prognostic values of ER, PR, and HER-2 status have been reported for early and advanced breast cancer [8–10, 19, 20], but to our knowledge, this is the first report of the significance of these surrogate markers in IBC patients, with clear links between breast cancer subtype and OS and LRR outcomes. These findings are consistent with a study by Bertucci et al. [11] in which gene expression profiling was used to confirm the presence of molecular subtypes in IBC; however, that study had only 37 IBC patients and did not correlate subtype with outcome. Our results suggest that stratification of breast cancer subtypes through routine analysis of ER, PR, and HER-2 status is clinically useful for estimating survival and recurrence in patients with IBC.

Breast cancer subtyping, in addition to being predictive of survival and metastasis, is also prognostic for local recurrence in non-IBC patients [8, 9, 13, 20]. We showed that breast cancer subtypes can be prognostic for LRR in IBC patients; this finding suggests that, even though IBC is often considered a systemic disease, the risk for LRR remains an important clinical problem, particularly for patients with TN IBC. Therefore, locoregional treatment intensification should be considered on an individual basis. We previously found that accelerated hyperfractionated radiotherapy (66 Gy at 1.5 Gy per fraction delivered twice daily versus 60 Gy at 2 Gy per fraction once daily) led to better local control of IBC [21], but this came at the cost of late skin toxicity (29% versus 15%) [22], leading to the recommendation that patients at low risk for recurrence (e.g., aged >45 years, with taxane chemotherapy and a good response to neoadjuvant chemotherapy) be given conventionally fractionated radiation [22]. In this regard, a recent report from Memorial Sloan-Kettering Cancer Center showed a 5-year LRR rate of 13% using once-daily radiation for patients treated after 1995 [23], which is only slightly higher than the 8% LRR rate in patients treated at MD Anderson after 1994 [22]. The results of the current study provide the rationale for trials of conventional radiation treatment for selected ER^+ subtypes, for patients with $ER^+HER\text{-}2^+$ disease receiving HER-2–directed therapy, and for intensifying radiation with or without a concurrent radiosensitizer in patients with TN cancer.

TN IBC, like its non-IBC counterpart, is particularly challenging to treat, given its aggressiveness and the ineffectiveness of endocrine and anti–HER-2 therapy. Efforts to identify subtype-specific potential targets have led to epidermal growth factor receptor (EGFR), Src, and Ras signaling [24] and patterns of kinase overexpression in ER^- tumors; the latter study showed that tumors that overexpress a cluster of genes control-

Table 2. Univariate analysis of factors influencing overall survival, locoregional recurrence, and distant metastasis in patients with inflammatory breast cancer

	Overall survival			Locoregional recurrence			Distant metastasis		
Variable	**Hazard ratio**	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**	**Hazard ratio**	**95% CI**	***p*-value**
Patient factors									
Age									
>45 yrs	1.00								
≤45 yrs	0.88	0.60–1.31	.52	1.37	0.80–2.36	0.26	1.28	0.89–1.82	.18
Race									
White	1.00								
Hispanic	1.10	0.63–1.90	.74	1.41	0.60–3.34	0.43	1.23	0.74–2.03	.43
African American	1.39	0.77–2.50	.27	1.87	0.76–4.62	0.17	1.14	0.63–2.09	.66
Other	0.31	0.04–2.24	.25	0.67	0.91–4.93 **	0.70	–	–	–[a]
Menopausal status									
Postmenopausal	1.00								
Premenopausal	0.88	0.60–1.28	.49	1.71	0.99–2.96	0.05	1.14	0.80–1.62	.48
Perimenopausal	0.61	0.22–1.70	.35	0.51	0.07–3.78	0.51	1.09	0.47–2.53	.83
Tumor factors									
Lymphovascular invasion									
Positive	1.00								
Negative	0.57	0.36–0.89	.01	0.17	0.07–0.42	<0.001	0.54	0.35–0.82	.004
Nuclear grade									
3	1.00								
<3	0.43	0.25–0.74	.003	0.38	0.16–0.89	0.003	0.59	0.37–0.93	.02
Hormone receptor status									
Positive	1.00								
Negative	2.19	1.49–2.23	<.001	3.44	1.84–6.45	<0.001	1.91	1.33–2.74	<.001
HER-2 status									
Positive	1.00								
Negative	1.12	0.77–1.64	.55	1.18	0.67–2.06	.56	0.87	0.61–1.23	.43
Molecular subtype									
TN	1.00								
HER-2$^+$	0.62	0.39–0.98	.04	0.42	0.25–0.90	.02	0.75	0.48–1.16	.19
ER$^+$	0.35	0.22–0.57	<.001	0.18	0.08–0.39	<.001	0.39	0.25–0.62	<.001
ER$^+$HER-2$^+$	0.39	0.21–0.74	.004	0.30	0.12–0.78	.01	0.65	0.37–1.14	.13
Non-TN	0.44	0.31–0.65	<.001	0.29	0.17–0.50	<.001	0.55	0.38–0.79	.001
Treatment factors									
Taxane used									
Yes	1.00								
No	1.94	0.90–4.18	.09	2.79	1.01–7.72	.05	1.39	0.57–3.41	.47
Hormone therapy used									
Yes	1.00								
No	0.32	0.20–0.50	<.001	0.437	0.23–0.79	.006	0.54	0.37–0.78	.001
Anti–HER-2 therapy (primary)									
No	1.00								
Yes	0.73	0.44–1.22	.23	0.54	0.25–1.14	.11	0.75	0.48–1.17	.21
Pathologic complete response									
Yes	1.00								
No	3.77	1.84–7.75	<.001	3.41	1.23–9.44	.02	2.84	1.57–5.16	.001
Surgical margin status									
Positive	1.00								
Negative	0.82	0.40–1.70	.59	0.34	0.16–0.70	.003	0.69	0.37–1.30	.25
% nodes positive									
≥20%	1.00								
<20%	0.50	0.32–0.78	.002	0.27	0.14–0.53	<.001	0.49	0.33–0.73	<.001
Extracapsular extension									
Yes	1.00								
No	0.64	0.42–0.99	.05	0.50	0.28–0.89	.02	0.69	0.46–1.02	.07
Radiation received									
Yes	1.00								
No	2.91	1.68–5.05	<.001	1.96	0.78–4.95	.15	3.02	1.78–5.11	<.001
Radiation dose (continuous)	0.96	0.92–0.99	.02	1.00	0.94–1.06	.98	0.97	0.93–1.00	.08
Radiation fractionation									
Once a day									
Twice a day	1.48	0.86–2.52	.16	1.33	0.63–2.81	.45	1.32	0.83–2.09	.24

[a]No distant metastatic failures in "other" group so it was dropped from the analysis.
Abbreviations: CI, confidence interval; ER, estrogen receptor; HER-2, human epidermal growth factor receptor; TN, triple negative.

Table 3. Multivariate Cox regression analysis of variables influencing overall survival, locoregional recurrence, and distant metastasis in patients with inflammatory breast cancer

Variable	Adjusted hazard ratio	95% confidence interval	*p*-value
Overall survival			
Molecular subgroup			
TN	1.00		
HER-2$^+$	0.51	0.27–0.95	.033
ER$^+$	0.25	0.13–0.47	<.001
ER$^+$HER-2$^+$	0.32	0.14–0.75	.009
Non-TN	0.38	0.23–0.64	<.001
% nodes positive			
≥20%	1.00		
<20%	0.38	0.22–0.64	<.001
Radiation dose (continuous)	0.94	0.90–0.99	.019
Other factors			NS
Locoregional recurrence			
Molecular subgroup			
TN	1.00		
HER-2$^+$	0.39	0.19–0.82	.01
ER$^+$	0.09	0.03–0.23	<.001
ER$^+$HER-2$^+$	0.20	0.07–0.59	.003
Non-TN	0.19	0.10–0.36	<.001
Lymphovascular invasion			
Positive	1.00		
Negative	0.18	0.06–0.54	.002
% nodes positive			
≥20%	1.00		
<20%	0.28	0.13–0.62	.001
Other factors			NS
Distant metastasis			
Molecular subgroup			
TN	1.00		
HER-2$^+$	0.99	0.52–1.87	.97
ER$^+$	0.31	0.18–0.54	<.001
ER$^+$HER-2$^+$	0.63	0.30–1.33	.23
Non-TN	0.44	0.27–0.71	.001
Anti–HER-2 therapy			
No	1.00		
Yes	0.47	0.24–0.92	.03
Radiation dose (continuous)	0.94	0.90–0.98	.007
% nodes positive			
≥20%	1.00		
<20%	0.40	0.25–0.62	<.001
Other factors			NS

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor; NS, not significant; TN, triple negative.

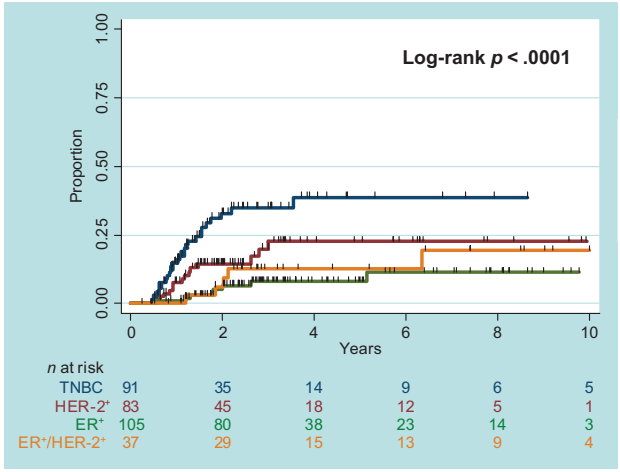

Figure 2. Rate of locoregional recurrence according to breast cancer subtype.

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

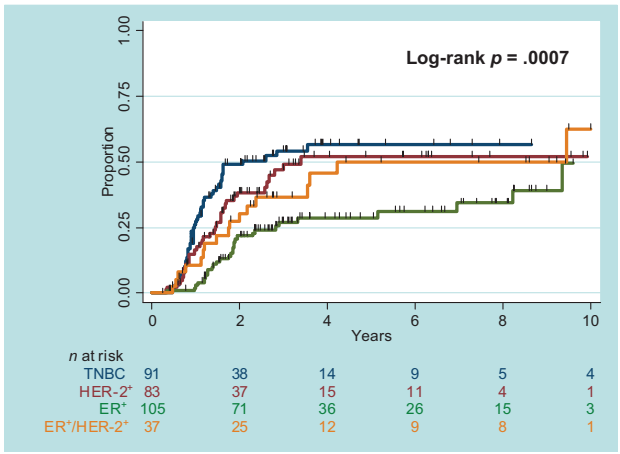

Figure 3. Rate of distant relapse according to breast cancer subtype.

Abbreviations: ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

ling the S6 kinase pathway were associated with an extremely poor prognosis [25]. Clinical trials of EGFR inhibitors for metastatic TN breast cancer are under way, and MD Anderson is initiating a phase II study with panitumumab as part of the preoperative chemotherapy regimen for patients with primary IBC without HER-2 overexpression. Other possible agents that may be tested for TN disease include Hedgehog inhibitors, the Src kinase inhibitor dasatinib, the mammalian target of rapamycin inhibitor everolimus [26], and inhibitors of nuclear factor-κB [27], cyclin E, and Skp2 [28].

Given the poor survival rates associated with IBC despite the advent of trimodality therapy (5-year OS, 59%), new IBC-specific molecular targets are being sought to improve the outcome of patients with IBC. Efforts undertaken to date revealed three potential markers that are overexpressed in IBC relative

to non-IBC: RhoC, a GTPase involved in cytoskeletal reorganization [29]; *WISP3*, a tumor suppressor gene [29, 30, 31]; and eIF4G1, a translation-initiation factor that promotes IBC tumor cell survival and perhaps metastasis [32, 33]. These markers may eventually serve as IBC-specific therapeutic targets.

A limitation of our study is its retrospective nature and consequent patient and treatment selection bias and variability in prognostic factors. However, this limitation may be alleviated to some extent by the large sample size of our cohort and significant number of events. Recently, a multinational registry was created at MD Anderson for the intent of prospectively establishing risk factors and prognostic factors for IBC. Another limitation of our study is the classification of breast cancer using immunohistochemically based surrogate markers (ER, PR, and HER-2), which provides only an approximation of genotype-identified molecular subgroups. Recent studies have shown that newer immunohistochemically based markers, such as Ki-67 [2–4, 34], EGFR, and CD5/CD6 [19, 35], can be used to further refine breast cancer classification. Despite the shortcomings of using receptor status to classify subtypes, receptor status is readily obtained and much less expensive and time-consuming than gene profiling. At this time, it seems to yield clinically relevant information on prognosis that may help in guiding therapy. Another potential limitation was our use of 10% staining as a cutoff value for classifying ER expression. In 2010, the American Society of Clinical Oncology and College of American Pathologists guidelines were changed to recommend that $<1\%$ be used to define ER negativity. Thus, our findings may not necessarily represent patients with ER^- disease diagnosed after 2010. Finally, at 38 months for living patients, our median follow-up time was fairly short, particularly given the tendency of ER^+ breast cancers to recur >5 years after treatment. Because TN disease tends to recur within the first 5 years, the short follow-up may have influenced the differences in the LRR that we found. However, the median time to LRR for the two ER^+ subgroups (ER^+ and $ER^+HER\text{-}2^+$) were 36 months and 35 months, respectively, whereas the median time to LRR for the two ER^- subgroups ($HER\text{-}2^+$ and TN) were 26 months and 19 months, respectively. This difference strongly supports the argument that ER negativity predicts early LRR and may explain, in part, the higher 5-year LRR rate among ER^- patients. Moreover, ER negativity seems to predict a higher rate of LRR at longer follow-up times as well. For example, at 8 years, the LRR rates in our study remained high for ER^- patients (39% for TN patients, 23% for $HER\text{-}2^+$ patients), compared with ER^+ patients (13% for ER^+ patients and 19% for $ER^+HER\text{-}2^+$ patients). One other observation that is worth commenting on is that the pCR rate in the TN cohort in our study was only 14%, despite 96% of patients receiving a taxane. This appears low relative to published literature, wherein the pCR rates for TN patients generally are $>25\%$ in non-IBC patients. The lower pCR rate in TN patients diagnosed with IBC likely reflects the aggressive nature of IBC and its resistance to therapy. This notion is supported by a study that included 40% IBC patients, in which the pCR rate was only 9.5% [36].

In summary, our findings indicate that breast cancer subtype, as approximated by the surrogate markers ER, PR, and HER-2, is significantly associated with OS and LRR outcomes in patients with IBC. The TN subtype consistently predicted the worst outcomes. This information may be useful in determining the aggressiveness of therapies aimed at controlling distant and locoregional disease. It also underscores the need to understand the biology underlying the aggressiveness of IBC and to identify new molecular targets specific to IBC, especially TN IBC.

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