Austin Journal of Clinical Case Reports

Open Access

Austin Publishing Group

Case Report

Predictive Factors for Late (>5 Years) Distant Recurrences in Hormone Receptor (HR) Positive, Human Epidermal Growth Factor Receptor 2 (HER2) Negative Breast Cancer Patients: >20 Year Follow Up

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Received: March 18, 2017; **Accepted:** June 15, 2017; **Published:** July 06, 2017

Abstract

Background: Hormone Receptor (HR) positive Breast Cancer (BC) by virtue of tumor dormancy can present with delayed systemic recurrence after adjuvant therapy, frequently years after initial diagnosis. The malignant cells remain quiescent or proliferate very slowly until they progress to overt cancer.

Methods: Over 2500 charts of HR+/HER2 negative BC patients were reviewed. Patients with follow up <5 years, recurrence within 5 years and all local recurrences < or >5 years were excluded. 35 late distant recurrences were identified. Data was analyzed with 50 patients from the same group without recurrences during the same period. Following factors were used for analysis: age at diagnosis, longest tumor diameter, smoking history, clinical stage at diagnosis, Lymph Node Involvement (LNI), tumor-grade, histology, Estrogen Receptor (ER) status, Progesterone Receptor (PR) status, duration of adjuvant therapy (≤5 years, >5 years) and treatment modalities. Multivariate analysis was conducted using logistic regression and proportional hazards models.

Results: The median/mean age at diagnosis was 58/58.5 years. Tumor size, T-stage at diagnosis, and duration of adjuvant therapy were associated with late relapse (p≤ 0.025, p≤ 0.012, p≤ 0.037 respectively). T-stage at diagnosis was the only independent predictor identified; with an estimated odds ratio of 2.62 (95% CI: 1.22, 5.64).

Conclusion: In univariate analysis, the tumor diameter, T-stage at diagnosis and duration of adjuvant therapy are associated with both recurrence and time to relapse. Patients who received adjuvant endocrine therapy ≥5 years had decreased rate of late recurrences. In multivariate analysis, T-stage at diagnosis is the only independent predictor.

Introduction

Breast cancer is a heterogeneous group of cancers that have varying degrees of clinical behavior and are driven by hormonal status or HER2 status. Advances in treatment of breast cancer have evolved as we have achieved a greater understanding of its molecular foundations. Despite these advances there remains a dearth of knowledge on reasons for late recurrences in hormone positive breast cancer. One prevailing hypothesis is that late distant recurrences in hormone positive breast cancer are felt to be due to tumor dormancy where malignant cells remain quiescent or proliferate very slowly until they progress to overt cancer. The delayed recurrence of hormone receptor-positive breast cancer remains a significant clinical challenge as approximately 50% of recurrences in HR-positive disease occur after the first 5 years of initial diagnosis and anti-hormonal treatment. Adjuvant treatment with endocrine therapy reduces the recurrence risk in patients with HR-positive breast cancer over all time periods by 39% but can lead to a number of adverse events that make compliance to treatment difficult [1]. For these reasons it is critically important to identify clinicopathological features that can better predict risk of late recurrence. Models such as the Breast Cancer Index (BCI) have been developed and can predict early (0-5 years) and late risk of distant recurrence in early stage breast cancer patients (ER positive and lymph node-negative breast cancer) but these models have not been developed in more advanced breast cancers and furthermore there remains a dearth of studies that have analyzed clinical factors that can predict late recurrence [2]. The aim of this study was to identify clinical and pathological factors at diagnosis that are associated with delayed systemic recurrence in hormone positive (lymph node positive and lymph node negative) breast cancer patients.

Methods and Analysis

After obtaining Cleveland Clinic Institutional Review Board (IRB) approval, we reviewed over 2500 charts of HR+/HER2 negative BC patients. The patients that were included in analysis required a biopsy proven diagnosis of hormone receptor positive (ER/PR) BC and had to have a minimum follow up of 5 years or more. Patients were excluded if they had relapse <5 years or had follow up less than 5 years. In study group only late (>5 years) and distant metastases were included. All local recurrences or contra lateral breast recurrences

Citation: Randhawa J, Charif M, Deeb A, Haque S-U, Spiro T, Haddad A, et al. Predictive Factors for Late (>5 Years) Distant Recurrences in Hormone Receptor (HR) Positive, Human Epidermal Growth Factor Receptor 2 (HER2) Negative Breast Cancer Patients: >20 Year Follow Up. Austin J Clin Case Rep. 2017; 4(2): 1119.

Table 1: Baseline characteristics (continuous variables; values presented as median (min, max), mean ± SD).

Factor	Total (N=85)	Relapse (N=35)
Age at diagnosis	58.0(26.0,85.0)	58.5±13.7
Age at relapse (n=35)	63.0(33.0,90.0)	65.5±14.5

(less than 5 years or more than 5 years) were excluded. Amongst the 2500 charts reviewed we identified 35 patients (study group) that met our inclusion criteria. We chose 50 patients (control group) who did not relapse and had similar follow up period as compared to study group. As an example of how this was done, we identified a patient who had developed distant metastatic disease 7 years after diagnosis and the patient that was picked for the control group also had 7 years follow up and no distant metastatic disease or no evidence of recurrence at 7 years. All of the patients that were included in this analysis were followed for at least 5 years, so results of this analysis were conditional on patients being alive and disease free 5 years from their initial diagnosis.

The goals of the analysis were:

1. To identify differences in clinical and pathological features between those who had a distant late relapse versus those who did not.

2. To determine if there are any independent predictors of future relapse.

All analyses that were performed were two-tailed and were performed at a significance level of 0.05. SAS 9.3 software (SAS Institute, Cary, NC) was used for all analyses.

The following parameters were used for univariable analysis: age at diagnosis, tumor diameter, smoking history, overall stage at diagnosis, T stage at diagnosis, lymph nodes, tumor grade, histology, estrogen/progesterone receptor, duration of adjuvant therapy and treatments received. Univariable associations between recurrences and clinical features were assessed using Wilcoxon rank sum, Kruskal-Wallis tests and Chi-square tests. Multivariable analysis was conducted using a logistic regression model with forward selection. Time to event data was analyzed using proportional hazards models. Time to relapse was measured from the date of diagnosis to the date of relapse or last follow-up (Table 1 and 2).

Descriptive information

Baseline characteristics for the patients are shown in Table 1 (continuous variables) and Table 2 (categorical variables). Continuous variables were summarized as Mean ± SD, median and range and categorical variables are summarized as frequency counts and percentages. Consistent with other studies the majority of our patients were early stage breast cancer presenting with Stage 1 or 2 disease breast cancer. We also found that while most patients had early stages of breast cancer there were varying modalities of treatment with 89% of patients receiving surgery and either radiation, chemotherapy or both. Our study also found that 75% of patients completed at least 5 years of endocrine therapy.

Factor associations

For our univariable analysis we analyzed age at diagnosis, tumor diameter, smoking history, overall stage at diagnosis, T stage

Table 2: Baseline characteristics (categorical variables).

Factor	N (%) (Total=85)
Age at diagnosis	
≤ 50	26(30.6)
50 – 59	20(23.5)
≥ 60	39(45.9)
Smoking history[1]	
Never	13(17.8)
Ex-smoker	19(26.0)
Current smoker	41(56.2)
Overall stage at diagnosis[1]	
1	37(57.8)
2	23(35.9)
3	4(6.3)
T stage at diagnosis[1]	
T_1	47(56.0)
T_2	32(38.1)
T_3 or T_4	5(6.0)
Longest tumor diameter[1]	
< 2cm	41(57.7)
2-3cm	16(22.5)
≥ 3cm	14(19.7)
Lymph nodes	
No	52(62.7)
Yes	31(37.3)
Tumor grade[1]	
Well/moderated differentiation	50(69.4)
Poorly differentiated	22(30.6)
Histology[1]	
Ductal	61(74.4)
Lobular	16(19.5)
Other	5(6.1)
Progesterone receptor[1]	
Negative	26(32.9)
Positive	53(67.1)
Duration of adjuvant therapy 1[1]	
None	8(9.8)
≤ 4 years	12(14.6)
5 years	50(61.0)
>5 years	12(14.6)
Duration of adjuvant therapy 2[1]	
None or ≤ 4 years	20(24.4)
≥ 5 years	62(75.6)
Treatments	
Chemotherapy + Surgery	13(15.3)
Radiation + Chemotherapy + Surgery	36(42.4)

Radiation + Surgery	26(30.6)
Surgery	10(11.8)
Brain metastasis at recurrence	
Absent	34(97.1)
Present	1(2.9)
Adjuvant therapy	
No	8(9.76)
Yes	73(90.24)
Status	
Alive	68(80.0)
Dead	17(20.0)

[1]Missing values: Smoking history =12, Overall stage at diagnosis = 21, T stage at diagnosis =1, Longest tumor diameter = 14, Tumor grade = 13, Histology = 3, Progesterone receptor = 6, Duration of adjuvant therapy 1 = 3, Duration of adjuvant therapy 2= 3 Adjuvant therapy = 3.

at diagnosis, lymph nodes, tumor grade, histology, progesterone receptor, duration of adjuvant therapy and treatments received and are listed in Table 3. We defined their relationship to distant late recurrence as a hazard ratio. The majority of clinical variables at diagnosis were not associated with distant late recurrences. However tumor diameter (cm), T stage at diagnosis and duration of adjuvant therapy were associated with distant recurrences. We found that having an advanced breast cancer as well as a bigger tumor at diagnosis was more likely to result in a distant recurrence (HR of 2.22 and 1.67 respectively) and duration of adjuvant therapy provided a significant protective effect (HR 0.67). When we looked at duration of adjuvant endocrine therapy with 5 years as our cutoff we found that receiving 5 years of adjuvant therapy was the most protective against late distant recurrence (HR of 0.47).

Logistic regression

Based on our univariate analyses in Table 3, tumor diameter (cm), T stage at diagnosis and duration of adjuvant therapy were considered for inclusion in the model. The results after forward model selection are shown in Table 4. After adjusting for these variables only T stage at diagnosis independently predicted late distant recurrence with an estimated odds ratio of 2.62 (95% CI: 1.22, 5.64, p=0.013)

Time to relapse analysis

Factors affecting relapses with hazard ratios, the corresponding 95% confidence intervals and P-values are shown in Table 3. The T stage at diagnosis, and duration of adjuvant therapy are associated with time to relapse (p=0.003, and 0.037 respectively). None of the other factors examined was associated with survival (All p>0.083). Thus, tumor size or T stage at diagnosis, and duration of adjuvant therapy were considered for inclusion in the multivariable survival model, and after forward model selection, T stage at diagnosis was the only independent predictor identified; with an estimated hazard ratio of 2.22 (95% CI: 1.32, 3.72, p=0.003).

Discussion

Hormone receptor positive breast cancer is the most common subtype among all breast cancers. The tumors with ER positive/PR positive accounts for 55% of all breast cancers whereas ER-positive/PR negative and ER-negative/PR positive account for 16% and 4%, respectively [3]. Hormone positive BC is frequently associated with older age, low-grade tumors, and with negative lymph nodes. These tumors have a distinct clinical behavior characterized by a slower rise in risk of recurrence with a late onset of metastasis even in patients with early stage disease at diagnosis [4]. They display distinct clinical behavior from Triple Negative BC (TNBC) in that the risk of first distant recurrence in TNBC is highest in the first 2 years after initial treatment and then decreases thereafter. Whereas women with ER-positive tumors have stable rates of first distant recurrence over time with recurrences occurring delayed and anywhere from 5-10 years and sometimes beyond 10 years after initial breast cancer diagnosis [5].

Hormone receptor positivity is highly predictive of response to endocrine therapy and has been shown to prolong survival in patients with ER positive and/or PR positive tumors. Furthermore the length of endocrine therapy is clearly associated with reduction in the rate of delayed recurrence [6-8]. The EBCTCG meta-analysis study concluded that receiving adjuvant tamoxifen for 5 years resulted in about 41% reduction in relative risk of distant metastases [9]. Aromatase Inhibitors (AI) has also been shown to reduce the risk of recurrence. One study compared AI therapy to Tamoxifen in postmenopausal women and found that 5 years of AI therapy resulted in a 29% proportional reduction in risk of recurrence in comparison to 5 years of tamoxifen. Another study looked at sequential hormonal therapy and found that use of AIs after 2-3 years of tamoxifen was associated with a 40% decrease in risk of recurrence [10,11]. To further offset the risk of late distant recurrences more recent studies such as the ATLAS and aTTom studies have demonstrated that prolonged adjuvant hormonal therapy for 10 years can further reduce the risk of late recurrences [12,13]. Our analysis also showed similar findings to these larger studies despite its small sample size; 75% of patients completed adjuvant hormonal therapy and 87% of these patients showed no evidence of recurrence of disease at follow up.

However, the side effects of extended endocrine therapy are not trivial and should always be weighed against the projected benefits. Clinical pathological features typically associated with recurrence include size of tumor, lymph node involvement, grade of tumor and can vary across studies. In fact our study identified initial T stage as the only independent predictor of late recurrence although there was a trend identified with lymph node positive status (p=0.083, Table 3). These differences in clinical factors highlight the heterogeneity of disease and patient populations across different studies; and therefore more sophisticated tools are necessary to better identify those that require prolonged hormonal therapy. Models have been developed to identify these patients who would benefit the most from prolonged therapy. The breast cancer index can help to identify patients at high risk for late distant recurrence who might benefit from extended endocrine therapy [14]. The PAM50 risk-of-recurrence score showed that the late distant recurrence free survival is significantly different between Luminal A/B molecular subtypes (luminal B *vs.* luminal A; Hazard ratio 2.49, P<0.01) [15]. The Endo Predict score can identify a subgroup of patients with excellent long-term prognosis after 5 years of endocrine therapy. In the study, the test stratified 64% of patients at risk after 5 years into a low-risk subgroup with an absolute risk 1.8% of late distant metastasis at 10 years of follow-up [16]. The HOXB13/IL17BR (H/I) biomarker (in ER positive and lymph node

Table 3: Univariable comparisons (for column "total", "no relapse", "relapse", data are presents as Median (range) or N (%)).

	Total	No Relapse	Relapse		Hazard Ratio	
Factor	**(N=85)**	**(N=50)**	**(N=35)**	**P**	**(95%CI)[4]**	**P[5]**
Age at diagnosis	58.0 (26.0, 85.0)	61.5 (30.0, 80.0)	55.0 (26.0, 85.0)	0.21[1]	1.00 (0.97, 1.02)	0.86
Age at diagnosis				0.096[2]	0.76 (0.52, 1.12)	0.16
≤ 50	26 (30.6)	11 (22.0)	15 (42.9)			
50-59	20 (23.5)	12 (24.0)	8 (22.9)			
≥ 60	39 (45.9)	27 (54.0)	12 (34.3)			
Smoking history				0.81[2]	0.94 (0.61, 1.45)	0.79
Never	13 (17.8)	6 (15.4)	7 (20.6)			
Ex-smoker	19 (26.0)	11 (28.2)	8 (23.5)			
Current smoker	41 (56.2)	22 (56.4)	19 (55.9)			
Overall stage at diagnosis				0.142	1.71 (0.88, 3.34)	0.12
1	37 (57.8)	27 (61.4)	10 (50.0)			
2	23 (35.9)	16 (36.4)	7 (35.0)			
3	4 (6.3)	1 (2.3)	3 (15.0)			
T stage at diagnosis				***0.012[2]***	2.22 (1.32, 3.72)	***0.003***
T_1	47 (56.0)	32 (64.0)	15 (44.1)			
T_2	32 (38.1)	18 (36.0)	14 (41.2)			
T_3 or T_4	5 (6.0)	0 (0.0)	5 (14.7)			
Tumor diameter				0.11[2]	1.67 (1.08, 2.58)	***0.020***
< 2cm	41 (57.7)	29 (67.4)	12 (42.9)			
2-3cm	16 (22.5)	8 (18.6)	8 (28.6)			
≥ 3cm	14 (19.7)	6 (14.0)	8 (28.6)			
Lymph nodes				0.18[2]	1.82 (0.93, 3.56)	0.83
No	52 (62.7)	33 (68.8)	19 (54.3)			
Yes	31 (37.3)	15 (31.3)	16 (45.7)			
Tumor grade				0.27[2]	1.38 (0.62, 3.03)	0.43
Well/moderated	50 (69.4)	34 (73.9)	16 (61.5)			
Poorly	22 (30.6)	12 (26.1)	10 (38.5)			
Histology				0.99[2]	0.63 (0.33, 1.22)	0.17
Ductal	61 (74.4)	37 (74.0)	24 (75.0)			
Lobular	16 (19.5)	10 (20.0)	6 (18.8)			
Other	5 (6.1)	3 (6.0)	2 (6.3)			
Progesterone receptor				0.58[2]	0.82 (0.39, 1.74)	0.61
Negative	26 (32.9)	15 (30.6)	11 (36.7)			
Positive	53 (67.1)	34 (69.4)	19 (63.3)			
Duration of adjuvant therapy 1				***0.0172***	0.68 (0.48,0.98)	0.037
None	8 (9.8)	3 (6.4)	5 (14.3)			
≤ 4 years	12 (14.6)	3 (6.4)	9 (25.7)			
5 years	50 (61.0)	31 (66.0)	19 (54.3)			
>5 years	12 (14.6)	10 (21.3)	2 (5.7)			
Duration of adjuvant therapy 2				***0.005[2]***	0.47 (0.24, 0.93)	***0.031***
None or ≤ 4 years	20 (24.4)	6 (12.8)	14 (40.0)			
≥ 5 years	62 (75.6)	41 (87.2)	21 (60.0)			
Treatments[6]				0.12[2]	0.94 (0.65, 1.35)	0.72

C + S	13 (15.3)	10 (20.0)	3 (8.6)			
R + C + S	36 (42.4)	20 (40.0)	16 (45.7)			
R + S	26 (30.6)	17 (34.0)	9 (25.7)			
S	10 (11.8)	3 (6.0)	7 (20.0)			

[1]Wilcoxon rank rum test, or Kruskal-Wallis test
[2]Chi-square test
[3]P-values and Hazard ratio (95%CI) for the comparison of ductal verse lobular
[4]The first line of each facter serves as the reference group; hazard ratios >1 indicate an increase in risk the levels increase; ratios <1, a decrease.
[5]P-values from Wald test
[6]R=Radiation; C=Chemotherapy; S=Surgery

Table 4: Results of logistic regression models using forward selection.

Factor	Odds Ratio (95% CI)	P-value
T stage at diagnosis	2.62 (1.22, 5.64)	0.013

negative breast cancer) demonstrated an association with a decrease in late recurrence in patients receiving extended letrozole therapy (odds ratio [OR] =0.35; 95% confidence interval [CI] =0.16 to 0.75; P=0.007) [17].

Other than tumor hormone receptor status, different risk factors have been studied and found that age and tumor characteristics with a peak of recurrence at about 2 years in patients who are younger than 50 years at diagnosis, having positive lymph nodes and tumor size of more than 2 cm at diagnosis [5]. There is growing evidence that tumor size at diagnosis and nodal status may be helpful in predicting the delayed recurrence in hormone positive patients [18-20]. In our study the tumor size, T-stage at diagnosis, and duration of adjuvant therapy were associated with late relapse ($p \leq 0.025$, $p \leq 0.012$, $p \leq 0.037$ respectively) however T-stage at diagnosis was the only independent predictor identified; with an estimated odds ratio of 2.62 (95% CI: 1.22, 5.64) and an estimated hazard ratio of 2.22 (95% CI: 1.32, 3.72). Yamashita, et al. reported similar findings with large tumor size and high lymph node category as predictors of late recurrence in both pre-menopausal (T-stage p value <0.0001; nodal category p value <0.0001) and post-menopausal (T-stage p value 0.009; nodal category p value 0.0006) women [21].

Treatment decisions after initial diagnosis of HR breast cancer is determined by clinicopathological features and include presence of pathologically involved lymph nodes, large tumor size, high tumor grade, lymphovascular invasion, and/or high risk of recurrence based on a genomic assay (e.g., Recurrence Score [RS] >31 on the 21-gene recurrence assay) [22-24]. For patients who have completed treatment, studies have identified that a gene signature can be utilized to stratify risk of late distant metastases (>5-15 years). This study showed that enrichment in genes involved in immune response may play a role in suppressing anti-tumoral immunity enabling the dormant tumor cells to re-enter the cell cycle to form metastases [25]. Another study identified that the persistence of circulating tumor cells (after completion of adjuvant chemotherapy) in patients with either hormonal receptor positive or negative tumors, is also associated with a higher risk of late-disease relapse compared to those who were negative for persistently circulating tumor cells (36.4% *vs.* 11.2%, P<0.001) [26-29].

Our study has limitations in that it was a retrospective study and had small sample sizes. Despite these limitations our findings show that T stage at diagnosis is an important predictor for late recurrence and this appears to be consistent with larger studies. While these findings may not appear surprising, it does provide us a simple and cost effective parameter (T-stage) to underscore optimal therapy options and could be used when discussing risks *vs.* benefits of extended hormonal therapy in hormone positive HER2 negative breast cancer patients.

Conclusion

Conditional on being alive and disease-free after 5 years, T stage at diagnosis and duration of adjuvant therapy were associated with both recurrences and time to relapse in univariable analysis; however T stage at diagnosis was the only independent predictor for late distant recurrence.

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Austin J Clin Case Rep - Volume 4 Issue 2 - 2017
ISSN : 2381-912X | www.austinpublishinggroup.com

Citation: Randhawa J, Charif M, Deeb A, Haque S-U, Spiro T, Haddad A, et al. Predictive Factors for Late (>5 Years) Distant Recurrences in Hormone Receptor (HR) Positive, Human Epidermal Growth Factor Receptor 2 (HER2) Negative Breast Cancer Patients: >20 Year Follow Up. Austin J Clin Case Rep. 2017; 4(2): 1119.