Residual Risk of Breast Cancer Recurrence 5 Years After Adjuvant Therapy

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There is limited prognostic information to identify breast cancer patients who are at risk for late recurrences after adjuvant or neoadjuvant systemic therapy (AST). We evaluated the residual risk of recurrence and prognostic factors of 2838 patients with stage I–III breast cancer who were treated with AST between January 1, 1985, and November 1, 2001, and remained disease free for 5 years. Residual recurrence-free survival was estimated from the landmark of 5 years after AST to date of first recurrence or last follow-up using the Kaplan–Meier method. The log-rank test (two-sided) was used to compare groups. Residual recurrence-free survival rates at 5 and 10 years were 89% and 80%, respectively, and 216 patients developed a recurrence event. The 5-year residual risks of recurrence for patients with stage I, II, and III cancers were 7% (95% confidence interval [CI] = 3% to 15%), 11% (95% CI = 9% to 13%), and 13% (95% CI = 10% to 17%), respectively (P = .02). In multivariable analysis, stage, grade, hormone receptor status, and endocrine therapy were associated with late recurrences. Breast cancer patients have a substantial residual risk of recurrence, and selected tumor characteristics are associated with late recurrences.

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Adjuvant or neoadjuvant systemic therapy (AST) for breast cancer improves survival, yet a substantial number of women remain at risk for late recurrences (1,2). Identifying patients who are at risk for late recurrences has clinical relevance because extended adjuvant endocrine therapy with letrozole improves the disease-free survival of postmenopausal women with estrogen receptor (ER)– or progesterone receptor (PR)–positive tumors after 5 years of tamoxifen therapy (3). Extended adjuvant endocrine therapy is recommended for postmenopausal women with endocrine responsive breast cancers (4–6); however, limitations in the ability to predict the magnitude of the risk of late recurrence may contribute to some patients receiving unnecessary extended adjuvant endocrine therapy and others receiving no treatment. Few studies have evaluated the magnitude of the risk of late recurrence among patients who remain disease free 5 years after AST, which is a clinically relevant estimate for weighing the risks and benefits of extended adjuvant endocrine therapy (7). We therefore identified a cohort of patients with early-stage breast cancer and determined the magnitude of the residual risk of breast cancer recurrence after 5 years from the start of AST and the prognostic significance of patient and tumor characteristics.

Patients included in this study were retrospectively selected from the Protocol Data Management Systems (PDMS) and the Breast Cancer Management Systems (BCMS) databases of patients who were treated with AST at the University of Texas M. D. Anderson Cancer Center (MDACC) between January 1, 1985, and November 1, 2001. Only patients who were enrolled in systemic treatment clinical trials were included before January 1, 1997, because clinical data on nonprotocol patients were not entered into any databases before that date. Patients were eligible if they: 1) were women who were diagnosed with American Joint Committee on Cancer pathologic stages I, II, or III breast cancer; 2) underwent surgery at MDACC; 3) received AST consisting of adjuvant or neoadjuvant chemotherapy and/or endocrine therapy; and 4) were alive and remained disease free 5 years from the start of AST. A total of 3064 patients who met study criteria were identified from the PDMS and BCMS databases. Two hundred and twenty-six patients were excluded because they were male (n = 9), had incomplete staging information or stage IV disease (n = 53), had no information available regarding date of surgery (n = 14), did not receive definitive surgery for the primary breast cancer (n = 21), or died or were found to have a breast cancer recurrence within 5 years from start of AST (n = 129). The final study population consisted of 2838 patients.

Follow-up information was obtained by medical record review and matched with the MDACC Tumor Registry, which annually mails letters to patients who are known to be alive to determine their clinical status. The study was approved by the MDACC Institutional Review Board, which granted a waiver of informed consent for this study.

The primary study endpoint was time to breast cancer recurrence, which was defined as local lymph node or breast recurrence, metastasis to other sites, or second primary breast cancer. Residual recurrence-free survival was calculated from the landmark of 5 years from the start of AST to the date of first disease recurrence or last follow-up. We used this landmark because the majority of women with hormone receptor–positive tumors completed 5 years of adjuvant endocrine therapy, and we were interested in evaluating the residual risk of recurrence after the completion of AST. Patients who died

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CONTEXT AND CAVEATS

Prior knowledge

Adjuvant and neoadjuvant systemic therapy (AST) improves the survival of breast cancer patients, but there is still a risk that the disease will recur years later.

Study design

Disease recurrence among breast cancer patients who were disease free 5 years after AST (the landmark) was estimated 5 and 10 years after landmark. Multivariable analysis was used to identify factors associated with recurrence.

Contributions

Rates of recurrence-free survival at 5 years and 10 years after landmark were 89% and 80%, respectively. The risk of recurrence 5 years after therapy increased with tumor stage (stage 1: 7%, stage II: 11%, and stage 3: 13%) and was also associated with tumor grade, hormone receptor status, and endocrine therapy.

Implications

Breast cancer patients who undergo AST are at risk of late recurrences, and this risk is associated with certain characteristics of the original tumor.

Limitations

HER2/neu status was not included in the analysis because the data were not available; aromatase inhibitor treatment was not included because too few women received it.

From the Editors

without a recurrence or who were not known to have a recurrence at the date of last contact were censored. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models. The *P* values in the univariate analysis were based on the log-rank test, and the 5- and 10-year estimates and 95% confidence intervals were based on the Kaplan–Meier estimates, with standard error based on Greenwood estimator. Recurrence-free survival was considered in a multivariable setting with Cox proportional hazards models. Age at diagnosis (≤35, 36–59, or ≥60 years), year of start of AST (before 1992 or 1992 or later), hormone receptor status (ER positive and/or PR positive, or ER negative and PR negative), chemotherapy (anthracycline, anthracycline and taxane, other, or none), endocrine therapy (tamoxifen, aromatase inhibitor, tamoxifen and aromatase inhibitors, other, or none), stage (I, II, or III), surgery type (breast conserving or mastectomy), radiation (yes or no), and grade (1, 2, or 3) were considered for inclusion in the multivariable model and were evaluated by both the Wald test and the likelihood ratio test. The proportional hazards assumption was tested for the variables included in the multivariable model, and the global *P* value was .20, indicating that the assumption was not violated for the fitted multivariable Cox model (8). The Kaplan–Meier product limit method (9) was also used to estimate residual recurrence-free survival, and the log-rank test was used to compare groups. Tumors that were ER or PR positive were defined as hormone receptor positive. All statistical tests were two-sided, and *P* values less than .05 were considered statistically significant. We used SAS version 9.1 (SAS Institute, Cary, NC) to perform the analyses.

The majority of patients (52%) were postmenopausal; 9% were black, 12% Hispanic, 73% white, and 3% of other ethnicities (Table 1). The median follow-up time for the cohort after 5 years from the start of AST was 28 months (range = 0.02 to 185.6 months). The 5- and 10-year residual recurrence-free survival rates (10 and 15 years from start of AST) were 89% and 80%, respectively, and 216 patients developed a recurrence event. The median time from surgery to start of adjuvant therapy was 35 days (range = 1 to 955 days) and that from the start of neoadjuvant therapy to surgery was 107 days (range = 29 to 608 days). Adjuvant tamoxifen therapy was not routinely prescribed to premenopausal women until 1998. Patients with stages I, II, and III disease had a residual 5-year risk of recurrence of 7% (95% CI = 3% to 15%), 11% (95% CI = 9% to 13%), and 13% (95% CI = 10% to 17%), respectively. The small number of stage I patients (n = 3) who were at risk for an event at 15 years from the start of AST makes the 10-year residual risk estimate unreliable (Figure 1). The residual risk of recurrence was statistically significantly higher for patients with hormone receptor–positive tumors than for those with hormone receptor–negative tumors in a stratified analysis by endocrine therapy ($P < .001$; Table 1). Patients with hormone receptor–positive tumors had a higher residual risk of recurrence than patients with hormone receptor–negative tumors regardless of menopausal status (data not shown).

The multivariable model included hormone receptor status, endocrine therapy, stage, surgery type, and grade. Factors that were associated with increased risk of recurrence 5 years after the start of AST were stage III vs stage I disease (HR = 2.49, 95% CI = 1.33 to 4.66; $P = .004$), stage II vs stage I disease (HR = 2.13, 95% CI = 1.21 to 3.75; $P = .009$), and hormone receptor–positive tumors not treated with endocrine therapy vs hormone receptor–negative tumors (HR = 1.84, 95% CI = 1.19 to 2.87; $P = .006$). Patients with hormone receptor–positive tumors who were treated with endocrine therapy had an approximately 50% higher residual risk of recurrence than patients with hormone receptor–negative tumors, but this difference was not statistically significant (HR = 1.49, 95% CI = 0.95 to 2.34; $P = .08$). Patients with grade 3 tumors had a lower residual risk of recurrence than patients with grade 1 tumors (HR = 0.47, 95% CI = 0.23 to 0.95; $P = .036$). We also evaluated the clinical characteristics that were associated with residual risk of recurrence among patients with hormone receptor–positive tumors who received chemotherapy and endocrine therapy or endocrine therapy alone. Among these patients, the residual risk of recurrence was influenced by the same factors as observed in the overall population. There was also no association in the residual risk of recurrence between hormone receptor–positive patients who were treated with chemotherapy plus endocrine therapy vs those treated with endocrine therapy alone (data not shown).

These findings agree with previous studies showing a higher annual risk of recurrence among patients with larger tumors and lymph node involvement who were treated with AST and followed for 5–15 years (10,11). In this study, low-grade and positive hormone receptor status, which are associated with favorable short-term prognosis (12,13), were associated with a higher residual risk of recurrence. Studies (14,15) have demonstrated that the survival advantage of hormone receptor–positive tumors is time dependent, because at longer follow-up, patients with hormone receptor–negative tumors have a survival

Table 1. Residual recurrence-free survival from 5 years after adjuvant or neoadjuvant systemic therapy (landmark)*

Characteristic	No. of patients	No. of recurrences	Univariate analysis, recurrence-free survival % (95% CI) 5 Years	10 Years	*P*	Multivariable Cox model Hazard ratio (95% CI)	*P*
Overall	2838	216	89.2 (87.4 to 90.8)	80.5 (76.8 to 83.6)			
Age (median = 50 y, range = 21–87 y)						—	
≤35 y	220	16	91.3 (85.4 to 94.9)	85.5 (72.0 to 92.8)			
36–59 y	1991	161	88.6 (86.5 to 90.5)	80.4 (76.3 to 83.8)			
≥60 y	627	39	90.5 (85.7 to 93.8)	75.8 (61.9 to 85.2)	.44		
Menopause status						—	
Pre and peri	1365	118	89.3 (87.0 to 91.3)	80.8 (76.0 to 84.8)			
Post	1472	98	88.9 (86.0 to 91.3)	79.8 (73.8 to 84.5)	.90		
Unknown	1	0					
Race/ethnicity						—	
White	2057	148	88.8 (86.6 to 90.7)	80.7 (76.3 to 84.4)			
Black	259	21	90.3 (84.1 to 94.2)	79.6 (67.3 to 87.7)			
Hispanic	332	36	86.1 (80.2 to 90.4)	75.5 (64.7 to 83.5)			
Other	93	4	95.9 (87.8 to 98.7)	85.2 (49.7 to 96.4)	.099		
Unknown	97	7					
Histology						—	
Ductal	2198	170	89.1 (87.1 to 90.9)	80.6 (76.6 to 84.0)			
Lobular	184	16	86.7 (75.6 to 92.9)	64.5 (41.4 to 80.4)			
Other	136	9	90.3 (80.2 to 95.4)	90.3 (80.2 to 95.4)	.55		
Unknown	320	21					
Hormone receptor (HR) status						—	
Negative	645	34	92.9 (89.7 to 95.1)	88.7 (83.2 to 92.4)			
Positive	1872	149	87.0 (84.3 to 89.2)	76.9 (71.3 to 81.6)	<.001		
Unknown	321	33					
Stage							
I	678	17	93.1 (84.9 to 96.9)	76.4 (51.6 to 89.6)		1.00 (referent)	
II	1613	135	88.8 (86.5 to 90.7)	80.6 (75.9 to 84.5)		2.13 (1.21 to 3.75)	.009
III or inflammatory	547	64	87.3 (83.4 to 90.3)	79.0 (72.6 to 84.1)	.014	2.49 (1.33 to 4.66)	.004
Grade							
1	107	11	85.7 (69.6 to 93.6)	55.1 (26.9 to 76.3)		1.00 (referent)	
2	1243	112	87.4 (84.4 to 89.9)	75.7 (69.5 to 80.9)		0.70 (0.35 to 1.39)	.31
3	1343	75	91.4 (88.9 to 93.3)	87.6 (83.1 to 90.9)	.003	0.47 (0.23 to 0.95)	.036
Unknown	145	18					
Skin involvement						—	
Negative	2689	199	89.5 (87.7 to 91.1)	81.1 (77.5 to 84.2)			
Positive	109	15	81.0 (68.2 to 88.8)	67.3 (44.6 to 82.4)	.031		
Unknown	40	2					
Extent of surgery							
Breast conserving	969	38	92.9 (89.6 to 95.2)	84.7 (75.2 to 90.8)		1.00 (referent)	
Mastectomy	1869	178	87.9 (85.8 to 89.8)	79.2 (75.1 to 82.6)	.003	1.47 (0.99 to 2.18)	.059
Chemotherapy type						—	
Anthracycline	1383	150	88.8 (86.6 to 90.6)	79.1 (74.5 to 83.0)			
Anthracycline and taxane	878	31	86.8 (72.8 to 93.9)	—			
Other	168	22	87.2 (80.3 to 91.8)	83.8 (75.9 to 89.3)			
None	409	13	95.6 (91.5 to 97.8)	—	.56		
Radiotherapy						—	
No	1192	98	89.0 (86.2 to 91.3)	77.6 (70.3 to 83.3)			
Yes	1618	115	89.4 (86.9 to 91.4)	82.4 (77.9 to 86.0)	.48		
Unknown	28	3					
Endocrine therapy						—	
Tamoxifen	1037	87	84.7 (80.3 to 88.2)	69.1 (58.6 to 77.4)			
Aromatase inhibitor	42	1	—	—			
Tamoxifen and aromatase inhibitor	420	5	—	—			
Other	8	1	—	—			
None	1299	118	90.4 (88.3 to 92.1)	84.0 (80.3 to 87.1)	.001		
Unknown	32	4					

(Table continues)

Table 1 (continued).

Characteristic	No. of patients	No. of recurrences	Univariate analysis, recurrence-free survival % (95% CI) 5 Years	10 Years	*P*	Multivariable Cox model Hazard ratio (95% CI)	*P*
Endocrine therapy by HR status							
No							
HR negative	645	34	92.9 (89.7 to 95.1)	88.7 (83.2 to 92.4)		1.00 (referent)	
HR positive	490	74	85.7 (81.8 to 88.9)	76.2 (69.7 to 81.5)		1.84 (1.19 to 2.87)	.006
Yes							
HR positive	1377	74	86.4 (81.8 to 89.9)	79.8 (71.8 to 85.7)	<.001	1.49 (0.95 to 2.34)	.084
Unknown	326	34					

* CI = confidence interval. Multivariable analyses were adjusted for stage, grade, surgery type, hormone receptor status, and endocrine therapy. *P* values were calculated using two-sided log-rank test for univariate analyses and two-sided Wald tests for multivariable analyses.

rate that is similar to or more favorable than that of patients with hormone receptor–positive tumors. In the current study, among the patients with hormone receptor–positive breast cancer, higher stage and lower grade were also associated with residual risk of recurrence. The receipt of chemotherapy in addition to endocrine therapy did not influence the residual risk of recurrence; however, these results should be considered with caution because the sample consisted of a mixed population of hormone receptor–positive tumors, some of whom (n = 44) were enrolled in a randomized study of adjuvant endocrine therapy alone vs chemotherapy alone (16).

The higher residual risk of recurrence associated with hormone receptor–positive tumors has important clinical implications. There are no proven therapeutic options for extended adjuvant endocrine therapy for premenopausal women who have completed 5 years of tamoxifen therapy (17–20). The magnitudes of the residual risk of recurrence for pre- and postmenopausal patients were within the range (8%–20%) considered appropriate to recommend AST at the time of diagnosis, indicating a need for the continued development of risk reduction strategies for these survivors.

A limitation of our study is that we were unable to assess the prognostic significance of Her2/neu expression because these data were not available. In addition, few patients received adjuvant therapy that included aromatase inhibitors before 2001, and therefore, the residual risk of recurrence associated with this treatment was not assessed. Extended adjuvant endocrine therapy after aromatase inhibitor treatment has not been evaluated in randomized trials, and the benefits are undefined. The strengths of the study are the large sample size of ethnically diverse patients who were treated with AST with long-term follow-up.

In conclusion, this study demonstrates that patients with early-stage breast cancer who are disease free at 5 years after AST have a substantially increased residual risk of recurrence. Extended adjuvant endocrine therapy is currently available only for postmenopausal patients with hormone receptor–positive disease, and these patients should be considered for treatment after careful evaluation of the risks and benefits. More research is needed to identify host and tumor characteristics that are associated with late breast cancer recurrences to individualize initial AST and extended adjuvant endocrine therapy.

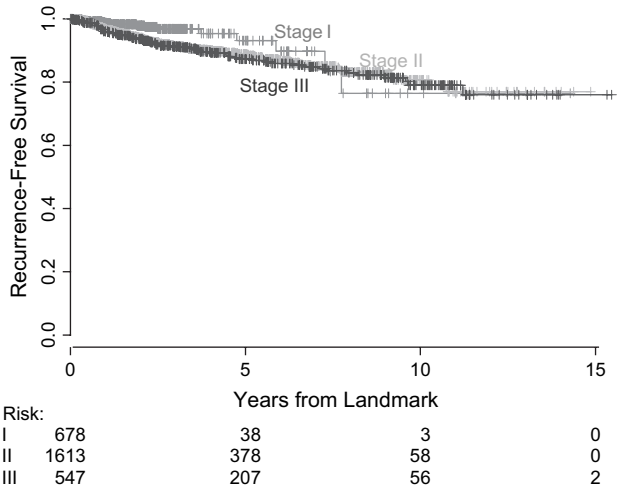

Figure 1. Kaplan–Meier analysis of residual recurrence-free survival according to stage at diagnosis. Point estimates of recurrence-free survival, 95% confidence intervals, and *P* values are shown in the univariate analyses in Table 1.

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