Risk of Synchronous Distant Recurrence at Time of Locoregional Recurrence in Patients With Stage II and III Breast Cancer (AFT-01)

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A B S T R A C T

Purpose

National Comprehensive Cancer Network guidelines recommend systemic staging imaging at the time of locoregional breast cancer recurrence. Limited data support this recommendation. We determined the rate of synchronous distant recurrence at the time of locoregional recurrence in high-risk patients and identified clinical factors associated with an increased risk of synchronous metastases.

Methods

A stage-stratified random sample of 11,046 patients with stage II to III breast cancer in 2006 to 2007 was selected from the National Cancer Database for participation in a Commission on Cancer special study. From medical record abstraction of imaging and recurrence data, we identified patients who experienced locoregional recurrence within 5 years of diagnosis. Synchronous distant metastases (within 30 days of locoregional recurrence) were determined. We used multivariable logistic regression to identify factors associated with synchronous metastases.

Results

Four percent experienced locoregional recurrence ($n = 445$). Synchronous distant metastases were identified in 27% ($n = 120$). Initial presenting stage ($P = .03$), locoregional recurrence type ($P = .01$), and insurance status ($P = .03$) were associated with synchronous distant metastases. The proportion of synchronous metastases was highest for women with lymph node (35%), post-mastectomy chest wall (30%), and in-breast (15%) recurrence; 54% received systemic staging imaging within 30 days of a locoregional recurrence.

Conclusion

These findings support current recommendations for systemic imaging in the setting of locoregional recurrence, particularly for patients with lymph node or chest wall recurrences. Because most patients with isolated locoregional recurrence will be recommended locoregional treatment, early identification of distant metastases through routine systemic imaging may spare them treatments unlikely to extend their survival.

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INTRODUCTION

Although less common in the modern era, locoregional recurrence after treatment of breast cancer remains a concern. Locoregional recurrence historically has been considered a risk factor for distant recurrence and associated with a poorer overall prognosis. In retrospective series, between 3% and 68% of patients with locoregional recurrences have synchronous distant metastases at the time of presentation,¹⁻⁸ and many patients who

present with isolated locoregional recurrence do not remain disease free in long-term follow-up.^{9,10}

On the basis of these data, National Comprehensive Cancer Network guidelines recommend systemic staging imaging to evaluate for distant recurrence at the time of a locoregional recurrence.¹¹ However, much of the data upon which these recommendations are based preceded modern era therapy and therefore may not be applicable to contemporary patients with breast cancer. Our primary objective was to determine the rate of synchronous distant recurrence at the time of locoregional

ASSOCIATED CONTENT

Listen to the podcast by Dr Schott at ascopubs.org/jco/podcasts

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recurrence in high-risk patients and to identify clinical factors associated with an increased risk of synchronous metastases. Secondary objectives were to describe the current use of systemic staging imaging per National Comprehensive Cancer Network guidelines and to assess the overall prognostic significance of a locoregional recurrence. The findings from this study will inform the use of systemic staging imaging at the time of locoregional recurrence and provide beneficial information about the prognostic significance of the event during discussions between patients and providers.

METHODS

Data Source

The National Cancer Database (NCDB), created as a joint program between the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society, is a large national cancer registry that captures approximately 70% of all newly diagnosed cancers in the United States. In 2015, an estimated 1,500 CoC-accredited hospital cancer programs participated in the NCDB and contributed data on patient characteristics (ie, sociodemographics, comorbidities), tumor characteristics, first-course treatments received, and survival. The University of Wisconsin Institutional Review Board approved the study.

Patient Cohort and Data Collection Procedure

The current analysis was part of a CoC special study to evaluate recurrence (both local and distant) within the NCDB. Patients were eligible for participation in the special study if they were diagnosed at a CoC-accredited site in 2006 to 2007 with stage II or III breast cancer, were older than age 18 years, and underwent surgical treatment as a part of first-course therapy. Patients diagnosed in 2006 to 2007 were included to ensure 5 complete years of follow-up. Patients with stage I cancer were excluded given their excellent prognosis and lower likelihood of recurrence. Exclusion criteria were a history of cancer before the patient's index breast cancer or a new primary cancer, recurrence (locoregional or distant), or death before the beginning of the abstraction period, which began 3 months after the patient's first surgical procedure.

A stage-stratified sample of 10 patients was selected at random for abstraction from each of the 1,231 CoC facilities that were accredited in 2006 and 2007. We maximized generalizability by randomly selecting a small number of patients at a large number of representative institutions. As part of a special study, cancer registrars abstracted information on date and type of locoregional and distant breast events, imaging received (date, intent of scan, results), biopsies, and mortality. The window for abstraction began 90 days after surgery and continued for 5 years. Breast events were defined as follows: local recurrence (in situ or invasive in-breast recurrence after lumpectomy, new ipsilateral primary after lumpectomy, or chest wall recurrence after mastectomy), regional recurrence (ipsilateral supraclavicular or ipsilateral axillary lymph nodes), and distant recurrence (visceral, bone, distant nodal recurrence, or other). All patients were followed for 5 years unless they developed a distant recurrence or died, at which point they were censored; abstraction continued after a locoregional breast event. A total of 1,217 facilities participated (99%), with 11,360 patient records submitted. An additional 314 patients were excluded because they developed recurrence before completion of active treatment ($n = 139$), had an unknown date of surgery ($n = 165$), or had an unknown recurrence date ($n = 16$). The final sample size was 11,046 patients.

Outcome Variables

The primary outcome of interest for this study was the presence of synchronous distant metastases at the time of a locoregional recurrence. We defined a synchronous distant metastasis as one diagnosed within

30 days of a locoregional recurrence. Of the patients with a locoregional recurrence, 55% of distant metastases were identified within this 30-day window. The remaining distant metastases were identified a median 338 days (interquartile range, 188 to 650 days) from the locoregional recurrence (Appendix Fig A1, online only).

Secondary outcomes were the use of systemic staging imaging (computed tomography [CT] scans, positron emission tomography/CT scans, magnetic resonance imaging) at the time of locoregional recurrence. We considered imaging that occurred 30 days before and through 30 days after the date of a locoregional recurrence to be staging imaging. We also examined 5-year overall survival.

Explanatory Variables

Patient characteristics included age at diagnosis, race, and insurance status. Tumor characteristics included stage, tumor size, nodal status, estrogen/progesterone receptor status, and human epidermal growth factor receptor 2 status at the time of diagnosis. Site registrars specifically abstracted human epidermal growth factor receptor 2 status during the special study because it had not been systematically recorded during the 2006 to 2007

Table 1. Patient, Tumor, and First-Course Treatment Characteristics at Initial Presentation

Characteristic	Overall Cohort, No. (%)
No. of patients	11,046
Age group, years	
≤ 50	3,061 (28)
> 50-70	5,192 (47)
> 70	2,793 (25)
Race	
White	9,299 (84)
Black	1,282 (12)
Other	465 (4)
Insurance status	
Private	5,941 (54)
Uninsured	478 (4)
Medicaid	832 (8)
Medicare or other government	3,795 (34)
Stage	
II	7,801 (70)
III	3,245 (30)
Tumor size, cm	
≤ 2	3,126 (28)
2-5	6,442 (58)
> 5	1,277 (12)
Node	
Negative	3,544 (32)
1-3 positive	4,620 (42)
≥ 4 positive	2,572 (23)
Unknown	310 (3)
ER/PR	
ER or PR positive	8,261 (75)
ER and PR negative	2,637 (24)
Unknown	117 (1)
HER2	
Amplified	2,117 (19)
Not amplified	8,161 (74)
Unknown	768 (7)
Locoregional treatment (first course)	
Breast-conserving surgery	542 (5)
Breast-conserving surgery plus radiation	4,298 (39)
Mastectomy	3,173 (29)
Mastectomy plus radiation	2,814 (26)
Receipt of chemotherapy	8,077 (73)
Receipt of endocrine therapy	7,355 (67)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

Table 2. Proportion of Locoregional Recurrence by Type of Breast Surgery Received as Part of First-Course Treatment

Recurrence Type	Treatment, No. (%)		
	All Surgery Types	Breast-Conserving Surgery*	Mastectomy*
No. of patients	11,046	4,929	6,117
Locoregional	445 (4)	200 (4)	246 (4)
Lymph node†	164 of 445 (37)	56 of 200 (23)	108 of 246 (44)
Chest wall	137 of 445 (31)	NA	138 of 246 (56)
In-breast	144 of 445 (32)	144 of 200 (72)	NA

Abbreviation: NA, not applicable.

*With or without radiation.

†Some patients with lymph node recurrences also had chest wall or in-breast recurrence.

study period. First-course treatment covariates were type of surgery and receipt of radiation, chemotherapy, and hormonal/endocrine therapy. We categorized a priori the type of locoregional recurrence as ipsilateral in-breast after breast-conserving surgery, chest wall after mastectomy, and lymph node (ipsilateral supraclavicular lymph node or ipsilateral axillary lymph nodes with or without a concomitant breast/chest wall recurrence).

Analysis

We calculated the proportion of patients with locoregional recurrences within 5 years and described the types of locoregional recurrences. The χ^2 test was used to compare the distribution of patient, tumor, and treatment characteristics for patients with and without a locoregional recurrence. We then calculated the proportion of patients with synchronous distant metastases. Multivariable logistic regression was used to determine factors associated with synchronous metastases at the time of locoregional recurrence.

We summarized the type of systemic staging imaging performed at the time of locoregional recurrence and used χ^2 tests to determine patient factors associated with the receipt of systemic staging imaging. Finally, Kaplan-Meier survival curves were estimated for patients with and without locoregional recurrence. Patients were censored at the time they were lost to follow-up (4% of the overall cohort). Multivariable Cox proportional

hazards regression was used to evaluate the impact of the various types of locoregional events on the number of days from diagnosis to death within 5 years.

RESULTS

As defined by the sampling strategy, 70% of the 11,046 patients in the study had stage II cancer and 30% had stage III cancer at diagnosis. Patient demographic, tumor, and treatment characteristics for the overall cohort are listed in Table 1. A locoregional recurrence was detected in 4% of patients (445 of 11,046) within the first 5 years after diagnosis (Table 2). An additional 1,305 patients experienced distant recurrence without a local recurrence during the study period.

Staging Imaging Performed at Time of Locoregional Recurrence

Fifty-four percent of patients (n = 240) who experienced a locoregional recurrence underwent systemic staging imaging

Fig 1. Overview of locoregional and distant recurrence (DR) on the basis of imaging at time of locoregional recurrence.

within 30 days of the recurrence (Fig 1); 103 patients underwent positron emission tomography/CT imaging as the first imaging study after a locoregional recurrence (43%), whereas the remaining 126 received a combination of chest, abdomen, and pelvic cross-sectional imaging and bone scans. Brain imaging was performed for only 11 patients (5%). Receipt of systemic imaging varied by type of recurrence, with 67% of patients with lymph node recurrences, 53% with postmastectomy chest wall recurrences, and 40% with in-breast recurrences undergoing imaging ($P < .001$). The only other factors associated with receipt of imaging was receipt of chemotherapy as part of first-course treatment (59% v 43% who received v did not receive chemotherapy, respectively; $P = .003$) and stage (55% v 45% with stage II v stage III disease at presentation, respectively; $P = .03$).

Another 22% of patients with locoregional recurrence but no synchronous metastases developed distant recurrence during the study period (Fig 1). No difference was found in likelihood of developing future distant recurrences on the basis of receipt of imaging at time of locoregional recurrence (no imaging, 27%; imaging 34%; $P = .2$).

Presence of Synchronous Metastatic Disease at Time of Locoregional Recurrence

Twenty-seven percent of patients with a locoregional recurrence had synchronous distant metastases within 30 days (Fig 1). After controlling for patient demographic, tumor, and first-course treatment characteristics, the factors most strongly associated with the presence of synchronous distant metastases at the time of a locoregional recurrence were the initially presenting clinical stage and the type of locoregional recurrence (Table 3). Thirty-five percent of patients with lymph node recurrence had synchronous distant metastases compared with 30% with a postmastectomy chest wall recurrence and 15% with an in-breast recurrence (Fig 2). Furthermore, 37% of patients who presented initially with stage III disease versus 20% who presented with stage II disease had synchronous distant metastases. Patients with stage III disease and a lymph node or chest wall recurrence were more likely to have a synchronous distant metastases than those with stage II disease; no difference by stage was seen for patients with an in-breast recurrence (Appendix Table A1, online only).

Overall Prognostic Significance of a Locoregional Recurrence

Overall survival was poorer for patients with a locoregional recurrence (5-year survival: chest wall recurrence, 46%; lymph node recurrence, 53%; in-breast recurrence, 71%) compared with patients who did not experience a recurrence (5-year survival, 82%; Fig 3). Of the cohort with a locoregional recurrence, 51% remained without distant recurrence during the study period (synchronous distant recurrence, 26%; nonsynchronous distant recurrence, 22%). The observed poorer prognosis for patients with a locoregional recurrence remained true on adjusted analysis, especially for patients who experienced a postmastectomy chest wall recurrence (hazard ratio [HR], 3.0; 95% CI, 1.2 to 3.7) or a lymph node recurrence (HR, 2.6; 95% CI, 1.1 to 3.2). However, even patients who experienced an in-breast recurrence after breast-conserving surgery experienced poorer overall survival (HR, 1.6; 95% CI, 1.2 to 2.1).

Table 3. Multivariable Analysis of Factors Associated With the Presence of Synchronous Distant Metastases at the Time of Locoregional Recurrence (n = 445)

Characteristic	OR (95% CI)	P
Patient		
Age group, years		
≤ 50	Ref	
> 50-70	0.9 (0.5 to 1.6)	.600
> 70	0.4 (0.2 to 1.0)	.100
Race		
White	Ref	
Black	1.1 (0.6 to 2.0)	.800
Other	1.5 (0.4 to 6.2)	.500
Insurance status		
Private	Ref	
Uninsured	1.4 (0.4 to 4.8)	.600
Medicaid	2.0 (0.9 to 4.8)	.100
Medicare or other government	2.8 (1.3 to 5.8)	.010
Cancer at initial presentation		
Stage		
II	Ref	
III	1.7 (1.1 to 3.0)	.040
Estrogen/progesterone receptor		
Positive	1.1 (0.5 to 2.4)	
Negative	Ref	.800
HER2		
Not amplified	Ref	
Amplified	0.7 (0.4 to 1.2)	.200
Unknown	0.4 (0.1 to 2.0)	.300
Treatment of initial cancer		
Chemotherapy	0.9 (0.5 to 1.9)	.800
Endocrine therapy	1.0 (0.5 to 2.2)	.900
Radiation therapy	1.7 (1.0 to 3.1)	.100
Location of locoregional recurrence		
Ipsilateral breast	Ref	
Chest wall	2.1 (1.0 to 4.5)	.040
Lymph node	2.1 (1.1 to 4.2)	.030
Receipt of systemic imaging	4.8 (2.7 to 8.4)	< .001

NOTE. Boldface indicates significance at $P < .05$.

Abbreviations: HER2, human epidermal growth factor receptor 2; OR, odds ratio; Ref, reference.

DISCUSSION

In this national cohort of patients with stage II and III breast cancer, locoregional recurrence as the first breast cancer event after definitive treatment occurred uncommonly. However, we found that 27% of patients with a locoregional recurrence had synchronous distant metastases at the time of their locoregional breast event. Furthermore, these locoregional events were associated with poorer overall survival, especially for patients with postmastectomy chest wall or lymph node recurrences. These findings are consistent with those from older studies¹⁻¹⁰ and demonstrate that locoregional recurrences are prognostically significant, even in the face of modern-era treatment.

In the current study, the risk of synchronous distant metastases differed significantly on the basis of the initial presenting stage and type of locoregional recurrence. At baseline, patients with stage III disease versus stage II disease had an increased risk of developing distant metastases¹²; thus, a higher risk of synchronous distant metastases at the time of a locoregional event also can be observed on the basis of stage. Variation according to type of locoregional recurrence is consistent with clinical acumen because

Fig 2. (A) Proportion of patients with synchronous distant metastases on the basis of type of locoregional recurrence. (B) Proportion of patients with synchronous distant metastases on the basis of initial presenting stage.

chest wall and lymph node recurrence both can be perceived as an indication of more-aggressive disease (as demonstrated in Fig 1). In contrast, in-breast recurrence is an expected event in a defined proportion of patients.^{13,14} The finding that 15% of patients with in-breast recurrence after breast conservation had synchronous distant recurrence, regardless of the initial presenting clinical stage, suggests that in-breast recurrence represents more than a strictly local process.

Although the majority of patients (58%) received systemic staging imaging at the time of a locoregional recurrence, the absolute rate varied significantly on the basis of the type of locoregional recurrence. Providers appear to have strong intuitions about which types of locoregional events were more likely to have synchronous distant metastases because they were significantly more likely to scan patients with postmastectomy chest wall or lymph node recurrences. However, synchronous distant metastases were relatively common regardless of the type of recurrence. The presence of distant recurrence may affect recommended treatment of the locoregional recurrence because limited, if any, surgery and/or radiation likely would be recommended if distant metastases are identified. Providers should consider systemic imaging for patients with locoregional recurrence who may be at a relatively higher risk

of synchronous distant metastasis, specifically those with post-mastectomy chest wall or lymph node recurrences.

Some limitations to this study exist. First, the data were collected retrospectively by site registrars not directly involved in the patients' care, which may have led to inaccuracies in the data, although measurement error is not likely to have affected the groups differentially. Direct chart abstraction was necessary to obtain the level of detail required. To minimize risk of error, we provided detailed abstraction instructions for the special study, piloted the data abstraction with the registrars at our own institution as well as at 18 other CoC facilities, and convened weekly registrar webinars to address commonly experienced issues. Second, we were unable to distinguish patients who presented with symptomatic versus asymptomatic distant metastases. Although this field was abstracted by registrars, the working definition of this variable made clear differentiation between symptoms from local and distant metastases difficult. The registrars were instructed to document why imaging was ordered; options included both follow-up for new sign/symptom and imaging performed as part of staging work-up for newly detected malignancy. Both definitions could be appropriate for patients who present with a new locoregional recurrence. We included only patients with stage II and III breast cancer. The sampling strategy led to a cohort where 70% of the patients had stage II disease and 30% had stage III and does not reflect the distribution of breast cancer in the general population, which limits the generalizability of the findings to patients with earlier-stage cancer who may have a lower baseline risk of distant metastases. In addition, the sampling strategy abstracted 10 patients per CoC institution, regardless of the underlying breast cancer volume at the institution. This approach may overweigh the experience of low-volume institutions. Next, we defined a priori synchronous distant metastases as those diagnosed within 30 days of a local recurrence. The sample included 14 patients diagnosed with distant metastases between 30 and 90 days after a local recurrence. Therefore, our definition of synchronous metastases may slightly underestimate the true likelihood of synchronous metastases. Furthermore, given the relatively low rate of locoregional events, we were unable to perform subgroup analyses that examined factors associated with synchronous metastases within each recurrence type (ie, factors associated with synchronous metastases among patients with a lymph node recurrence). Finally, this retrospective cohort study was in patients

Fig 3. Overall survival on the basis of type of first recurrence.

who did not routinely receive systemic imaging. Variation in use of imaging by type of recurrence, therefore, may explain some of the variability in frequency of synchronous distant metastases. However, we saw no difference in late distant recurrence during the study period for patients who did or did not undergo imaging.

In conclusion, the findings support the consideration of systemic staging imaging at the time of a locoregional recurrence for patients who present initially with stage II or III breast cancer. These patients may have a moderate risk for synchronous distant metastases, especially those with postmastectomy chest wall or lymph node recurrences. Whether early identification of these distant metastases improves survival is unclear (and unanswerable on the basis of these data). However, because all these patients will undergo additional treatment of their locoregional recurrence, early identification of distant metastases through routine systemic staging imaging at the time of locoregional recurrence may spare them unnecessary surgical and radiation treatment and lead to improved quality of life in the face of a life-threatening illness.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Fig A1. Time between local recurrence and distant recurrence.

Table A1. Proportion of Synchronous Distant Metastases on the Basis of Initial Presenting Stage and Type of Locoregional Recurrence			
Recurrence Site	Breast Cancer Stage, No. (%)		
	Stage II	Stage III	Any Stage
No. of patients	265	180	445
Lymph Node	28 of 95 (30)	30 of 69 (43)	58 of 164 (35)
Chest Wall	8 of 52 (15)	33 of 85 (39)	41 of 137 (30)
In-breast	17 of 118 (14)	4 of 26 (15)	21 of 144 (15)