Original Study

Incidence and Patterns of Distant Metastases for Patients With Early-Stage Breast Cancer After Breast Conservation Treatment

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Abstract

This study analyzed the risk and pattern of distant metastases after breast conservation therapy (BCT) for early-stage breast cancer using a competing risk model. Non–breast cancer deaths were the most common event and bone was the most common metastatic site. There was no clinically relevant increased risk of metastases at a specific site based on any patient characteristic examined. Site-specific imaging should be driven by concerning patient-specific signs or symptoms.

Background: Breast conservation treatment (BCT), consisting of breast conservation surgery followed by definitive radiation therapy (RT), has been shown to be effective for early-stage breast cancer. Patterns of metastatic failure by specific anatomic site are not well described in the literature. **Methods:** A total of 1754 patients with stage I or II invasive carcinoma of the breast treated with BCT between 1977 and 2003 were identified. Patients were scored based on first site of metastasis: bone, brain, lung, liver, or other. Non–breast cancer deaths, contralateral breast cancer, and second malignancies were treated as competing risks events. Cumulative incidence functions for each competing event were calculated using competing risk methodology. Univariate analysis was performed to determine the hazard ratio (HR) associated with patient and tumor characteristics. **Results:** The most common event was non–breast cancer death (16.5% at 15 years; 95% confidence interval [CI], 13.9%-19.4%). The most common exclusive first site of metastasis was bone (5.9% at 15 years). The 4 most common anatomic sites of distant metastases as the first exclusive event were bone (41.1%), lung (22.4%), liver (7.3%), and brain (7.3%). **Conclusion:** The present study has demonstrated the site-specific risks of metastases. These data support current clinical practice of screening for site-specific metastatic disease after BCT based on concerning patient-specific signs or symptoms.

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Introduction

Breast conservation treatment (BCT), consisting of breast conservation surgery followed by definitive radiation therapy (RT), has been shown to be effective for early-stage breast cancer. Six large randomized trials have shown equivalent survival outcomes of BCT compared with mastectomy.[1-6] In addition, BCT has the potential advantage of improved cosmesis. Despite multimodality treatment, approximately 20% to 30% of women with early-stage breast cancer still experience distant metastases.[7-10] Breast cancer remains the leading cause of cancer-related deaths worldwide among women, largely secondary to the impact of distant metastases.[11]

Patterns of metastatic failure by specific anatomic site are not well described in the literature. In addition, methods to predict which patients will experience metastases and at which sites remain limited. Predicting the incidence of metastases at specific sites could allow physicians to more accurately identify patients for specific screening and prevention methods and to better tailor individualized clinical management.

The current analysis was performed to examine the incidence and patterns of the development of metastases at specific sites—including brain, lung, bone, and liver—in women with early-stage breast cancer who were treated with BCT. This study aims to identify patient

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and tumor characteristics as well as other prognostic factors associated with the development of metastases.

Methods

The study cohort was derived from the 1902 consecutive women with invasive carcinoma of the breast treated with breast conservation surgery followed by definitive RT at the Hospital of University of Pennsylvania between 1977 and 2003. All women had unilateral invasive carcinoma of the breast at presentation. Patients with a contralateral breast or a nonbreast second malignancy (excluding nonmelanoma skin cancers) diagnosed before or during radiation were excluded from analysis (n = 134). One patient in whom a peritoneal metastasis developed as the first and only site of metastatic disease was not included because of the limitation of the statistical model. Patients who died of breast cancer but without recorded evidence of distant metastases or a contralateral breast malignancy were excluded from analysis (n = 13). Therefore the final study cohort consists of 1754 patients.

All women presented with American Joint Committee on Cancer *(AJCC) Staging Manual,* 5th edition, clinical and pathologic stage I or II (T1-2N0-1) disease.[12,13] Patients who had 4 or more pathologically positive lymph nodes, classified by *AJCC Staging Manual*, 5th edition, as N1 disease, were reclassified as pN2 or pN3 disease (stage III) based on the AJCC *Staging Manual,* sixth and seventh editions. The surgical treatment in all patients included surgical excision (lumpectomy) of the primary tumor. Patients also underwent axillary lymph node staging either through sentinel lymph node mapping and biopsy or through an axillary lymph node dissection, generally encompassing levels I and II.

The study population was limited to women who received standard tangent radiation fields with a primary tumor bed boost to a total tumor bed dose (sum of tangential fields and breast boost) of ≥60 Gy. The median dose of the whole breast tangential fields was 46 Gy (mean, 46.10 Gy; range 44-52.67 Gy) within 4.5 to 5 weeks. The radiation energy used was generally 6-MV photons, but higher energies were used as indicated for a larger separation between the medial and lateral aspects of the chest wall. The boost was delivered using electrons of varying energy in 1587 women (90.5%), iridium implants in 140 women (8%), orthovoltage in 8 women (0.5%), and photons in 19 women (1%). The median total dose to the tumor bed was 63 Gy (mean, 64.84 Gy; range, 60-72.40 Gy). The clinical decision regarding the total dose was based on a variety of factors, including final margin status of the primary tumor excision, whether or not reexcision was performed, the presence or absence of tumor at reexcision if performed, and the volume of the boost field. Radiation methods at our institution have been previously described.[7,9]

The median follow-up time, defined from the start of RT, among 1754 patients was 7.4 years (range, 27 years). Metastatic disease was defined as the presence of metastatic disease diagnosed by radiologic imaging studies and clinical evaluation. Pathologic confirmation was not required for the diagnosis of metastatic disease. Clinical records for these patients were reviewed and the site of metastasis, date of diagnosis of metastasis, and whether it was the first, second, or third site was recorded. Patients were scored based on first site of metastasis: bone, brain, lung, liver, or other.

Patient, tumor, and treatment characteristics were summarized by descriptive statistics. Overall survival was defined from the start date of the RT to the date of death from any cause or the date censored at last follow-up. Patients were scored as distant metastases developing at the time of the first evidence of distant metastatic disease after the start of RT. Deaths from causes other than breast cancer, development of contralateral breast cancer, and a new second malignancy occurring before any distant metastases were treated as competing risks events. Second malignancies were non–breast cancers that were diagnosed after initial breast cancer diagnosis and treatment, excluding nonmelanoma skin cancers. Cumulative incidence functions, ie, the failure probabilities before experiencing any events, for each competing event were calculated using competing risk methodology.[12,13]

In metastatic site–specific analysis, the event of distant metastases was further divided into 5 categories; exclusive first site of metastasis (brain, bone, lung, liver) or multiple sites of first metastases. More than 1 site of metastases occurring within 1-month intervals of each other was considered as multiple sites of metastases. The cumulative incidences of each site of metastasis were calculated.

Fine and Gray's competing risk regressions for the hazard ratio (HR)[14] were used to evaluate whether any patient, tumor, or treatment characteristics were associated with the risk of distant metastases at specific sites. This approach is similar to the usual Cox proportional hazards regression model that provides estimation of HRs to measure covariate effects but allows other competing events to influence failure. Because of limited failures in some distant metastatic sites, only univariate analyses were performed. All statistical tests were 2 sided, and P values $< .05$ were considered statistically significant.

Results

Table 1 lists the patient and tumor characteristics. Median age was 54 years (mean, 54 years; range, 21–89 years). Most patients had node-negative disease (66.1%) with negative margins at the primary tumor resection (59.5%). Adjuvant chemotherapy was given in 20.4% of patients, hormonal therapy was given in 19.7% of patients, and both chemotherapy and hormonal therapy were administered in 16.1% of patients.

The 5-, 10-, and 15-year cumulative incidence of each competing event is shown in Table 2 and displayed in Figure 1. The most common event for patients with early-stage breast cancer was non–breast cancer death, at a failure probability of 16.5% (95% CI, 13.9%-19.4%) by 15 years. It can be seen that the risk of death from non–breast cancer deaths begins to exceed breast cancer deaths about 17 years after the start of radiotherapy (Figure 1). The most common exclusive first site of distant metastasis was bone at every time point, including a failure probability of 5.9% (95% CI, 4.6-7.4%) at 15 years (Table 2). Contralateral breast malignancies are more common than second malignancies.

The 4 most common anatomic sites of distant metastases as the first exclusive event were bone (41.1%), lung (22.4%), liver (7.3%), and brain (7.3%). In 21.9%, there were multiple sites of disease at presentation of metastatic spread (Table 3). Figure 2 shows that the majority of first metastases occur by 15 years but there are first events occurring 20 years after RT as well.

Univariate analysis of the patient and tumor characteristics with site-specific distant metastases was performed (Table 4). Patient or

Table 1 Patient and Tumor Characteristics

Variable	n	%
Age at Diagnosis (y)		
20-39	226	12.9
40-49	444	25.3
50-59	515	29.4
60-69	369	21
70-89	30	1.7
Year of RT Treatment		
1977-1990	920	52.5
1991-2003	834	47.6
Tumor Size (cm)		
≤ 2.0	753	42.9
2.0-5.0	356	20.3
Unknown	645	36.8
Pathologic T Stage		
T1	1337	76.2
T2	417	23.8
Pathologic N Stage		
Node negative	1160	66.1
Node positive	416	26.2
1-3 positive lymph nodes	317	76.2
4-9 positive lymph nodes	71	17.1
≥ 10 positive lymph nodes	28	6.7
Unknown	178	10.2
Final Margins of Primary Tumor Resection		
Negative	1022	59.5
Positive	136	7.9
Close	188	11
Unknown	371	21.6
Pathologic Staging		
T1, node negative	1041	59.4
T2, node negative	254	14.5
T1, node positive	296	16.9
T2, node positive	163	9.3
Total Radiation Dose to Tumor Bed (Gy)		
60-63	900	51.3
> 63	854	48.7
Estrogen Receptor Status		
Positive	1006	57.4
Negative	387	22.1
Not obtained/unknown	361	20.1
Progesterone Receptor Status		
Positive	798	45.5
Negative	485	27.7
Not obtained/unknown	471	26.9
HER2 Status		
Positive	150	8.6
Negative	429	24.5
Not obtained/unknown	1175	67
Adjuvant Therapy		
None	768	43.8
Chemotherapy alone	357	20.4
Hormonal therapy alone	345	19.7
Chemotherapy and hormonal therapy	282	16.1

Abbreviations: HER2 = human epidermal growth factor receptor 2; RT = radiation therapy

Table 2 Estimated Cumulative Incidence of Non–Breast Cancer Death, Distant Metastasis, Contralateral Breast Cancer, and Second Malignancy Using Competing Risk Analysis

Variable	5 Years	10 Years	15 Years
Non–Breast Cancer Death	3.4	8.2	16.5
Distant Metastasis			
Isolated brain	0.6	0.7	1.3
Isolated bone	3.6	5.5	5.9
Isolated lung	2.2	2.9	3.2
Isolated Liver	0.5	1.8	0.2
Multiple sites of first metastases	1.8	2.8	3.1
Contralateral Breast Cancer	3.7	7.8	10.3
Second Malignancy	2.0	4.4	6.2

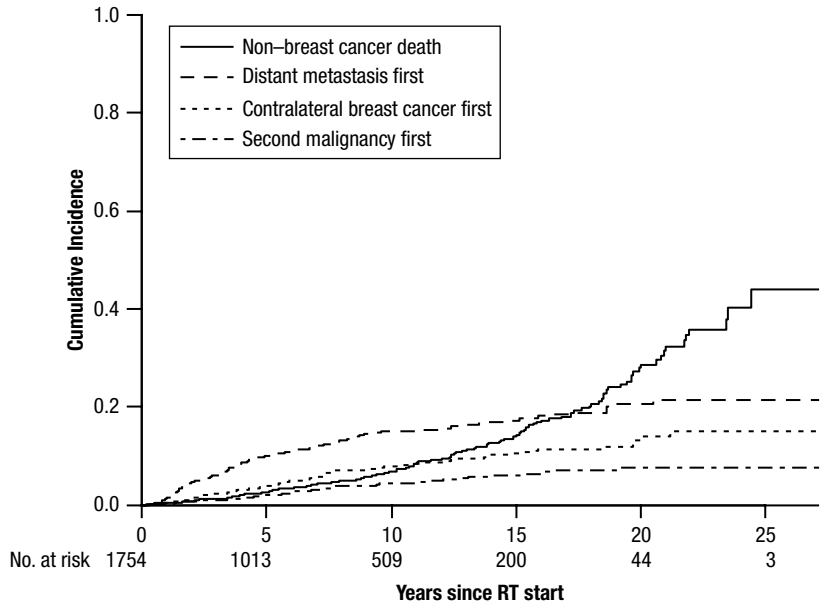
tumor characteristics were identified that were associated with an increased risk of distant metastases at specific sites.

Discussion

These results document the incidence and patterns of distant metastases and confirm that BCT has favorable results in women with early-stage invasive breast carcinoma through 15 years after treatment. Nonetheless, a significant number of distant metastases do occur at least 15 years after BCT, indicating that physicians should be mindful of any patient symptoms that could indicate new metastatic disease even many years after definitive treatment. A number of patient and tumor characteristics as well as treatment modalities may alter the risk of site-specific distant metastases, but the risk is not large enough to justify personalized surveillance after BCT.

As survival rates improve with earlier detection and increased use of more efficacious chemotherapy and targeted agents, there is expected to be a commensurate increase in the prevalence of early breast cancer survivors who are at risk for the development of metastatic disease. Currently, the American Society of Clinical Oncology and the National Comprehensive Cancer Network guidelines for patients with early-stage breast cancer include semiannual or annual history,

Figure 1 Cumulative Incidence of Non–Breast Cancer Death, Distant Metastases, Contralateral Breast Malignancy, and Second Malignancy as First Events After BCT



Abbreviation: RT = Radiation Therapy.

Table 3 Distribution of the First Event by Specific Distant Metastases Sites

	n	%
Death (Non–Breast Cancer)	185	10.6
DM		
Isolated Brain	14	0.8
Isolated Bone	79	4.5
Isolated Lung	43	2.5
Isolated Liver	14	0.8
Multiple sites of first metastases	42	2.4
CLB	120	6.8
SMN	68	3.9
Total	585	

Abbreviations: CLB = contralateral breast; DM = distant metastasis; SMN = second malignancy.

physical examination, and mammogram but no routine laboratory or imaging of potential metastatic sites.[15,16] The results of this study reinforce this current practice by showing that there is no site of metastasis with a large enough increased risk for any given patient or tumor characteristic to justify site-specific metastatic screening.

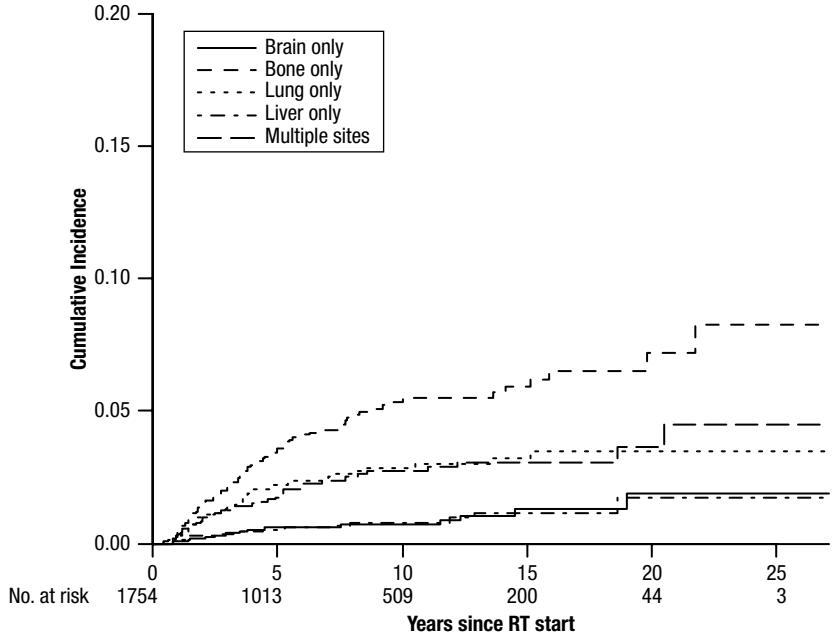
The overall rates of distant metastases seen in this study are consistent with previous studies. Our institution previously reported on the 15-year results of BCT, in which 13% of patients experienced distant metastases as the first event (defined as local, regional, distant recurrent, contralateral breast cancer, or second malignancy).[9] The distant metastasis rate from the National Surgical Adjuvant Breast and Bowel Project B-06 is also comparable at a distant metastasis rate as the first event at 20 years of 25%.[1] With the advancement of systemic treatment and improved overall patient outcomes, the current rate of distant metastases are likely less than that published in this study.

We found that bone metastases were the most common metastatic site overall and as any first site or the exclusive first site of metastasis. Lung, liver, and brain were the next most common sites, in descending order of incidence. This is consistent with data reported by Kennecke et al who found that bone is the most likely metastatic site for all cancer subtypes, with the exception of basal-type tumors, which are associated with high rates of lung metastases (18.5%).[17]

There are several important conclusions from these data. First, distant metastases occur in all 4 major metastatic sites 15 years or more after RT. Second, bone is the most common site of metastasis and often occurs in isolation. Third, brain is the least common site and can occur in isolation but at a lower risk. Forth, it is common for patients to present with multiple sites of metastasis initially. Therefore treating physicians should consider a lower clinical threshold for additional imaging at the time of diagnosing metastasis if there is a clinical suggestion of another site of metastasis. Fifth, there were multiple statistically significant increases in the risk of a specific metastatic site based on a patient or tumor characteristic; however, the HRs generally contain large CIs. Therefore these data do not support the use of site-specific metastatic screening.

Efforts have been made to establish predictive guidelines for the development of a given metastatic site. Graesslin et al found that age,

Figure 2 Cumulative Incidence of Exclusive First Site-Specific Metastasis Including Brain, Bone, Lung, and Liver as Competing Events, Along With Multiple Sites of First Metastases



Abbreviation: RT = Radiation Therapy.

grade, negative estrogen receptor (ER) status, negative human epidermal growth factor receptor 2 (HER2) status, number of metastatic sites, and short disease-free survival are all independent and significant predictors of the development of brain metastasis. The authors then developed a nomogram to predict the probability of brain metastasis in nonbrain metastatic disease: Prognostic points are assigned for age; histologic grade; status of ER, progesterone (PR), and HER2; delay between diagnosis and first metastasis; and number of metastatic sites.[18]

The presence of steroid hormone receptors in breast cancer produces conflicting results in predicting the incidence of distant metastasis. Several studies have shown ER/PR presence to decrease the incidence of distant metastasis,[19] others show an unchanged incidence in the setting of hormonal therapy,[20] and yet others demonstrate an increase in the incidence.[21] ER-negative (ER^-) tumors have been shown to be associated with early metastasis relative to ER-positive (ER^+) tumors.[17,22,23] These conflicting data support this study in the conclusion that it is not appropriate to screen a population for site-specific metastasis given the presence or absence of steroid hormone receptors.

One limitation of this study is that the adjuvant therapy used during the era of this cohort is not necessarily representative of modern-era adjuvant chemotherapy, hormonal therapy, and biological therapy, such as anti-HER2 therapy with trastuzumab. For example, despite the majority of tumors being ER^+/PR^+, only 36% of patients received adjuvant hormonal therapy. In addition, most of the tumors reported in the present study predate the era of routine HER2 testing, and trastuzumab for $HER2^+$ breast cancer was introduced after the majority of patients in our cohort were treated, although trastuzumab has been shown to reduce recurrence risk.[24] The trends in increased use of chemotherapy and the use of hormonal therapy and targeted agents could affect both the cumulative probability of distant metastases and the relative incidence at each metastatic site.

With regard to identification of metastases, we identified each metastatic site by conventional imaging (radiography, bone scan, computed tomography, and magnetic resonance imaging). There could exist a misclassification bias in that metastases too small for detection by imaging were not detected and radiographic findings that were suggestive of tumor could in fact be benign, as biopsy confirmation was not required for classification in our study nor is it routinely used in clinical practice. This potential for misclassification bias, however, affects all patient subgroups.

Conclusion

This study reports the 15-year incidence of specific metastatic sites (brain, lung, bone, and liver) in a large cohort of women with early-stage breast cancer treated with BCT at a single institution and followed prospectively. Distant metastasis is a frequent, incurable outcome after BCT and can occur at least up to 15 years after primary treatment. We have added to the expanding knowledge of patient and tumor characteristics and treatment modalities associated with the development of metastases. The risk of multiple sites of metastases was increased by specific characteristics; however, the magnitude

Table 4 Univariate Analysis of Exclusive Site of First Metastasis and Multiple Sites by Risk Factors

Variable	Brain		Bone		Lung		Liver		Multiple	
	HR	*P* Value	HR	*P* Value	HR	*P* Value	HR	*P* Value	HR	*P* Value
Age at Diagnosis	0.91	0	0.99	.12	0.98	.07	0.97	.14	0.98	.21
Year of RT Treatment										
1991-2003 vs. 1999-1990	0.56	.37	0.74	.23	0.17	< .01	0.79	.68	1.1	.77
Total Radiation Dose to Tumor Bed										
> 63 vs. 60-63 Gy	1.19	.74	1.23	.36	2.79	< .01	3.33	.06	0.77	.39
Pathologic T Stage										
T2 vs. T1	2.31	.12	2.31	0	2.29	< .02	4.14	< .01	1.41	.3
Pathologic N Stage										
N1 vs. N0	1.1	.88	3.44	0	2.02	.02	2.77	.06	1.56	.17
Final Margins of Primary Tumor Resection										
Positive vs. negative	1.51	.6	1.74	.12	0.72	.66	3.11	.19	0.73	.6
Close vs. negative	NA	NA	1.38	.37	1.71	.25	1.27	.83	0.39	.19
Unknown vs. negative	1.07	.92	1.27	.4	2.37	.01	3.92	.03	0.89	.75
Estrogen Receptor Status										
Negative vs. positive	3.79	.02	0.63	.13	2.97	< .012	0.67	.61	1.25	.55
Unknown vs. positive	0.93	.94	0.42	.01	1.57	.27	1.19	.79	0.71	.43
Progesterone Receptor Status										
Negative vs. positive	2.08	.28	0.78	.37	1.49	.29	1.33	.67	2.15	.03
Unknown vs. positive	1.65	.46	0.51	.02	1.46	.3	1.35	.65	0.75	.51
HER2 Status										
Positive vs. negative	NA	NA	0.51	.38	NA	NA	NA	NA	0.7	.66
Unknown vs. negative	2.79	.32	1.43	.29	3.44	.04	0.8	.73	0.96	.92
Adjuvant Therapy										
Chemotherapy alone	3.03	.05	2.5	< .011	1.19	.62	6.05	< .019	1.32	.45
Hormonal therapy alone	0.49	.51	1.95	.03	0.32	.06	1.98	.47	0.26	.07
Chemotherapy and hormonal therapy	NA	NA	1.91	.06	0.4	.14	2.57	.31	1.35	.47

Abbreviations: HER2 = human epidermal growth factor receptor; HR = hazard ratio; NA = not available; RT = radiation therapy.

of this risk is too small for the routine surveillance of site-specific metastases. The recommended practice guidelines with routine history, physical examination, and mammography should remain the standard for surveillance after BCT. Site-specific imaging should be driven by concerning patient-specific site or symptoms.

Clinical Practice Points

- BCT, consisting of breast conservation surgery followed by definitive RT, has been shown to be effective for early-stage breast cancer.
- Patterns of metastatic failure by specific anatomic site are not well described in the literature.
- Using competing risks methodology, we identified that the most common event after BCT was non–breast cancer death (16.5% at 15 years).
- The most common exclusive first site of metastasis was bone (5.9% at 15 years).
- The 4 most common anatomic sites of distant metastases as the first exclusive event were bone (41.1%), lung (22.4%), liver (7.3%), and brain (7.3%).
- On univariate analysis, multiple distinct patient, tumor, and treatment characteristics increased the risk of distant metastases to specific sites.
- These data support current clinical practice of screening for site-specific metastatic disease after BCT based on concerning patient-specific signs or symptoms.

Disclosure

The authors have stated that they have no conflicts of interest.

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