Temporality and Patterns of Metastatic Recurrence in Node-Positive Breast Cancer Following Trimodality Therapy

Opportunity for Improved Oligometastases Detection and Salvage Local Therapy

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Objectives: There is evidence that detection and treatment of oligometastases (≤ 5 lesions) may improve survival in breast cancer patients. However, there are no current national guidelines for screening of early, asymptomatic metastases. This study examined the patterns and timing of recurrence with respect to survival in node-positive breast cancer (NPBC) patients at higher risk for developing metastases.

Methods: A single-institution retrospective review of NPBC patients treated with trimodality therapy was performed to collect patient and disease characteristics, recurrence location, method of detection, and survival outcome. Univariate and multivariate analyses were done to identify factors associated with recurrence.

Results: Ninety-four NPBC patients treated at a safety-net hospital between 2008 and 2019 were identified. Twenty-one developed recurrence and were divided into oligometastatic (OM) (n = 10) or diffusely metastatic (DM) (n = 11) subgroups. Median recurrence-free survival in OM and DM was 18 and 36 months, respectively. Median overall survival (OS) for OM was not reached. Median OS for DM was 57 months. Four patients with OM progressed to diffuse disease in a median period of 17 months; median survival thereafter was 57 months. All patients with recurrence had distant metastases on initial detection, with the most common site being bone (14). Recurrence was most frequently detected by computed tomography (CT) (13), with the majority of disease located within the thorax region.

Conclusions: All NPBC patients had distant metastasis at time of recurrence. Patients with OM had shorter interval to recurrence yet longer OS compared with DM. This study highlights improved surveillance imaging for timely detection of OM breast cancer that may yet be amenable to aggressive local salvage therapy to prevent progression to diffuse disease.

Key Words: high-risk node-positive breast cancer, metastatic breast cancer recurrence, oligometastatic breast cancer, recurrence surveillance, local salvage therapy

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Node-positive breast cancer (NPBC) is associated with significantly higher recurrence and mortality after surgery and systemic therapy compared with early-stage BC confined to the breast. Radiation therapy (RT) has been shown to reduce the locoregional recurrence risk by at least two-thirds and is recommended in all patients with NPBC after surgery and systemic therapy, especially in those with 4 or more involved nodes.[1,2] Unfortunately, even after maximal locoregional control has been achieved by trimodality therapy (TMT), patients remain at elevated risk for distant metastases and subsequent BC mortality.[3]

Although systemic therapy remains the mainstay treatment modality for BC recurrence, there has been increased interest in identifying patients with subsets of favorable metastatic disease that can be treated differently. The "spectrum theory," first described by Hellman in 1994, describes the existence of cancer as a spectrum of localized to widely metastatic disease.[4] The "spectrum theory" was later refined to include the concept of oligometastases as an intermediate on the spectrum defined as a limited metastatic state of 5 or fewer lesions within a single or limited number of sites.[5] Since the description of oligometastases was established, there has been a shift in cancer research to focus on the treatment of oligometastatic (OM) disease while the disease burden remains minimal and is still potentially salvageable from progression to diffusely metastatic (DM) disease.[6–14] Several studies have demonstrated that aggressive local management of OM disease using ablative RT can achieve excellent local control (70% to 90%) with minimal associated toxicity and is associated with increased disease-free intervals and overall survival (OS).[3,7,8,15–19]

The National Comprehensive Cancer Network (NCCN) currently does not recommend metastatic screening imaging in the absence of clinical signs and symptoms. This is despite evidence that the risk of BC death is decreased by 50% if recurrence events are detected early while the disease process is still relatively asymptomatic.[6,20] The American Society of Clinical Oncology (ASCO) similarly provides no recommendations for imaging

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The authors declare that they had full access to all of the data in this study and the authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

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surveillance following primary therapy with curative intent based on the paucity of studies providing evidence for the benefit of early detection of limited or asymptomatic recurrences.[21] The NCCN and ASCO guidelines are predicated on the satisfactory detection of locoregional recurrence by physical examination and mammography. However, these methods may not detect distant metastasis until they are symptomatic late sequalae of disease progression. This study examines the rates, patterns, and extent of recurrence in high-risk BC patients following curative intent TMT. In addition, it delineates which imaging modalities first detected these recurrences in order to elucidate a surveillance imaging strategy for the timely detection and treatment of asymptomatic, distant oligometastases before progression to DM disease.

PATIENTS AND METHODS

Population

This is a single-institution, IRB-approved, retrospective chart review of women at a safety-net hospital with non-metastatic, unilateral, clinical or pathologic NPBC between 2008 and 2019 who completed definitive TMT with surgery, chemotherapy, and RT. Details of demographic information, disease characteristics, treatment, and imaging studies performed following RT to detect recurrence were recorded. For those with detected recurrences, details of involved sites were recorded to determine the recurrence status as either OM (defined as ≤ 5 metastatic lesions) or DM (defined as >5 metastatic lesions). Information on the imaging modality which first detected the recurrence(s) was then collected for these cohorts, along with reasons for imaging, if available.

Endpoints and Statistical Analyses

Local, regional, and distant recurrence, recurrence-free survival (RFS), and OS rates were analyzed. Local recurrence was defined as recurrent disease in the ipsilateral chest wall or breast; regional recurrence was defined as recurrent disease in the ipsilateral axillary, internal mammary, or supraclavicular nodes; and distant recurrence was defined as metastatic disease in any other site. End of RT was chosen as the reference point as it typically follows surgery and systemic therapy, representing the end of TMT for NPBC. RFS was calculated as time from completion of RT to any recurrence event. OS was calculated as time from completion of RT to death because of any cause.

Categorical variables were described as frequencies and percentages and included age (below 55 y or 55 y or above), tumor grade (low/intermediate or high), estrogen receptor (ER)/human epidermal growth factor receptor 2 (HER2) receptor status (ER+/HER2−, ER−/HER2+, ER+/HER2+, or ER−/HER2−), clinical and pathologic T-stage (T0-2 or T3-4) and N stage (N0-1 or N2+), extranodal extension and lymphovascular invasion, surgery type (mastectomy or breast-conserving surgery), chemotherapy (neoadjuvant or adjuvant), and hormone therapy. Continuous variables were described as medians and interquartile ranges (IQR) (where reportable), and included age, follow-up time, and time from RT to first detected recurrence. Summary statistics were reported by recurrence status (nonrecurrent or recurrent) and by recurrence subtype (OM or DM).

All variables were coded for analysis, and independence between groups was assessed using the χ^2 test. RFS and OS rates were analyzed using the Kaplan-Meier method and compared using 2-sided log-rank tests. Variables that were independently associated with RFS were identified through univariable and multivariable Cox proportional hazards models. All *P*-values were 2-sided with a significance level of <0.05. SPSS (Version 27; IBM Corp., Armonk, NY) was used for all analyses.

RESULTS

From 2008 to 2019, we identified 95 patients with axillary NPBC who received chemotherapy, surgery, and definitive RT. One patient recurred while undergoing RT and was excluded from the study, yielding a total sample size of 94 (see Figure, Supplemental Digital Content 1, http://links.lww.com/AJCO/A402, which demonstrates the consort diagram of the nested cohort included in final analyses). Known baseline characteristics for these groups are listed in Tables 1 and 2. The median follow-up for the entire study population was 50 months (IQR: 24 to 76). The median age at time of diagnosis of primary cancer was 50 years (IQR: 42 to 58). Among the total study population, 73 patients did not develop recurrence following completion of TMT. Ten developed OM recurrence and 11 developed DM recurrence following completion of RT. Five-year recurrence rate following RT among the entire study population was estimated to be 26.46% (Fig. 1).

On univariable analysis, only adjuvant chemotherapy was found to have a statistically significant association with better RFS (Table 3). The hazard ratio for adjuvant chemotherapy was

TABLE 1. Baseline Characteristics for Nonrecurrent and Recurrent Patients

Variable	No Recurrence, n (%)	Recurrence, n (%)
Age, y		
>55	26 (35.6)	8 (38.1)
≤55	47 (64.4)	13 (61.9)
Grade		
Low/Intermediate	29 (40.8)	12 (60.0)
High	42 (59.2)	8 (40.0)
Receptor status		
ER+/HER2−	41 (59.4)	12 (57.1)
ER−/HER2+	6 (a8.7)	1 (4.8)
ER+/HER2+	13 (18.8)	3 (14.3)
ER−/HER2−	9 (13.0)	5 (23.8)
cT stage		
T0-2	43 (75.4)	12 (60)
T3-4	14 (24.6)	8 (40)
cN stage		
N0-1	43 (71.7)	14 (70)
N2+	17 (28.3)	6 (30)
LVSI		
Negative	17 (27.9)	5 (27.8)
Positive	44 (72.1)	13 (72.2)
ENE		
Negative	16 (31.4)	2 (12.5)
Positive	35 (68.6)	14 (87.5)
Surgery type		
Mastectomy	54 (74.0)	16 (76.2)
BCS	19 (26.0)	5 (23.8)
pT stage		
T0-2	55 (77.5)	13 (65.0)
T3-4	16 (22.5)	7 (35.0)
pN stage		
N0-1	10 (13.9)	1 (4.8)
N2+	62 (86.1)	20 (95.2)
Chemotherapy		
Neoadjuvant	28 (38.4)	12 (60.0)
Adjuvant	45 (61.6)	8 (40.0)
Hormone therapy		
Yes	58 (79.5)	15 (71.4)
No	15 (20.5)	6 (28.6)

All *P*-values of χ^2 comparisons were not statistically significant.

BCS indicates breast-conserving surgery; ENE, extranodal extension; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LVSI, lymphovascular space involvement.

TABLE 2. Baseline Characteristics of Oligometastatic and Diffusely Metastatic Patients

Variable	Oligometastatic, n (%)	Diffusely Metastatic, n (%)
Age, y		
>55	3 (30.0)	5 (45.5)
≤55	7 (70.0)	6 (54.5)
Grade		
Low/Intermediate	4 (44.4)	8 (72.7)
High	5 (55.6)	3 (27.3)
Receptor status		
ER+/HER2−	7 (70)	5 (45.5)
ER−/HER2+	0	1 (9.1)
ER+/HER2+	1 (10)	2 (18.2)
ER−/HER2−	2 (20)	3 (27.3)
cT stage		
T0-2	6 (60)	6 (60)
T3-4	4 (40)	4 (40)
cN stage		
N0-1	6 (60)	8 (80)
N2+	4 (40)	2 (20)
LVSI		
Negative	0	5 (50)
Positive	8 (100)	5 (50)
ENE		
Negative	1 (14.3)	1 (11.1)
Positive	6 (85.7)	8 (88.9)
Surgery type		
Mastectomy	9 (90)	7 (63.6)
BCS	1 (10)	4 (36.4)
pT stage		
T0-2	7 (70)	6 (60)
T3-4	3 (30)	4 (40)
pN stage		
N0-1	1 (10)	0
N2+	9 (90)	11 (100)
Chemotherapy		
Neoadjuvant	7 (77.8)	5 (45.5)
Adjuvant	2 (22.2)	6 (54.5)
Hormone therapy		
Yes	8 (80)	7 (63.6)
No	2 (20)	4 (36.4)

All P-values of χ^2 comparisons were not statistically significant.

BCS indicates breast-conserving surgery; ENE, extranodal extension; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LVSI, lymphovascular space involvement.

0.389 (95% confidence interval: 0.161-0.939, $P=0.036$), with neoadjuvant chemotherapy as the reference category. High-grade disease was found to have a borderline significant ($P<0.1$) association with RFS and was therefore included in the multivariable analysis. Adjuvant chemotherapy maintained significance on multivariable analysis with a hazard ratio of 0.359 (95% confidence interval: 0.148-0.870, $P=0.023$) (Table 4).

OM Recurrence

Of the 21 patients who developed recurrences, 10 (47.6%) had OM disease at first detection. The median RFS for these patients following RT was 18 months (IQR: 8 to 26) (Fig. 2A). Of the 10 patients who developed OM recurrence, 4 patients (40%) progressed to DM disease during the study period in a median time of 17 months (IQR: 5 to 18). Two of these 4 patients died following development of DM disease; the median survival among these 4 patients following disease progression was 57 months (IQR: 8 to 57). No other OM patients died during the study period. The median OS was not reached for the overall OM cohort in a median follow-up time of 63 months (Fig. 2B).

All OM patients had involvement of distant sites. Five patients had isolated distant metastases, 3 had concurrent regional and distant metastases, 1 had concurrent locoregional and distant metastasis, and 1 had concurrent local and distant metastases (see Figure, Supplemental Digital Content 2, http://links.lww.com/AJCO/A403, which illustrates the involved sites of recurrence among patients who developed OM and DM recurrence). Bone was the most frequent site of recurrence and was detected in 7 patients. Recurrences were most commonly detected by either computed tomography (CT) chest, CT chest/abdomen/pelvic, or CT abdomen/pelvis in 4 patients, followed by bone scan in 2 patients, and PET scan in 2 patients (see Table, Supplemental Digital Content 3, http://links.lww.com/AJCO/A404, which demonstrates recurrence site and imaging details for individual patients). The imaging studies were obtained most frequently after the development of clinically reported symptoms (70%), with no other form of surveillance imaging being performed within a minimum preceding time period of 1 year. Patients who underwent treatment for their recurrence received chemotherapy, or some combination of surgery, chemotherapy and hormone therapy (see Table, Supplemental Digital Content 4, http://links.lww.com/AJCO/A405, which demonstrates treatment of recurrence by group). One patient received SBRT in addition to chemotherapy.

Among the subset of 4 OM patients who later progressed to DM disease, 3 presented initially with bone disease. Two of them had isolated distant metastases, 1 had concurrent local and distant metastases, and 1 had concurrent locoregional and distant metastases.

DM Recurrence

Eleven of 21 patients (52.4%) with recurrent disease had DM recurrence at time of first detected recurrence. The median RFS following RT for these patients was 36 months (IQR: 13 to 48) (Fig. 2A). Of these 11 patients, 2 patients died because of their disease during the study period. The median OS for this cohort was 57 months in a median follow-up time of 44 months (Fig. 2B).

All DM patients had involvement of distant sites, with 8 patients having distant metastases alone, 1 patient having concurrent regional and distant metastases, and 2 patients having concurrent locoregional and distant metastases (see Figure, Supplemental Digital Content 2, http://links.lww.com/AJCO/A403, which illustrates the involved sites of recurrence among patients who developed OM and DM recurrence). Bone involvement was most common, being detected in 7 patients, followed by lung, detected in 6 patients. Recurrences were detected by either CT chest, CT chest/abdomen/pelvic or CT abdomen/pelvis (9 patients), and PET scan (2 patients) (see Table, Supplemental Digital Content 3, http://links.lww.com/AJCO/A404, which demonstrates recurrence site and imaging details for individual patients). Similar to the OM group, most of these imaging studies (77%) in the DM group were obtained following the development of clinical symptoms, with no other form of surveillance imaging being performed within a minimum preceding time period of 1 year. Patients who underwent treatment for their recurrence received either chemotherapy or hormone therapy (see Table, Supplemental Digital Content 4, http://links.lww.com/AJCO/A405, which demonstrates treatment of recurrence by group).

DISCUSSION

This retrospective study presents the survival outcomes, recurrence rates, sites of recurrence, and the imaging studies that were performed to detect recurrences in 94 patients with

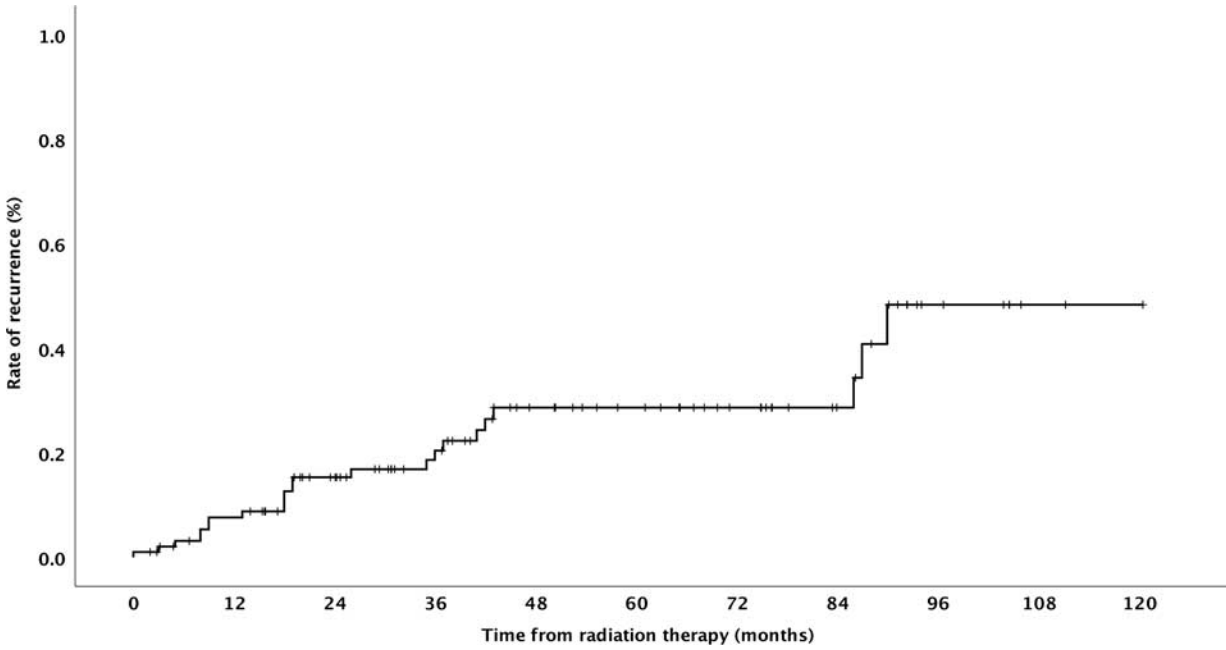

FIGURE 1. Rate of metastatic recurrence following completion of radiation therapy.

node-positive, invasive BC treated with chemotherapy, surgery, and adjuvant RT at a single institution between 2008 and 2019. Our results demonstrate that in women with mostly pN2-3 BC treated with surgery, chemotherapy, and RT, the rate of recurrence remains high, at 26% at 5 years, with the majority of the recurrences detected within the first 3 years after initial TMT (see Figure, Supplemental Digital Content 5, http://links.lww.com/AJCO/A406, which illustrates a visual summary comparison of recurrence timelines for each patient). This is consistent with a previously reported risk of recurrence in pN1-3 BC of 25%.[1] Importantly, most of the patients with recurrence had imaging because of symptoms, and none had imaging to look for metastatic disease for at least a year before recurrence, highlighting a gap in which screening can result in earlier detection of recurrent disease.

Upon first detection of recurrence in our patient population, the most frequently observed sites by far were distant, and no other site was observed without concurrent distant site involvement. One explanation for this pattern is that adjuvant RT is highly efficacious in eliminating residual disease that may reside in the targeted locoregional field.[15,22] RT, however, does not address out-of-field metastatic disease. In absence of ancillary imaging studies suited to detect recurrence in these sites, distant metastatic lesions do not become clinically apparent until new symptoms herald disease progression, at which time the potential benefits of local ablative therapies may be lost.[3,19,23] Few studies to date have described and quantified the exact locations of metastatic recurrence following TMT, specifically at distant sites.[17,24–27] A recent study by Keilty et al[24] found that out of 93 BC patients who developed recurrence, 89 patients had involvement of distant sites, with metastases to bone, lungs, brain, and liver accounting for 62.2% of the sites. Similarly, the DBCG 8-2b and 8-2c trials reported that first distant metastases most often developed in bone, followed by lungs.[17] Our results are consistent with these reports, as the most frequently recorded sites of recurrence overall in our patients were bone, followed closely by lung. More research on chronologizing sites of recurrence, and more importantly OM recurrences, will be useful in determining surveillance strategies for to maximize detection and treatment of salvageable distant OM recurrence.

In our study, recurrence following RT in the 10 patients found to have OM disease on first detection occurred in a median time of 18 months, and from then the 4 patients who subsequently progressed to DM disease did so in a median time of 17 months, yielding a total time to diffuse metastases of 35 months. Of note, the other 6 patients neither progressed to diffuse metastases nor died based on available follow-up data. In contrast, recurrence occurred in a median time of 36 months in the 11 patients who were found to have DM disease on first detection. The striking similarity of these observations suggest strong that patients first detected to have DM recurrence may have had "silent" or minimally symptomatic OM disease that went unexamined until progression to larger volume symptomatic metastatic disease that prompted systemic or targeted imaging. Had patients in the DM group received surveillance imaging before symptomatic development, their disease could have been identified at the asymptomatic OM stage and their outcome dramatically changed. Although our study population was relatively small, our results nonetheless still contribute to the growing collection of literature suggesting that early detection and treatment of OM recurrences during the asymptomatic phase may improve OS.[3,28–30]

While no statistically significant OS difference was detected because of the paucity of death events recorded, our data shows that OM patients had numerically longer OS than the DM group despite having shorter disease-free intervals from completion of initial therapy. The median OS for our OM group was not reached, despite the median follow-up time being 20 months longer than that for our DM group. Even with the improved survival observed in OM patients compared with DM patients following TMT, it should be noted that both groups received overall similar systemic treatment for their recurrence. In our OM group, only 3 patients received surgery as a component of their salvage therapy, and only 1 received SBRT as a component of hers; no other patient received any local therapy. Interestingly, of these 4 patients who did undergo local therapy for their recurrence, only 1 experienced diffuse disease progression despite surgical management. The treatment profile of our study population thus represents a missed opportunity for improvement of

TABLE 3. Univariable Analysis of Factors Associated With Recurrence After Trimodality Therapy in Node-Positive Breast Cancer Patients

	Univariable Analysis	
	HR for DFS (95% CI)	***P***
Age		
<55	Reference	0.741
≥55	1.158 (0.484-2.768)	
Chemotherapy		
Neoadjuvant	Reference	0.036**
Adjuvant	0.389 (0.161-0.939)	
cN stage		
N0-1	Reference	0.984
N2+	1.010 (0.380-2.631)	
cT stage		
T0-2	Reference	0.123
T3-4	2.026 (0.826-4.967)	
ENE		
Negative	Reference	0.196
Positive	2.658 (0.604-11.699)	
Grade		
Low/Intermediate	Reference	0.091*
High	0.466 (0.190-1.139)	
Hormone therapy		
None	Reference	0.385
Received	0.671 (0.273-1.650)	
LVSI status		
Negative	Reference	0.791
Positive	1.150 (0.410-3.230)	
pN stage		
N0-1	Reference	0.299
N2+	2.898 (0.390-21.558)	
pT stage		
T0-2	Reference	0.109
T3-4	2.056 (0.851-4.970)	
Receptor status		
ER+/HER2−	Reference	0.675
ER−/HER2+	0.465 (0.061-3.567)	0.462
ER+/HER2+	0.774 (0.220-2.721)	0.69
ER−/HER2−	1.477 (0.526-4.150)	0.459
Surgery type		
BCS	Reference	0.662
Mastectomy	1.250 (0.461-3.390)	

*Statistically significant ($P < 0.1$).
**Statistically significant ($P < 0.05$).
BCS indicates breast-conserving surgery; CI, confidence interval; DFS, disease-free survival; ENE, extranodal extension; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; LVSI, lymphovascular space involvement.

TABLE 4. Multivariable Analysis of Factors Associated With Recurrence After Trimodality Therapy in Node-Positive Breast Cancer Patients

	Multivariable Analysis	
	HR for DFS (95% CI)	***P***
Chemotherapy		
Neoadjuvant	Reference	0.023**
Adjuvant	0.359 (0.148-0.870)	
Grade		
Low/Intermediate	Reference	0.067*
High	0.431 (0.175-1.061)	

*Statistically significant ($P < 0.1$).
**Statistically significant ($P < 0.05$).
CI indicates confidence interval; DFS, disease-free survival; HR, hazard ratio.

patient outcomes, especially given recent evidence that aggressive local therapy—specifically SBRT—has been demonstrated to improve RFS and OS.[3] That the majority of OM patients who received aggressive local management of their recurrence subsequently did not develop diffuse disease lends support to the reported benefit of salvage therapy for low disease burden. Had all 10 of our OM patients been treated aggressively with ablative therapy and/or surgery, it is reasonable to hypothesize that the OM and DM groups may have had an even bigger OS difference than was observed.

The NCCN Panel provided its recommendation against the routine imaging of asymptomatic patients on the basis of there being no evidence of survival benefit.[20] In tune with NCCN guidelines, the first ASCO guidelines for BC follow-up—published in 1999—also cautioned against the routine use of CT imaging, based on available data at that time which suggested no clinical benefit on detection of metastatic disease.[31–33] This stance was maintained in the subsequent 2006 and 2013 updates, largely based on conclusions offered by retrospective studies which also examined data collected before the 21st century.[21,34–36] However, the spatial resolution of CT imaging technology has since advanced significantly, resulting in markedly improved detection of metastatic disease.[37] We observed CT imaging to be most common modality which successfully first detected distant site metastases following symptomatic development of OM and DM recurrence in a median time of 18 and 36 months, respectively, with an associated improved survival benefit. In both groups, metastases were most frequently detected in bone—specifically, within the sternum, ribs, and thoracic spine (see Table, Supplemental Digital Content 1, http://links.lww.com/AJCO/A402, which demonstrates the site distribution of metastatic lesions and the imaging modality by which first detected for each patient). On the basis of the observation that most bone lesions (including those detected through modalities other than CT imaging) were localized exclusively to the thoracic region, it is reasonable to speculate that many of these metastases may have been detected at an early stage before symptomatic development using targeted CT imaging of the chest. That the next most commonly first detected site of metastatic involvement among both groups was lung strengthens the proposed utility of CT chest imaging as an advantageous screening method.

In addition to the superior ability of modern CT technology to detect metastases as compared with older technologies and alternative forms of imaging, remarkable improvements in scanning speed and iterative reconstruction algorithms have permitted the minimization of amount of radiation patients are exposed to without sacrifice of imaging quality.[38,39] Low-dose CT chest imaging could therefore reasonably be considered as a low-cost high-yield screening tool that could successfully detect early-stage metastatic disease, with additional work up to follow if the results are abnormal. Future prospective studies investigating the detection rates of asymptomatic disease using CT-based screening, especially low-dose CT chest, are needed. If the studies can demonstrate improved detection rates of OM disease amenable to aggressive local therapy such as surgery or SBRT, and therefore resulting in improved OS and disease-free survival, it would change the current notion that routine imaging surveillance in high-risk BC is ineffective and the cost cannot be justified.[21,40]

Limitations

The major limitation of this study is its retrospective design, which inherently renders the data and results prone to bias. For example, despite controlling for confounding

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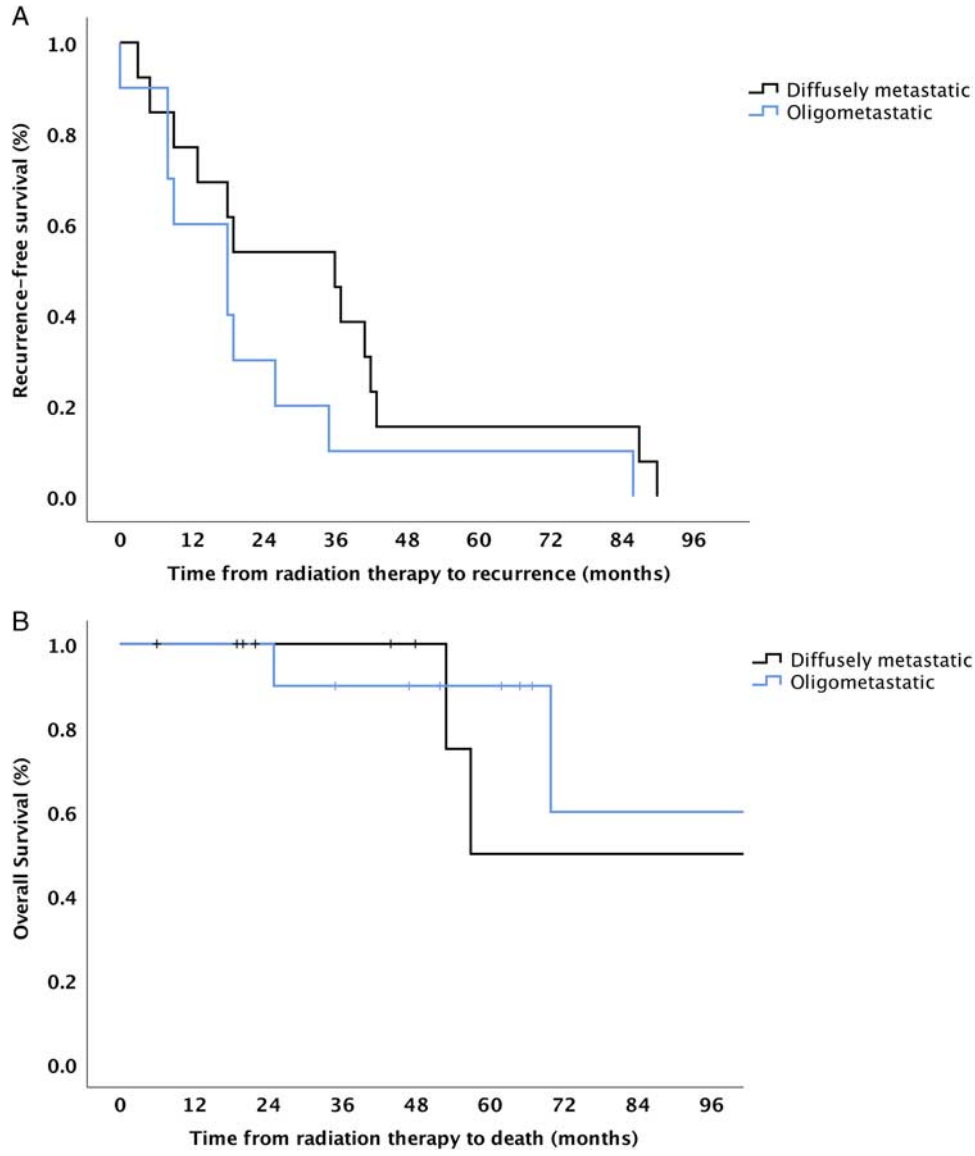

FIGURE 2. A, Recurrence-free survival following radiation therapy and (B) overall survival following radiation therapy for oligometastatic and diffusely metastatic patients. full color online

variables, adjuvant chemotherapy was associated with better outcome. The authors believe that this finding does not reflect the efficacy of chemotherapy at varying timing, but rather the neoadjuvant chemotherapy group selecting for higher disease burden at presentation than the adjuvant group. In addition, with our small sample size of 94 patients with 21 patients experiencing metastatic recurrence and even fewer recorded deaths, statistical power remained low, and significance was not reached for most associations, limiting the degree to which our results can be generalized to the overall population. Patients with metastatic disease, particularly those with DM disease, often have limited survival. In our study, such patients frequently enrolled in hospice care after which their mortality status could not be definitively determined from the electronic medical record. However, this limitation is likely to underestimate the mortality rates of the DM group and would lend additional support to the proposal that OM disease has better outcome than DM disease. Despite such limitations, the results we have reported nonetheless demonstrate a consistent pattern and are in line with the existing literature.

CONCLUSIONS

Our study found that around a quarter of women with NPBC will develop distant recurrences, most within the first 3 years. While a variety of imaging modalities resulted in first detection of recurrence, nearly all findings would have been detectable on a CT scan of the chest. While patients who had OM disease had significantly shorter RFS from end of TMT for the primary, they had improved OS compared with those found to have diffuse metastases at first recurrence. The better OS in OM disease is only expected to improve with the adoption of aggressive local therapy with SBRT and/or surgery. Early detection of asymptomatic, OM disease, therefore, possesses

significant potential in improving patient outcome in the setting of NPBC, and additional studies are needed to establish optimal screening strategies that can shift the paradigm of management of recurrent, metastatic BC.

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