Late Recurrence Following Early Breast Cancer

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The Oncology Grand Rounds series is designed to place original reports published in the Journal *into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in the* Journal of Clinical Oncology, *to patients seen in their own clinical practice.*

Case Presentations

Case 1. A 54-year-old woman presents for consultation. In 2015, she underwent lumpectomy and sentinel lymph node biopsy for a 1.8-cm estrogen receptor (ER)–positive 90%, progesterone receptor (PR)–positive 90%, and human epidermal growth factor receptor 2 (HER2)–negative, grade II invasive ductal carcinoma. One of three sentinel lymph nodes was positive. Germline genetic testing at diagnosis was negative. The patient enrolled in the RxPonder study and was found to have a 21-gene recurrence score of 5. She was randomly assigned to receive chemoendocrine therapy and received four cycles of docetaxel and cyclophosphamide followed by radiation, oophorectomy, and initiation of adjuvant aromatase inhibitor therapy. She has continued on an adjuvant aromatase inhibitor for 6 years and is without clinical evidence of recurrence. She has grade 1 joint pains attributed to aromatase inhibitor therapy. Her bone density has remained normal. She presents to discuss ongoing options to reduce her risk of recurrence of breast cancer.

Case 2. A 59-year-old woman presents with a palpable inguinal mass. Fifteen years before, she was diagnosed with a T2N1M0 ER-/PR-positive, HER2-negative invasive lobular breast carcinoma for which she underwent mastectomy and axillary lymph node dissection. She received adjuvant docetaxel, doxorubicin, and cyclophosphamide for six cycles followed by radiation therapy. Her adjuvant endocrine therapy regimen included tamoxifen for 1 year followed by 4 years of anastrozole. Positron emission tomography-computed tomography obtained at the current presentation was consistent with metastatic disease to multiple lymph nodes, vertebral bodies, and liver (Fig 1). Biopsy of an inguinal lymph node revealed ER-positive (90%), PR-negative, and HER2-negative carcinoma consistent with a breast primary. The patient presents for consultation and discussion of treatment options.

Clinical Challenges in Evaluation and Treatment

Two contemporary challenges in breast oncology are apparent in these cases: (1) assessing the risk of late recurrence and optimizing adjuvant therapy to prevent late recurrence, plus (2) managing clinically overt distant metastatic breast cancer presenting many years after diagnosis. The report by Pedersen et al[1] that accompanies this article both extends our knowledge of the scope of this challenge and provides insight into survival patterns for patients with early versus late recurrence.

Late recurrence of breast cancer, typically considered recurrence more than 5 years after initial diagnosis and treatment, is a significant clinical problem, particularly with hormone receptor (HR)–positive disease, for which approximately half of the recurrences present beyond year 5.[2] Analyses of over 20,000 patients in the Danish Breast Cancer Group clinical database who were diagnosed with breast cancer between 1987 and 2004 and who were disease-free 10 years after diagnosis revealed a 17% cumulative incidence of recurrence between 10 and 32 years after diagnosis, with greatest risks of recurrence in this late time period observed in patients with larger tumors, nodal involvement, and HR-positive disease at diagnosis.[3] The Early Breast Cancer Trialists' Collaborative Group meta-analysis of almost 63,000 participants in 88 trials who were diagnosed with breast cancer between 1976 and 2011 demonstrated that the recurrence risk for HR-positive breast cancer persists at a stable rate between 5 and 20 years after diagnosis with risk of recurrence associated with tumor size, nodal status, and tumor grade at diagnosis.[4] Although these large data sets composed of patients diagnosed many years ago may overstate the problem of late recurrence in patients treated with contemporary therapies, given the large population of breast cancer survivors, the number of individuals at risk for late recurrence remains large, and the risk of late recurrence does not appear to abate with time.

Five years of adjuvant endocrine therapy approximately halves the risk of breast cancer recurrence, with benefits observed through 10 years after diagnosis.[5] Recent trials have evaluated extended courses of adjuvant endocrine therapy for 7-10 years with the

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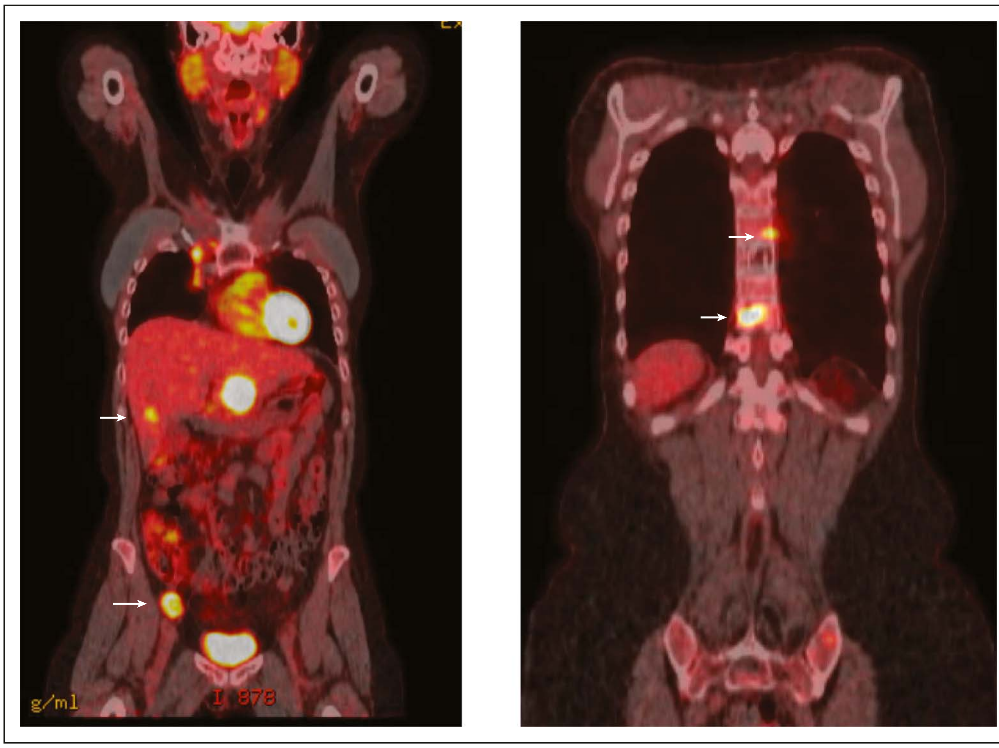

FIG 1. PET-CT obtained at presentation with inguinal lymphadenopathy in case 2. PET-CT demonstrates metastatic involvement in lymph node, bone, and liver. Representative lesions are highlighted by arrows. CT, computed tomography; PET, positron emission tomography.

intent of further reducing risk of late recurrence, although the observed impact of extended therapy on disease outcomes has been modest (Table 1).[6,7] At present, although patients remain at continued risk of breast cancer recurrence following 10 years of adjuvant endocrine therapy, though only limited data are available on sustained therapy beyond 10 years. Although the manuscript by Pedersen et al suggests more favorable outcomes broadly for late breast cancer recurrences, which are more frequently HR-positive, compared with earlier recurrences, metastatic breast cancer to distant sites remains incurable, and further risk-reducing strategies, ideally targeted toward those at the highest risk of recurrence, are needed.

Tools to assess the risk of late recurrence. A critical challenge in this space is that, although the absolute number of patients at risk for late recurrence is high because of the large number of breast cancer survivors, only a minority of the overall pool of patients with breast cancer who are alive more than 5 years after diagnosis experience late recurrence. Extended adjuvant treatments carry toxicities and may be unacceptable to patients many years from diagnosis without clear assessment of their risk. At the same time, late incurable recurrence is a life-altering event. Tools to assess the ROR following 5 years of endocrine therapy are emerging. For example, the Clinical Treatment Score post-5 years (CTS5) calculator, which was developed with data from the Arimidex, Tamoxifen, Alone or in Combination trial and tested with data from the Breast International Group 1-98 trial, is an inexpensive and practical tool[8] to assess the ROR in years 5-10 that can be used in the clinic.[9] CTS5 uses characteristics including tumor size, grade, and nodal status plus patient age to calculate an individualized numeric risk of distant recurrence in years 5-10 with the output categorized as low, intermediate, or high risk.

Data obtained from multiparameter gene expression assays performed on primary breast tumor tissue, alone or in combination with clinical information, provide prognostic information about the risk of recurrence of breast cancer and, in some cases, predict benefit from adjuvant chemotherapy. Of the presently available multiparameter gene expression assays, the 50-gene Prosigna, Breast Cancer Index, and the 12-gene EndoPredict Score (EPClin) offer the greatest prognostic information about the risk of late distant recurrence of HR-positive breast cancer in years 5-10 after diagnosis.[10] In addition, in secondary analyses of the MA.17,[11] Trans-aTTom,[12] and IDEAL[13] trials, Breast Cancer Index-(H/I)-high scores predicted benefit from extended endocrine therapy. Key limitations of currently available tools to assess the risk of late recurrence include limited data regarding risk assessment beyond 10 years after diagnosis and for disease subtypes other than HR-positive, HER2-negative. Furthermore, most of these tools are not well validated in premenopausal women with breast

TABLE 1. Trials Assessing Extended Adjuvant Endocrine Therapy in Early Breast Cancer

Trial	No.	Median Follow-up, years	Intervention	Disease-Free Survival Hazard Ratio or Recurrence-Free Survival Hazard Ratio (95% CI)	Overall Survival Hazard Ratio (95% CI)
Tamoxifen after 5 years of tamoxifen					
ATLAS	6,846	7.6	Additional 5 years of tamoxifen	0.84 (0.76 to 0.93)[a]	0.87 (0.78 to 0.97)
Aromatase inhibitor after tamoxifen					
MA.17	5,187	5.3	Aromatase inhibitor for 5 years after 5 years of tamoxifen	0.68 (0.56 to 0.83)[b]	0.99 (0.79 to 1.24)
MA.17R	1,918	6.3	Extended aromatase inhibitor after aromatase inhibitor for 5 years, with possible additional prior tamoxifen	0.80 (0.63 to 1.01)[b]	0.97 (0.73 to 1.28)
ABCSG 6a	856	5.2	Aromatase inhibitor for 3 years after 5 years of tamoxifen	0.62 (0.40 to 0.96)[a]	0.89 (0.53 to 1.34)
DATA	1,660	4.4	Aromatase inhibitor for 3 or 6 years after 2-3 years of tamoxifen	0.79 (0.62 to 1.02)[b]	0.91 (0.65 to 1.29)
Extended endocrine therapy with an aromatase inhibitor after 5 years of antiestrogen therapy					
IDEAL	1,824	6.6	Aromatase inhibitor for 2.5 or 5 years after 5 years of antiestrogen therapy	0.92 (0.74 to 1.16)[b]	1.04 (0.78 to 1.38)
NSABP B42	3,966	6.9	Aromatase inhibitor for 5 years after 5 years of antiestrogen therapy	0.85 (0.73 to 1.00)[b]	1.15 (0.92 to 1.44)
Adjuvant endocrine therapy treatment breaks					
SOLE	4,884	7.0	Aromatase inhibitor continuously or 9 months on then 3 months off each year in 5 years after initial antiestrogen therapy	1.03 (0.91 to 1.17)[b]	0.89 (0.75 to 1.06)

[a]Recurrence-free survival HR.
[b]Disease-free survival HR.

cancer in whom the disease can have a distinct natural history and who face the risk of late recurrence over many decades.

Challenges in addressing late recurrence. Many questions remain to be addressed as we seek to reduce the burden of late breast cancer recurrence. Although available risk stratification tools allow us to broadly select those at high risk and to target extended therapies to that group, they remain probabilistic. Additionally, existing risk assessment strategies are largely based on features present at diagnosis; thus, they do not offer dynamic risk assessment over time.

The biology of late recurrence of breast cancer appears to differ from that of early recurrence. Late distant recurrence is thought to arise from disseminated tumor cells that enter a phase of active growth following an extended period of dormancy. Patients without dormant cells are likely at minimal risk for late recurrence, whereas patients who have cells that have escaped from dormancy but who have not yet developed clinically overt metastases are likely at particularly high risk for distant recurrence. When escape from dormancy occurs and over what time period it progresses along the trajectory to clinically overt metastases may vary by individual. The processes that maintain cells in a dormant state and subsequently lead to escape from dormancy are thought to be multifactorial and remain to be fully understood. Factors potentially contributing to escape from dormancy include genomic instability, inhibition of autophagy, selective pressure from antineoplastic therapies, and metabolic factors.[14]

Biomarkers that can detect minimal residual disease (MRD), the presence of residual cancer in the absence of clinically overt metastases, offer promise for identification of patients in whom escape from dormancy has occurred. Such patients are at exceptionally high risk for progressing along the trajectory toward clinically overt distant metastases and may benefit from intensification of adjuvant therapy. However, which interventions might be effective in this space is currently unknown. Additionally, the time point(s) in the natural history of disease recurrence at which interventions may affect outcomes is unclear (Fig 2). If, as tumors escape dormancy, we are able to detect MRD, by when must we intervene to prevent progression toward radiologically detectable and symptomatic distant metastases? Might this vary among tumors? Emerging tools to assess MRD, as well as novel biologic treatments, hold the promise to meaningfully understand and alter the biology of late recurrence. Given the potential of these scientific advances, plus the large unmet clinical need, the National Cancer Institute sponsored a Clinical Trials Planning Meeting in May 2019, from which evolved REFINE-BrCa (Refining Adjuvant Therapy Through Identification and Escalation), a collaboration across National Clinical Trials Network group members who are developing clinical trials to address these key questions about breast cancer late recurrence.[15]

Circulating biomarkers such as circulating tumor deoxyribonucleic acid (ctDNA) and circulating tumor cells (CTC) hold particular promise as an MRD detection strategy, although the clinical utility and specific roles of these novel tools in the adjuvant setting remain to be elucidated. Two studies, Eastern Cooperative Oncology Group E5103[16] and the SUCCESS A[17] trial, have shown a strong relationship between CTC detection and risk of distant recurrence. ctDNA detection appears to be even more promising, with numerous platforms—both tumor-informed and agnostic—in retrospective studies demonstrating the relationship between ctDNA detection and very high risk of recurrence.[18] In addition to potential utility for identification of patients at high risk for distant metastases who may benefit from escalation of adjuvant therapy, MRD biomarkers, if modulated by therapy, have the potential to serve as early biomarkers of treatment efficacy. Given the promise of MRD detection, a number of prospective studies are underway to define clinical utility of these assays (Table 2). Importantly, to date, none of the published studies reporting the association of CTC or ctDNA with distant recurrence of breast cancer have incorporated regular interval imaging, which is not part of routine clinical care. Confirmation of clinical utility of these biomarkers will require demonstrating that they truly detect MRD before the development of radiologically detectable distant metastases.

A strategy to target MRD in the late adjuvant setting will require not only sensitive biomarkers, but highly effective therapies. In the current environment, a number of treatment options are recently available or in development for HR-positive breast cancer, including cyclin-dependent kinase 4/6 inhibitors, selective ER degraders, and others. Agents should be selected for efficacy in the postaromatase inhibitor setting, toxicity profile, and patient acceptability.

Patient perspective. As research to confirm the clinical utility of MRD biomarkers to identify patients at high risk of late recurrence and to select patients most likely to benefit from additional therapies in the late adjuvant setting progresses, careful attention to the patient experience will be critical. For individual patients who may consider themselves cured many years after diagnosis, learning their MRD status may be an unwelcome and confusing experience. Although it is well recognized that patients frequently overestimate or underestimate their risk of recurrence soon after diagnosis, little is known about patients' understanding of late recurrence risk. Before moving MRD assessment in the late adjuvant setting into the clinic, we must develop strategies to clearly communicate about the risk of late recurrence and about the concept and significance of MRD so that we can appropriately guide individual patients to or away from escalating adjuvant therapy to prevent late recurrence.

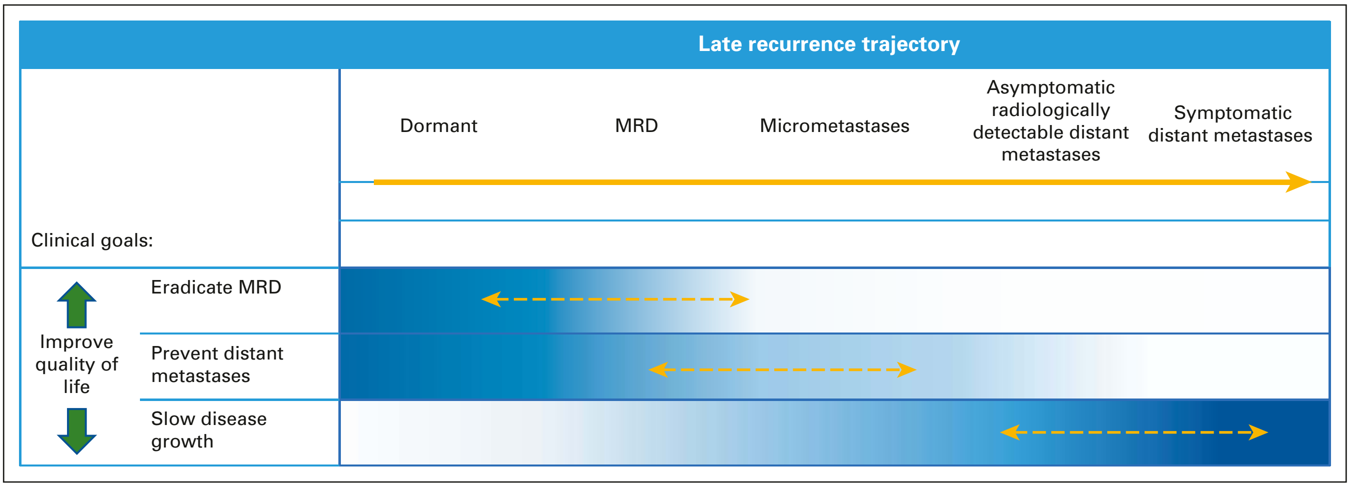

FIG 2. Schematic representation of disease states along the trajectory from dormancy toward symptomatic distant metastases. Clinical goals for disease states are shown in shaded blue. Improving quality of life is a clinical goal at all points along the trajectory of disease. Potential time points along the trajectory at which intervention may prevent progression along the trajectory are marked with dashed yellow arrows. MRD, minimal residual disease.

TABLE 2. Clinical Trials Using Circulating Biomarkers to Escalate Adjuvant Therapy for HR-Positive Breast Cancer

Trial Name (clinicaltrials.gov ID)	Interventional Study Sample Size	Screening Population	Study Population	Control Arm	Intervention Arm	Primary Outcome(s)
TRAK-ER (NCT04985266)	110	High-risk HR-positive/ HER2-negative ≥ 1 negative staging scan since diagnosis Completed 6 months to 7 years endocrine therapy Postmenopausal	ctDNA-positive No scan-detectable disease	Standard endocrine therapy	Palbociclib/ fulvestrant	ctDNA baseline prevalence ctDNA incidence Recurrence-free survival
DARE (NCT04567420)	100	High-risk HR-positive/ HER2-negative Stage II-III breast cancer Completed 6 months to 7 years endocrine therapy	ctDNA-positive No scan-detectable disease	Standard endocrine therapy	Palbociclib/ fulvestrant	ctDNA baseline prevalence ctDNA incidence Recurrence-free survival
LEADER (NCT03285412)	120	High-risk HR-positive/ HER2-negative Completed 6 months to 10 years endocrine therapy Postmenopausal	ctDNA-positive	Standard endocrine therapy	Ribociclib/ fulvestrant	1-year ctDNA clearance

Abbreviations: ctDNA, circulating tumor DNA; HER2, human epidermal growth factor-receptor-2; HR, hormone receptor.

Clinically overt late recurrence. At present, radiologically detectable or symptomatic distant metastases presenting years after diagnosis remains an important clinical issue, as seen in our second case. The accompanying report by Pedersen et al[1] shows improved survival for late versus early breast cancer recurrence (late recurrence defined in their study as recurrence 10 years from initial diagnosis) from a large single-country data set. Previous smaller reports have similarly found improved survival for those with late recurrence relative to those with early recurrence.[19–21] The report by Pedersen et al is the largest to date to review this question; notably though, the data on improved survival for late recurrences are strongest with regard to local recurrence.

Our Approach to Management

For patients at high risk of late recurrence, we have a conversation around continued risk. The CTS5 calculator is a facile tool to use in clinic to discuss risk in years 5-10 for postmenopausal patients. Some clinicians may consider a multiparameter gene expression assay for patients who are considering continuing adjuvant endocrine therapy in years 5-10 and in whom this result would influence their decision. Other factors, such as overall health, bone health, patient preference, and tolerance of endocrine therapy, contribute to these conversations.

In our first case, the patient had a CTS5 score of 3.42 with 6.6% risk of recurrence in years 5-10. Genomic assay testing was discussed, and the patient wished to pursue this testing. This test result returned as high-risk with 12.1% likelihood of recurrence in years 5-10. The patient has elected to remain on extended adjuvant endocrine therapy. This patient underwent lumpectomy as her surgical procedure and has the benefit of risk reduction of a second primary with continued antiestrogen therapy. This is also an opportunity to reinforce lifestyle factors that decrease the risk of breast cancer such as maintaining an ideal body weight and limiting alcohol use. Importantly, this patient and others at high risk for late recurrence will be eligible for trials seeking to decrease late recurrence events and should be offered these opportunities as they arise. Although we eagerly await the results of trials incorporating commercially available ctDNA assays, we currently recommend against using these tests in the adjuvant setting outside of a clinical trial. The utility of these tests must be more clearly defined before expansion into the clinic.

For patients with late distant recurrence of breast cancer after an extended period of disease dormancy as seen in our second case, we do not typically use time to recurrence as a primary tool to guide therapy as the disease biology will vary in individual patients. Nonetheless, with significant numbers, the report by Pedersen et al suggests that selected patients with late distant recurrence may have more indolent biology and thus, could be considered for initial de-escalated therapies such as endocrine therapy alone with initial close observation, although there are no clearly defined biomarkers to select such patients. Clinical judgment on a case-by-case basis is required.

Our patient presented with a significant disease burden and multiorgan involvement. Next-generation sequencing of the tumor and of blood, as well as germline DNA testing, did not reveal actionable targets. She was initially treated with anastrozole and palbociclib plus denosumab. Her disease progressed after 18 months on this therapy, shorter than the median progression-free survival observed in the first-line trials with upfront cyclin-dependent kinase inhibition, suggesting aggressive disease biology. Her disease progressed after 3 months on next-line fulvestrant and abemaciclib. The patient was then offered and enrolled on a clinical trial that sought to use epigenetics to enhance tumor susceptibility. Her tumor again progressed rapidly. Her disease is now responding to first-line chemotherapy.

For the many patients touched by the risk of late recurrence, considering clinical trials will be critical to further understanding the complex biology of this disease trajectory. Given the disease prevalence as well as the promises of precise biologically based risk stratification and novel treatment approaches, such trials could improve many lives and radically alter our approach to care in the late adjuvant space.

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