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Editorial

EDITORIAL

Surveillance After Treatment of Localized Breast Cancer: Time for Reappraisal?

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Evidence-based guidelines recommend surveillance after treatment of localized breast cancer including history, physical examination, and annual mammography (1,2). Laboratory tests including circulating tumor markers and imaging studies beyond mammography are not recommended in asymptomatic patients, although these recommendations are based on clinical trials done in an era when diagnostic, imaging and therapeutic options were limited (3). Recently, the U.S. Food and Drug Administration (FDA) granted regulatory approval for apalutamide in the treatment of nonmetastatic castration-resistant prostate cancer based on the endpoint of metastasis-free survival (4), and use of an integral biomarker (serum prostate-specific antigen [PSA]) to select men at high risk for developing metastasis and lacking distant disease based on standard diagnostic imaging (5). This paradigm provides a tenable model for evaluating a similar strategy in nonmetastatic breast cancer.

Application of such a strategy requires the use of biomarkers that exhibit and a high degree of analytic and clinical validity, which would be required to ultimately establish clinical utility—a biomarker-directed treatment change that results in clinical benefit (6). Similar to PSA in prostate cancer, circulating MUC-1 antigen assays (eg, CA15-3, CA 27.29) have been evaluated for surveillance in breast cancer, although the trials were underpowered, and survival was not improved for those who underwent surveillance (7–10). Other blood-based biomarkers offer potential for greater sensitivity and specificity in identifying individuals at high risk for recurrence, including circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA), microRNA, noncoding RNAs, and tumor-educated platelets (11). The only FDA-cleared, analytically validated assay is one that allows detection and enumeration of CTCs in metastatic breast, colorectal, and prostate cancer (CellSearch System, Menarini Silicon Biosystems, Bologna, Italy) (12,13). The assay involves an automated system for immunomagnetic capturing of cells that express epithelium-specific cell adhesion molecule (EpCAM) on the cell surface. CTCs are detectable in 65% of patients with metastatic breast cancer, and a CTC count of greater than 5 cells per 7.5 mL of blood is associated with statistically significant inferior progression-free survival and overall survival (12), providing evidence for clinical validity. Other studies have shown that CTCs are detectable using the same assay in about 20–25% of patients with localized nonmetastatic breast cancer. CTCs also provide independent prognostic information (whether obtained before or after surgery, including after neoadjuvant or adjuvant chemotherapy) providing additional evidence for clinical validity (14–16).

In this issue of *JNCI*, Trapp et al. report the association between CTCs detected 2 years after completion of adjuvant chemotherapy in 1087 patients with stage II–III breast cancer enrolled in the phase III SUCCESS A trial (17) in which CTCs were found to be prognostic at diagnosis (15). CTCs were detected in 18.2% of patients (median= 1 cell, range = 1–99 cells per 7.5 mL blood) at 2 years, and was associated with a 3.9-fold increased risk of death and a 2.3-fold higher recurrence risk in multivariable models that included clinicopathologic features and CTC status at baseline; sensitivity analysis showed this effect only in HER2-negative disease. Another report from this same study found that among 206 subjects enrolled in the SUCCESS study with follow-up information and known CTC status at 5 years, 7.8% were CTC-positive at 5 years (median = 1 cell, range = 1–53 cells per 7.5 mL blood), and was associated with a six-fold increase in recurrence (18). Finally, in a separate study including 353 patients with hormone receptor-positive, HER2-negative, stage II–III breast cancer treated with adjuvant chemotherapy and endocrine therapy, CTCs were detectable after a median follow-up of 5.1 years in 5.1% (median = 1 cell, range = 1–15 cells per 7.5 mL blood), and was associated with a 13.1-fold increase in recurrence risk in multivariable analysis adjusted for other prognostic covariates; the median time between the positive CTC assay and recurrence was 2.8 years (19). Because imaging was not performed in any of these trials at the time of the positive CTC assay, it is currently unknown

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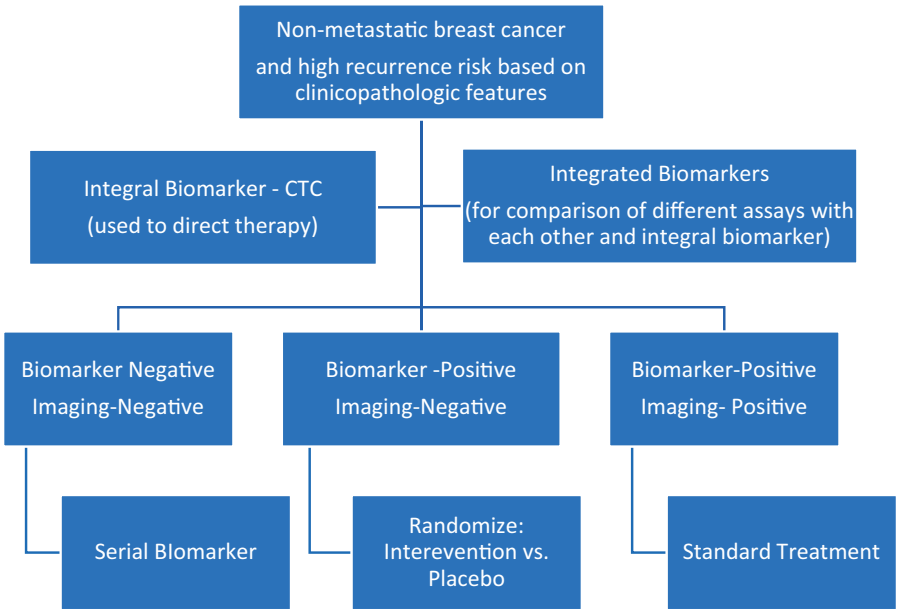

Figure 1. Schema of hypothetical clinical trial including CTCs and/or other "liquid biopsy" assays for testing novel treatment intervention to prevent metastasis. CTC = circulating tumor cell.

what proportion of CTC-positive subjects would be found to have clinical evidence of asymptomatic metastatic disease.

Despite convincing evidence of the analytic and clinical validity of the CTC assay, clinical utility has not been established. Only one study that was specifically designed to determine clinical utility failed to show improved survival in metastatic breast cancer when systemic chemotherapy was changed in patients with persistently high CTC count (>5 CTCs per 7.5 mL blood) after 3 weeks of chemotherapy (13). No studies have been specifically designed to evaluate whether CTCs or other novel biomarkers may be used for surveillance in order to select individuals with nonmetastatic breast cancer after local therapy at high risk of clinical recurrence (20). Moreover, methodology now exists to characterize CTCs rather than simply enumerate them, as well as to identify and quantify somatic tumor mutations in blood or urine (11). This could yield insights into the mechanism underlying disease recurrence such as tumor dormancy (21) and selection of treatment approaches. These strategies may be particularly promising for preventing early recurrence within 5 years of diagnosis typically associated with hormone receptor-negative breast cancer (22), or later recurrence up to 15 years or longer after diagnosis in hormone receptor-positive breast cancer (23). The availability of more effective therapies for metastatic breast cancer, such as immune checkpoint blockade for triple-negative disease (24), and CDK 4/6 inhibitors (25) or novel oral selective estrogen receptor downregulators (26) for hormone receptor-positive disease, offers potential for early intervention that could ultimately delay or even prevent metastasis.

The time has never been better for a reappraisal of surveillance in early breast cancer in a prospective clinical trial, with one potential design schematically depicted in Figure 1. Key elements of the trial include: 1) selection of patients with nonmetastatic breast cancer at high clinical risk of recurrence based on classical clinicopathologic features (27); 2) further enrichment of the high-risk population based on an integral biomarker such as the CTC assay, with imaging to exclude distant metastasis in CTC-positive patients; and 3) testing interventions that may delay or prevent distant metastasis in the CTC-positive cohort in whom imaging has excluded distant metastasis. Such a trial should include a cross-platform comparison of the integral CTC assay used for treatment selection with other CTC assays, ctDNA assays that are both prognostic and potentially predictive response to specific therapies (eg, ESR1 mutations and response to SERDs) (28–30), and serial assays to screen high-risk populations at multiple timepoints after diagnosis and before recurrence, or as an intermediate pharmacodynamic biomarker of drug response. We have never been better positioned to launch such a trial—until we do, the clinical utility of CTCs and other liquid biopsy biomarkers remains unproven in this setting.

Notes

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