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The Role of ctDNA in Breast Cancer: Prognosis and Clinical Utility

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Introduction

Breast cancer remains the most common cancer among women globally, with significant morbidity and mortality.[1] Current treatment for breast cancer, both in the early stage and metastatic setting, is based on a tumour biopsy and immunohistochemical detection of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) expression.[1] Though substantial research has been undertaken over the years to establish new prognostic and predictive biomarkers in breast cancer, most have not demonstrated significant clinical utility. Circulating tumour DNA (ctDNA) is increasingly used across various cancer types for precision medicine. In this article, we discuss the current roles of ctDNA in breast cancer prognosis and its clinical utility in treatment decision-making in early- and advanced-stage settings.

Technical Aspects

Cancer cells can shed DNA fragments into the circulation through the cellular breakdown of tumour cells via apoptosis and necrosis.[2] Circulating tumour DNA (ctDNA) comprises short fragments of DNA that can be detected and analyzed in the blood, providing a potentially minimally invasive approach for disease monitoring and evaluating response to therapy.[2]

Several approaches can be used for ctDNA detection. Tumour-agnostic approaches involve testing broadly for multiple mutations with a predetermined panel of genes, while tumour-informed assays are individualized tests based on mutations/alterations observed in the individual's tumour.[2]

Historically, for tumour-agnostic approaches, the same ctDNA assay would be used for each patient with breast cancer without needing prior knowledge of the primary tumour's mutations.[2] By testing for multiple mutations, this approach allows for the discovery of *de novo*/acquired genomic alterations that might correlate with treatment resistance and potentially serve as treatment targets. Therefore, this approach may play a more important role in the metastatic setting to detect emergent or truncal mutations that have developed over time.[2] However, this technique usually requires a higher tumoral fraction of total cell-free DNA and, therefore, can have a lower sensitivity.[2] Another consideration with some tumour-agnostic approaches is the potential false positive results due to clonal hematopoiesis of indeterminate potential (CHIP). Mutations in hematopoietic progenitor cells occur as part of aging, and these CHIPs can be mistaken for tumour mutations. Additional white blood cells/buffy coat testing can help account for and correct for these CHIP mutations.[2]

With tumour-informed assays, the patient's tumour is sequenced (either whole exome sequencing [WES] or whole genome sequencing [WGS]) and an individualized ctDNA assay of a range of variants is created. This extra step of sequencing and developing a unique assay can make this approach more time-consuming than tumour-agnostic approaches. However, tumour-informed assays are often more sensitive at detecting molecular recurrence of disease, though they may miss emergent mutations over time.[2] These characteristics make these approaches more valuable in the early-stage setting to detect early recurrences.[2]

The amount of ctDNA in the total blood is usually low; therefore, different techniques are used to amplify this signal, which contributes to the sensitivity of the assay (**Table 1**).[2,3]

ctDNA in Early Breast Cancer

Prognostic Value of ctDNA

Current surveillance in patients with early-stage breast cancer involves clinical history,

Technique	Description
Amplicon-based	In amplicon-based NGS, gene-specific amplicons are used to amplify certain genomic regions expected to harbour tumour-derived mutations prior to NGS. This is often combined with unique molecular barcodes to reduce errors. Can be used in both tumour-agnostic assays or personalized tumor-informed assays.[2,3] This technique can usually be performed with a simple workflow allowing for a high throughput. This may be at the cost of lower sensitivity for low-frequency mutations compared to ddPCR; however, the sensitivity is assay-dependent.
Hybridization capture	Specific DNA regions are captured by hybridization using targeted probes. Non-target molecules are washed away, meaning the remaining library is enriched for the regions of interest. Can be used in both tumour-agnostic assays or personalized tumor-informed assays.[2,3] This can be more sensitive than amplicon-based NGS; however, it often requires a more expensive and complex workflow.
Methylation analysis	Methylation patterns are specific to cell types. By using techniques such as bisulfite conversion, cancer-specific methylation patterns can be captured and amplified.[2,3]
ddPCR	The DNA sample is partitioned into multiple droplets, in which isolated PCR occurs. Analyzing each droplet individually increases the sensitivity and reproducibility.[2,3]
BEAMing	Magnetic beads with primers designed to target the regions of interest are emulsified into droplets, similar to ddPCR, allowing PCR amplification within the individual droplets.[2,3]

Table 1. Different techniques used in ctDNA assay; *courtesy of Mairi Lucas, MD and Stephen Chia, MD.*

Abbreviations: BEAM: beads, emulsion, amplification, and magnetics, **ctDNA:** circulating tumour DNA, **dd:** droplet digital, **NGS:** next-generation sequencing, **PCR:** polymerase chain reaction

breast examination, annual breast imaging, and further imaging based on symptoms. Historical trials did not demonstrate an improvement in overall survival (OS) when more intensive imaging surveillance was used which aimed to provide earlier detection of metastatic disease.[1] There is increasing interest in the use of ctDNA due to its sensitivity and specificity to monitor for recurrences in patients with early-stage breast cancer, and thus, potentially to act at an earlier time point.[4]

In one of the earlier and larger studies evaluating ctDNA for this purpose, Garcia-Murillas et al. used personalized tumour-informed digital PCR (dPCR) assays to test for ctDNA at predetermined time points in 101 patients with breast cancer who had received definitive surgery with no clinical evidence of metastatic disease.[4] Across breast cancer subtypes, ctDNA detection was associated with relapsed disease (hazard ratio [HR], 25.2; 95% confidence interval [CI], 6.7–95.6; p-value: <0.001) with a median lead time of 10.7 months before radiologically confirmed metastatic disease.[4] While patients who remained ctDNA-negative were less likely to relapse, 6 (21.6%) patients with ctDNA-negative results experienced a relapse, with 3 of these being with brain-only relapses.[4] The blood-brain barrier has long been postulated as the reason that the brain is a sanctuary site for metastatic disease, and also may result in less detectable ctDNA in patients with metastatic disease in the brain only.[4]

Further studies have shown that ctDNA is a prognostic factor across breast cancer subtypes and can detect relapse earlier than conventional imaging.[5,6] In a study by Coombes et al., 49 patients with early-stage breast cancer were monitored with ctDNA testing using a tumour-informed assay. Of the patients who relapsed, 89% (16/17) had detectable ctDNA, with ctDNA detection occurring a median of 8.9 months prior to clinical relapse.[5] It is noteworthy, though, that in studies in which ctDNA is analyzed and detected in real-time, the triggered imaging

studies often detect evidence of metastatic disease already at that time point.

Neoadjuvant treatment for breast cancer is now recommended in HER2+ breast cancer that is >2 cm or node-positive, as well as in triple-negative breast cancer (TNBC) with clinical T2 disease or greater.[1] Multiple trials have shown the prognostic implications of gaining a pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) in these subtypes.[1] For those who do not achieve a pCR, adjuvant therapy can be escalated to reduce the risk of breast cancer recurrence.[1] In 196 patients with early-stage TNBC, who had residual disease post-NAC, the detection of ctDNA post was associated with a significantly worse distant disease-free survival (DDFS) (median, 32.5 months vs. not reached; HR, 2.99; 95% CI, 1.38–6.48; p-value: 0.006) and OS compared to those who remained ctDNA-negative.[6]

In an exploratory analysis of the I-SPY2 trial, in which tumour-informed ctDNA testing was performed pre-NAC, during treatment, and prior to surgery in high-risk early breast cancer patients.[7] Patients who did not achieve a pCR but were ctDNA-negative post-NAC had a similar rate of recurrence as patients with a pCR, suggesting ctDNA may be more informative regarding prognosis than pCR.[7] This was also reflected in a study that showed that the detection of ctDNA can further delineate those who are most at risk of recurrence within the residual cancer burden (RCB) score categories in TNBC. ctDNA-positivity was associated with inferior 3-year OS (50% vs. 86%, p-value: 0.002) compared with ctDNA-negative disease in those with RCB II disease, with a trend towards worse outcomes in those with ctDNA-positive/RCB III disease.[8]

Clinical Utility in Early Stage

As the above studies have highlighted, ctDNA can be prognostic; however, what remains unclear and not adequately tested as the primary objective in large randomized clinical trials, is whether this information changes clinical practice and, more importantly, whether it significantly alters patient outcomes.

The MonarchE trial assessed the use of abemaciclib in patients with high-risk, ER-positive, HER2-negative disease. In this study, a cohort of patients was identified with sufficient primary tumour tissue available to perform WES and subsequently create a personalized tumour-informed assay (Signatera™ ctDNA assay – Natera Inc.) to assess the utility of ctDNA within this study.[9] Of the 910 patients reviewed, 8% were ctDNA-positive at baseline.[9] Of that group, 59% remained persistently ctDNA-positive on treatment with adjuvant abemaciclib, while the remaining 41% became ctDNA-negative (undetectable).[10] Patients who were ctDNA-positive at baseline had a worse invasive disease-free survival (IDFS) of 20% (95% CI, 12.5–82.0) at 4 years compared to 79.1% (95% CI, 76.4–82) in the baseline ctDNA-negative group (p-value: <0.001).[10] Importantly, rates of IDFS events varied between those who were persistently ctDNA-positive and those who became ctDNA-negative, with 100% and 42% having events, respectively.[10] The prognostic value of ctDNA was also observed within the persistently ctDNA-negative group, with only 14% having an IDFS event compared to 93% in the group who became ctDNA-positive over time.[10] The majority of the events in ctDNA-positive patients were distant relapses.[10] This further highlights the prognostic ability of ctDNA, but also suggests that abemaciclib may allow some patients to clear ctDNA and reduce their risk of cancer recurrence. The lead time between the ctDNA detection and IDFS events varied, but was relatively short at 7 months (range 0–48) in those originally ctDNA-negative that became ctDNA-positive. It remains unknown whether instituting or changing treatment at the point of ctDNA detection without clinical evidence of metastatic disease affects outcomes.[10]

The ongoing DARE trial enrolled and followed patients with high-risk ER-positive disease on adjuvant endocrine therapy with serial ctDNA screening every 6 months using a tumour-informed assay (Signatera™ ctDNA assay – Natera Inc.).[11] This study randomized patients who become ctDNA-positive to continue current therapy versus changing to palbociclib and fulvestrant.[11] The ctDNA positivity rate in the first test was 3.8%, and the anytime ctDNA detection rate among those with serial testing was 7.2%.[11] An interim analysis showed that 5 (16.7%) patients with ctDNA-positive disease also had asymptomatic disease on imaging.[11] It remains unknown what the optimal time interval for ctDNA testing is, and whether this varies between breast cancer subtypes. Outcomes for disease-free survival are awaited and will hopefully shed more light on the clinical utility of ctDNA in breast cancer in terms of treatment of ctDNA-positive disease in the absence of radiological evidence of metastatic

disease. Most importantly, the endpoint of these types of intervention studies should be OS, to overcome the issue of lead time bias.

The c-TRAK TN trial was a multicentre Phase II trial that integrated prospective ctDNA monitoring with a tumour-informed assay (Thermo Fisher Custom TaqMan Assay Design Tool) every 3 months up to 1 year post-completion of adjuvant therapy in patients with early-stage TNBC.[12] Patients who became ctDNA-positive and staging imaging-negative were randomized to observation or intervention with pembrolizumab.[12] Within 12 months, 27.3% of patients became ctDNA-positive; however, of the patients randomized to the intervention arm, 72% had metastatic disease on imaging at the time of ctDNA detection.[12] This again highlights two important questions regarding ctDNA testing in early breast cancer: firstly, regarding the sensitivity of the assay, and secondly, regarding the need for clarity on the optimal interval for testing.

Lastly, the ZEST trial was a Phase III trial assessing niraparib in patients with BRCA-mutant, ER-positive, HER2-negative breast cancer or TNBC, post-completion of definite therapy with detectable ctDNA and no radiological evidence of disease.[13] The ZEST trial was closed early due to a low randomization rate as only 8% of patients screened were ctDNA-positive, and 49% of these patients had radiological evidence of recurrence at the time of the positive ctDNA test.[14] These 40 patients were randomized to either placebo or niraparib, and the niraparib arm had a numerical longer recurrence-free interval. However, given the small number of patients, this trial was not powered to evaluate the efficacy of niraparib.[14]

Further studies are in progress assessing the clinical utility of ctDNA for early-stage breast cancer.

ctDNA in Metastatic Breast Cancer (MBC)

Prognostic Aspects of ctDNA in Metastatic Breast Cancer

In contrast to early-stage breast cancer, which is focused on the early detection of ctDNA or molecular recurrence in the absence of overt evidence of metastatic disease on imaging, ctDNA is detectable in the majority of patients with known MBC.[15]

Similar to the early-stage setting, an increase in the ctDNA tumour fraction in the metastatic setting is associated with worse outcomes.[15,16] In the LOTUS trial that assessed the oral AKT inhibitor ipatasertib with paclitaxel in first-line metastatic TNBC, a high ctDNA fraction was associated with worse progression-free survival regardless of the treatment arm.[17] A systematic review and meta-analysis by Dickinson et al. reviewed 75 studies that analyzed ctDNA data and survival outcomes in patients with MBC.[16] In this meta-analysis, the detection of specific ctDNA alterations was significantly associated with reduced survival (HR, 1.40; 95% CI, 1.22–1.58; p-value: <0.001), and this association was consistent across breast cancer subtypes (hormone receptor-positive, HER2-positive, and TNBC).[16]

Clinical Utility in MBC

Previous studies showed that detection of circulating tumour cells (CTCs) correlates with a higher risk of recurrence.[18] However, studies that adjusted treatment in the metastatic setting based on CTC did not improve outcomes.[18] Therefore, while the prognostic value of rising ctDNA in metastatic disease has been shown,[16,17] it remains unclear if changing treatment based on this instead of conventional imaging progression will lead to an improved OS. The clinical utility of ctDNA detection in MBC currently relates to its ability to detect specific mutations in tumour cells that match targeted therapies.

The mutational landscape in MBC is not static and changes over time with the emergence of different sub-clones. Repeat tumour biopsies of progressive metastatic sites can help identify new mutations and guide treatment options. However, a biopsy may not represent all malignant cells due to heterogeneity within metastatic sites.[19] ctDNA testing may provide more detailed information about the disease's mutational landscape and clonality based on variant allele frequency of the various genomic alterations shed.[19]

The LOTUS trial showed 100% concordance between ctDNA and tissue sequencing in patients with *PIK3CA* or *AKT1* mutations, suggesting the ctDNA may be an excellent non-invasive test to assess these mutations rather than undergoing further tissue biopsies, particularly for these specific mutations with available targeted treatments.[17]

The plasmaMATCH trial was an open-label, multicohort trial assessing the accuracy of ctDNA testing in advanced breast cancer, and the ability of ctDNA testing to select patients for targeted therapy based on the ctDNA

alterations detected.[20] Tests for ctDNA were done via two different technologies, dPCR and targeted sequencing with a 73 gene panel (Guardant360-Guardant Health). Where feasible, this was also compared to results from a tissue biopsy.[20] There was 96–99% agreement in identifying mutations between ctDNA dPCR and targeted sequencing.[20] However, it should be noted that there was greater discordance for ctDNA results regarding mutations with low allele frequency, which may reflect the sensitivity of the assay.[20] When dPCR ctDNA results were compared to tissue sequencing from contemporaneous and time-discordant biopsies, the sensitivity of ctDNA was 98% and 85%, respectively.[20] Mutations were identified by ctDNA in 51.1% of patients and 34.5% had a targetable mutation eligible for the treatment cohorts.[20] The outcomes in patients with targetable mutations who entered the treatment cohorts were similar to previous studies involving tissue testing, supporting the clinical validity of ctDNA testing for the identification of mutations as an alternative to tissue testing.[20]

The INAVO120 trial assessed the activity of inavolisib, a phosphoinositide 3-kinase (PI3K) inhibitor, in patients with advanced PIK3CA-mutated hormone receptor-positive/HER2-negative breast cancer.[21] Both ctDNA testing and tumour biopsy sequencing (using the *PIK3CA* Mutation Test, F. Hoffmann-La Roche Ltd) were allowed for mutation identification, highlighting the clinical confidence in ctDNA testing to accurately identify this mutation. Paired ctDNA samples obtained pre- and on-treatment were compared and showed a reduction in *PIK3CA* mutation allele frequency, postulating that ctDNA may have a role as a marker of early disease response.[21]

Conclusion/Discussion

In conclusion, ctDNA can detect molecular recurrences in early-stage breast cancer before conventional imaging techniques. Patients can become ctDNA-positive at different times throughout their treatment journey, with some lead time prior to radiological relapse in a proportion of patients. With multiple trials using different testing schedules and platforms, the optimal approach in terms of timing and type of test remains to be clearly defined. The lead time between ctDNA detection and radiological progression may differ between breast cancer subtypes and, more importantly, based on the assay's sensitivity, which will need to be factored into ctDNA testing approaches. The role of ctDNA in clinical practice in early-stage breast cancer is evolving with a current lack of knowledge on whether systemic treatment(s) after detection of molecular relapses leads to the elimination of detectable ctDNA and improves outcomes rather than simply contributing to lead time bias.

CtDNA demonstrates a strong prognostic ability in the metastatic setting, as rising ctDNA levels often precede radiologic progression. However, its clinical utility in guiding treatment changes is evolving as an established standard practice. ctDNA testing is becoming common in clinical practice where assay acquisition and access to appropriately matched targeted agent(s) is available. With metastatic disease, ctDNA testing can offer a non-invasive alternative to tissue biopsies for identifying mutations and may provide more comprehensive information regarding clonality, markers of treatment resistance, and potential treatment targets.

Ultimately, while ctDNA has proven to be a valuable tool for disease monitoring, more robust clinical trials are needed to establish its definitive role in guiding treatment decisions and improving long-term survival for patients with breast cancer before it will become more entrenched into everyday clinical practice.

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