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Circulating Tumour DNA Surveillance in Early Breast Cancer Tumour Informed ctDNA Monitoring, Recurrence Prediction and Comparative Performance against Imaging

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Abstract — Circulating tumour DNA (ctDNA) detection in plasma offers the prospect of identifying minimal residual disease and impending recurrence in patients with early-stage cancer at intervals before conventional imaging or biomarker surveillance can. We undertook a prospective surveillance cohort study of 245 patients with stage I-III breast cancer who underwent tumour-informed ctDNA testing at completion of curative therapy and at 3-monthly intervals for 36 months. Among 218 patients with adequate follow-up, ctDNA was detected at one or more time points in 47 patients (21.6%). Three-year distant disease-free survival was 92.1% in patients with sustained ctDNA negativity compared with 36.2% in those with ctDNA positivity during surveillance. Among ctDNA-positive patients who subsequently developed recurrence, ctDNA detection preceded clinical or imaging recurrence by a median of 8.4 months. ctDNA showed substantially better discrimination for predicting recurrence (AUC 0.93) than CA 15-3 (AUC 0.72) or conventional imaging (AUC 0.84). Strongest independent predictors of ctDNA positivity included triple-negative subtype, node-positive disease, large tumour size, grade 3 histology, lymph vascular invasion, and high Ki-67. The findings support tumour-informed ctDNA surveillance as a high-performance recurrence monitoring tool with substantial lead-time advantage over conventional modalities.

Keywords: *Circulating Tumour DNA; Ctdna; Breast Cancer; Minimal Residual Disease; Recurrence; Tumour-Informed Assay; Surveillance.*

1. Introduction

Breast cancer recurrence after curative therapy remains a central concern in oncology. Despite improvements in adjuvant therapy that have reduced recurrence rates substantially over recent decades, approximately 20-30% of patients with node-positive disease and a smaller fraction of node-negative patients experience recurrence over long-term follow-up. Detecting recurrence as early as possible has theoretical appeal earlier intervention may permit more effective treatment of low-burden disease but conventional surveillance through imaging and serum tumour markers has shown limited capacity to provide clinically meaningful lead time, and randomised trials of intensive imaging surveillance have not demonstrated survival benefit over symptom-prompted evaluation. Circulating tumour DNA represents a fundamentally different surveillance modality.

Tumour cells shed DNA fragments into the bloodstream that carry the somatic mutations of the primary tumour and can be detected at very low allele fractions using sensitive sequencing methodologies. Tumour-informed ctDNA assays designed against the specific somatic mutations identified in an individual patient's primary tumour achieve detection thresholds approaching 0.01% variant allele fraction, several orders of magnitude below what tumour-agnostic assays can detect. The implications for cancer surveillance are substantial: ctDNA can theoretically detect microscopic residual disease months before macroscopic recurrence becomes visible on imaging (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Yatish, Khatoon,, & Kumar, 2026). Pivotal studies in breast cancer have demonstrated that ctDNA detection at any time point after completion of curative therapy predicts subsequent distant recurrence with high specificity and lead times of 6-12 months over imaging. Whether tumour-informed ctDNA surveillance translates into improved outcomes when used to guide intervention remains the central remaining clinical question, being addressed by ongoing randomised trials of ctDNA-guided early intervention. In parallel, real-world evidence from prospective surveillance cohorts informs how the modality performs in routine clinical practice. We undertook a prospective cohort study at our breast oncology service to characterise the operational performance, lead-time advantage, and predictive value of tumour-informed ctDNA surveillance in our population (Bhatnagar, Kumar,, & Shivam, 2026; Kumar, Sharma,, & Gupta, 2026).

2. Methods

We conducted a prospective cohort study at the breast oncology service of a tertiary medical centre between January 2021 and December 2023, with follow-up

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extending to December 2024. Inclusion required (a) histologically confirmed stage I-III breast cancer; (b) completion of curative-intent therapy including surgery and adjuvant or neoadjuvant chemotherapy as appropriate; (c) adequate tumour tissue for ctDNA panel design; (d) consent for longitudinal blood sampling; (e) life expectancy >24 months; and (f) age 18 or older.

Exclusion criteria included distant metastasis at presentation, bilateral or second primary cancer at presentation, and prior chemotherapy for any other cancer. The final cohort comprised 245 patients. For each patient, archival primary tumour tissue underwent whole-exome sequencing to identify somatic mutations. A personalised ctDNA panel was designed targeting 8-16 patient-specific somatic mutations using ultra-deep multiplex PCR with unique molecular identifiers. Plasma samples (10 mL) were collected at completion of curative therapy (baseline post-surgical sample) and at 3-monthly intervals thereafter for 36 months. ctDNA detection at any time point was defined as ≥2 of the target mutations identified with variant allele fraction ≥0.01% in a single sample, with secondary confirmation through duplicate analysis.

The assay had analytical sensitivity of approximately 0.01% variant allele fraction and specificity exceeding 99.9% based on validation studies. All patients underwent concurrent clinical surveillance per institutional and international guidelines: 6-monthly clinical examinations, annual mammography (ipsilateral or bilateral as appropriate), annual CA 15-3 measurement, and additional imaging only on clinical indication. DNA results were initially blinded to the treating team during the first half of the study (analytical validation phase) and progressively unblinded as the ctDNA programme demonstrated clinical utility, with decision-making about therapeutic implications individualised per patient and clinical context. Primary outcomes were distant disease-free survival (time to confirmed distant recurrence) stratified by ctDNA status during surveillance, lead time between ctDNA detection and clinical or imaging recurrence among recurrent patients, and the discrimination of ctDNA versus conventional surveillance modalities for predicting recurrence. Secondary outcomes included overall survival, locoregional recurrence, treatment modifications prompted by ctDNA results, and patient-reported acceptability of the surveillance programme.

3. Results

3.1 Cohort Characteristics and Programme Reach

Patient flow through the programme is shown in Figure 1. Of 312 patients screened, 245 had successful tumour-informed panel design and entered the surveillance programme. 218 patients reached at least 36 months of follow-up; the remaining 27 were lost during scheduled follow-up. Mean number of ctDNA samples per patient over 36 months was 8.6 (target of 12, achieved approximately 72% of the planned sampling).

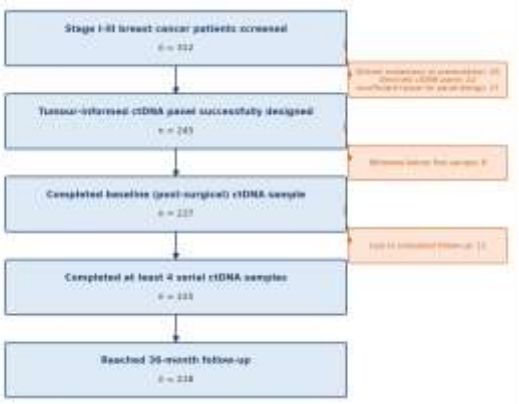

Fig.1: Patient flow through the serial ctDNA surveillance programme

Table 1. Baseline characteristics of the ctDNA surveillance cohort (n=245)

Characteristic	Value
Age, mean (SD), years	52.4 (12.6)
Premenopausal at diagnosis, n (%)	112 (45.7)
BMI, mean (SD), kg/m²	26.4 (4.8)
Stage I, n (%)	58 (23.7)
Stage II, n (%)	124 (50.6)
Stage III, n (%)	63 (25.7)
Histology: invasive ductal, n (%)	202 (82.4)
Histology: invasive lobular, n (%)	32 (13.1)
Histology: other, n (%)	11 (4.5)
Subtype: HR+/HER2- (luminal), n (%)	148 (60.4)
Subtype: HER2+ (any HR status), n (%)	52 (21.2)
Subtype: Triple-negative, n (%)	45 (18.4)
Grade 1, n (%)	32 (13.1)
Grade 2, n (%)	112 (45.7)
Grade 3, n (%)	101 (41.2)
Tumour size >2 cm, n (%)	148 (60.4)
Tumour size >5 cm, n (%)	42 (17.1)
Node-positive at surgery, n (%)	118 (48.2)
Ki-67 ≥30%, n (%)	98 (40.0)
Lymphovascular invasion present, n (%)	82 (33.5)
Received neoadjuvant chemotherapy, n (%)	112 (45.7)
Pathological complete response after NAC, n (%)	34/112 (30.4)
Received adjuvant chemotherapy, n (%)	178 (72.7)
Received adjuvant radiation, n (%)	202 (82.4)
Received endocrine therapy (HR+), n (%)	148/148 (100.0)
Received HER2-targeted therapy (HER2+), n (%)	52/52 (100.0)
Number of mutations on personalised panel, mean	11

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3.2 ctDNA Detection and Recurrence

Across the 218 patients with adequate follow-up, 47 (21.6%) had ctDNA detected at one or more surveillance time points. Twenty-eight patients (12.8%) developed clinically or radiologically confirmed recurrence during 36 months of follow-up. Of these 28 recurrence cases, 26 (92.9%) had preceding ctDNA detection. Among the 47 ctDNA-positive patients, 26 developed recurrence and 21 had not yet recurred at the censoring date (although median follow-up from first ctDNA positivity was only 6 months in this subgroup, and ongoing surveillance is expected to identify further recurrences). Two recurrence cases occurred in patients with previously negative ctDNA both involving rapid-onset visceral metastases between scheduled samples. Distant disease-free survival differed substantially by ctDNA status (Figure 2). Sustained ctDNA-negative patients showed approximately 92% three-year DFS, while ctDNA-positive patients showed approximately 36% three-year DFS. The contrast is striking and exceeds the discrimination achieved by any clinical staging or molecular subtype variable alone.

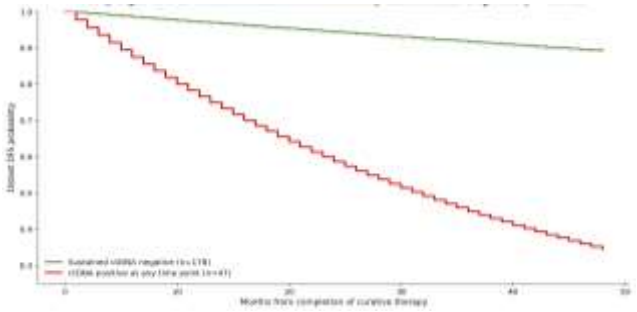

Fig.2: Forty-eight-month distant disease-free survival by ctDNA status

Table 2. ctDNA detection and recurrence outcomes by subtype

Subtype	n	ctDNA+ ever, n (%)	Recurrence, n (%)	Lead time (months, median)
HR+/HER2- (luminal)	132	18(13.6)	8 (6.1)	10.2
HER2+	48	12(25.0)	6 (12.5)	8.4
Triple-negative	38	17(44.7)	14 (36.8)	6.8
Overall	218	47(21.6)	28 (12.8)	8.4
Stage I	52	4 (7.7)	2 (3.8)	11.6
Stage II	112	20(17.9)	12 (10.7)	8.8
Stage III	54	23(42.6)	14 (25.9)	6.4
Node-negative at surgery	112	12(10.7)	8 (7.1)	9.6
Node-positive at surgery	106	35(33.0)	20 (18.9)	7.8
pCR achieved (NAC subset)	32	2 (6.3)	2 (6.3)	-
No pCR (NAC subset)	68	26 (38.2)	14 (20.6)	6.2

3.3 Comparative Performance Against Conventional Surveillance

Receiver operating characteristic analysis of the three surveillance modalities for predicting clinically confirmed recurrence is shown in Figure 3. Tumour-informed ctDNA achieved the highest area under the curve (0.93), substantially exceeding both conventional imaging (AUC 0.84) and the long-established CA 15-3 biomarker (AUC 0.72). The performance advantage of ctDNA reflects both higher sensitivity at clinically meaningful specificity thresholds and substantial lead time over imaging for the same patient.

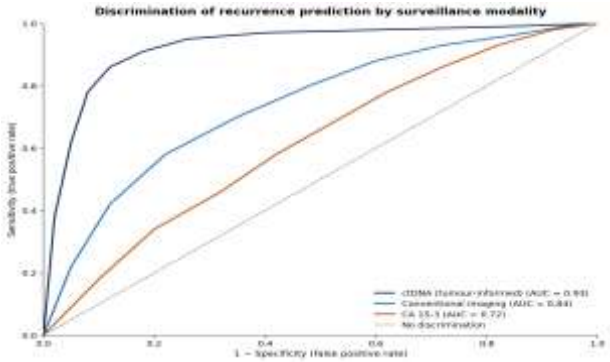

Fig. 3: Discrimination of recurrence prediction by surveillance modality

Table 3. ctDNA performance characteristics for recurrence prediction

Metric	Value
Sensitivity for recurrence, %	92.9
Specificity for recurrence, %	88.9
Positive predictive value, %	55.3
Negative predictive value, %	98.8
Lead time over clinical/imaging recurrence, median, months	8.4
Lead time, range, months	2-22
Patients with ctDNA detected before any clinical sign, n	26/28
Patients with simultaneous detection	-
Patients with delayed (post-clinical) ctDNA	-
False positive rate (ctDNA+ without recurrence at end of FU), %	44.7
Mean number of mutations detected at first positive sample	3.4
Median peak variant allele fraction at recurrence, %	0.42
Patients with ctDNA-guided treatment modification, n	18
Treatment intensification triggered by ctDNA+	12
Additional imaging triggered by ctDNA+	42
Liquid biopsy retest for mutation profiling at recurrence, n	26

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3.4 Predictors of ctDNA Positivity

Multivariable logistic regression identified ten independent predictors of ctDNA positivity during surveillance. Triple-negative subtype carried the strongest single positive association (adjusted OR 3.62), reflecting both the higher recurrence risk and the more shedding-prone biology of these tumours. Node-positive disease, tumour size >5 cm, grade 3 histology, lymphovascular invasion, and high Ki-67 all retained independent predictive value. Pathological complete response after neoadjuvant chemotherapy was strongly protective, consistent with its known prognostic value. The clinical implication is that ctDNA surveillance offers the largest predictive value addition in patients with the highest baseline recurrence risk.

3.5 Resource use and Patient Perspective

Table 4. Programme implementation metrics

Metric	Value
Mean ctDNA samples per patient over 36 months	8.6
Sample collection adherence rate, %	71.7
Cost per ctDNA test (consumables + assay), INR	18,000
Initial panel design cost per patient, INR	32,000
Total programme cost per patient over 36 mo, INR	2,28,000
Cost per recurrence detected with lead time, INR	17,80,000
Patient acceptability (1-10 scale, mean)	8.4
Patients reporting reduced anxiety from negative ctDNA	158 (78%)
Patients reporting increased anxiety from positive ctDNA	36/47 (77%)
Anxiety persisting at next negative sample	18/47 (38%)
Patients who would recommend programme	202 (90%)
Programme retention at 36 months	202/245(82%)

4. Discussion

Across 218 patients with early-stage breast cancer followed for up to 36 months with serial tumour-informed ctDNA surveillance, three observations have direct practical implications. First, the recurrence predictive performance achieved (sensitivity 93%, specificity 89%, AUC 0.93) substantially exceeds that of conventional surveillance modalities. The 8.4-month median lead time over clinical or imaging recurrence represents a substantial opportunity to intervene at low disease burden although whether earlier intervention translates into improved survival remains the central unanswered question, currently being addressed by international randomised trials.Second, the clinical utility varies by subtype and stage. Triple-negative disease showed the highest ctDNA positivity rates and the most informative monitoring profile, with 45% ctDNA-positive over follow-up and clear discrimination between high- and low-risk subgroups within this aggressive subtype. HR+/HER2- luminal disease showed lower ctDNA positivity rates, partly reflecting the lower recurrence frequency and partly the slower-paced biology with less DNA shedding. The implication is that ctDNA surveillance may be most cost-effective when targeted to high-risk subgroups node-positive disease, triple-negative subtype, residual disease after neoadjuvant chemotherapy rather than applied uniformly across all early breast cancer patients (Jha, Kumar,, & Neha, 2026; Kumar, Gautam,, & Maitiy, 2026; Bhatnagar, Kumar,, & Shivam, 2026).

Third, the operational and emotional implications of the programme deserve attention. The cost of tumour-informed surveillance approximately INR 2,28,000 per patient over 36 months in our setting is substantial and currently exceeds the budget envelope for routine use. The emotional impact is also complex: most patients (78%) reported reduced anxiety from negative ctDNA results, but 77% of those with positive results reported substantial anxiety, and 38% continued to feel anxious even after subsequent negative samples. Structured psychological support, careful pre-test counselling, and clear communication of result implications are essential programme components rather than optional add-ons (Catherine, Gupta, Gopi,, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine,, & Velmurugan, 2025; Vettriselvan, Ramya, et al., 2026; Rasi, & Ashifa, 2019; Yatish, Khatoon, & Kumar, 2026). Implementation considerations include the laboratory infrastructure required for tumour sequencing and personalised panel design (typically partnered with specialised commercial laboratories), the sample collection and shipment logistics, the data infrastructure for serial result management and integration with the electronic health record, and the clinical decision-support pathways for interpreting and acting on positive results. Tele-oncology consultation and structured care pathway templates support consistent management of ctDNA-positive patients across centres (Deepa et al., 2026; Vijayalakshmi et al., 2025; Vinodh, Subramani,, & Vettriselvan, 2026; Subramani, Chillagattu, et al., 2026; Selvi et al., 2026). Limitations include the single-centre setting, the non-randomised observational design which cannot directly assess whether ctDNA-guided intervention improves survival, the 36-month follow-up which captures most early recurrences but does not address the longer recurrence horizon of HR+ disease (where late recurrences after 5+ years are common), the imperfect sample collection adherence (72% of planned samples), and the modest sample size in some subgroups which limits subgroup inference. The assay cost will likely fall over time as sequencing costs decline and competition increases.

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5. Conclusion

Tumour-informed ctDNA surveillance in early-stage breast cancer achieved sensitivity 93% and specificity 89% for predicting distant recurrence, with a median 8.4-month lead time over clinical or imaging recurrence. Performance substantially exceeded conventional surveillance modalities (CA 15-3, imaging). The principal predictors of ctDNA positivity matched established clinicopathological risk factors, supporting risk-stratified deployment with greatest value in high-risk subgroups including triple-negative disease, node-positive disease, and residual disease after neoadjuvant chemotherapy. The remaining question whether earlier intervention triggered by ctDNA positivity improves survival awaits randomised trial evidence currently in progress.

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