Prospective Analysis of Circulating Tumor Cell Clearance and Dynamics with Adjuvant Radiotherapy in Locally Advanced Breast Cancer

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INTRODUCTION

- Detection of circulating tumor cells (CTCs) is an established adverse prognostic biomarker for clinical outcomes in non-metastatic breast cancer.
- The kinetics of CTC clearance with adjuvant radiotherapy (RT), the frequency of CTC emergence, and the evolution of CTC phenotypes during treatment remain incompletely characterized .
- Here we present the results of a prospective observational cohort study (MDA 2022-0601) evaluating the dynamics of CTC detection and response to adjuvant breast RT

STUDY DESIGN & METHODS

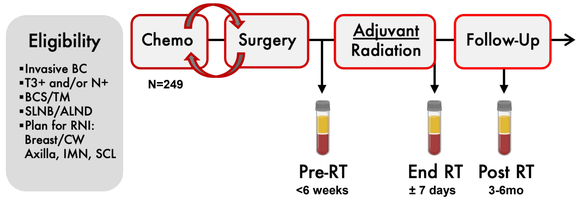


Figure 1. Study Eligibility, Schema (MDA 2022-0601), and CTC Assessment (CellSearch®) at up to 3 predefined timepoints: Pre-RT (<6 weeks Pre RT), End RT (within 7 days), Post RT (3-6 months after last treatment).

- Rates of CTC detection and CTC clearance with RT were estimated. CTC positivity was defined as ≥1 CTC/7.5 mL
- CTC status was compared between paired timepoints using McNemar's exact test. Longitudinal trajectories were summarized using first-order Markov transition probabilities.
- Associations with clinicopathologic variables were assessed using univariate logistic regression, Fisher's exact test, and Wilcoxon rank-sum tests as appropriate. Two-sided P < 0.05 was considered significant.
- Changes in absolute CTC and HER2+ CTC counts were assessed with Friedman and paired Wilcoxon tests.
- Longitudinal associations between timepoint and HER2-expressing CTCs were evaluated using population-averaged GEE logistic regression with patient-level clustering; mixed-effects logistic regression was used for confirmatory analyses in CTC-positive samples.

RESULTS

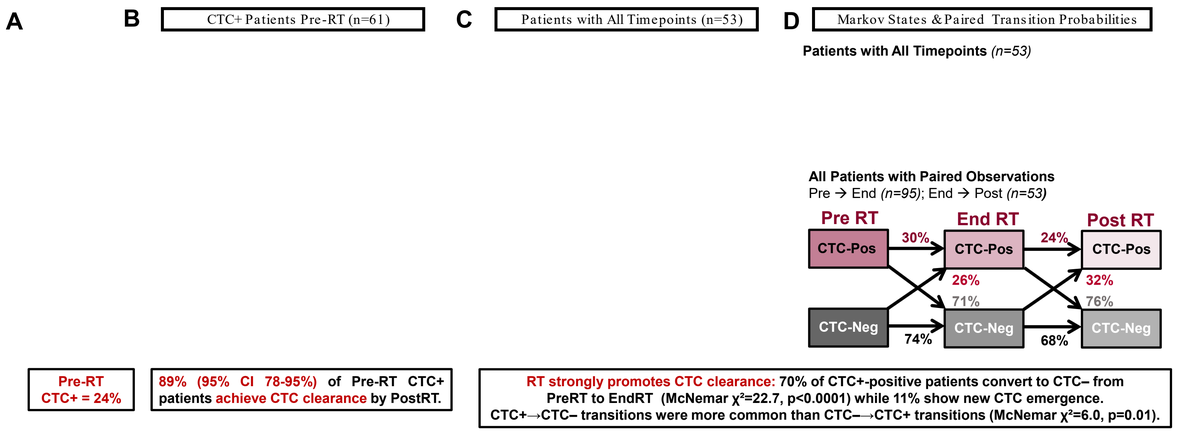


Figure 2. (A) Pre-RT CTC prevalence in the full cohort (n=249). (B) CTC trajectories among all Pre-RT CTC+ patients. (C) Three-timepoint Sankey transitions of clearance, emergence, and persistence. (D) Markov state probabilities and paired transition rates quantifying RT-associated CTC clearance and emergence dynamics.

Figure 3. Univariate logistic regression of clinicopathologic associations of CTC+ status at each timepoint (Odd's Ratios, 95% CI). **cN2-3 disease was associated with CTC+ status Pre-RT & End-RT but not Post-RT. In population-averaged analysis, cN2–3 conferred higher odds of CTC+ status across timepoints (Wald χ^2 = 8.61, P = 0.003).**

Figure 4. Distribution of CTC phenotypes over time, stratified by primary tumor HER2 status. **Phenotype distributions changed significantly over time in HER2-neg tumors (χ^2=19, p<0.001) but not Her2+ (P = 0.10). In GEE models, time was associated with HER2+ CTC prevalence (Wald χ^2=24.1, P<0.001), primarily by HER2-neg tumors (P<0.001).**

RESULTS

Figure 5. Median [IQR] absolute CTC count (gray) and CTC Her2+ count (pink) among CTC+ patients using Wilcoxon signed-rank test with continuity correction **Among patients with detectable CTCs Pre RT, RT significantly decreases the median number of detectable CTCs (p<0.001) and HER2+ CTCs (p<0.05).**

CONCLUSIONS

- **CTC status is dynamic during RT**, with frequent clearance and non-trivial emergence across paired timepoints.
- **RT induces rapid and durable CTC clearance** in **>85–90% of patients** with detectable CTCs prior to RT.
- **A small subset of CTC+ patients Pre-RT (~10%) demonstrates persistent CTC positivity after RT**, identifying a potential biologically resistant population for risk-adapted strategies.
- **HER2+ CTCs increase during RT**, particularly HER2-neg primary tumors, suggesting **phenotypic evolution under treatment pressure**.
- **Advanced nodal disease (cN2–3) is associated with higher odds of CTC positivity prior to and at the end of RT** but not Post RT.
- **Serial CTC monitoring during RT provides dynamic, biologically informative response assessment** beyond baseline risk stratification.

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