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Mitosis in Circulating Tumor Cells Correlates with Highly Aggressive Disease in Metastatic Breast Cancer

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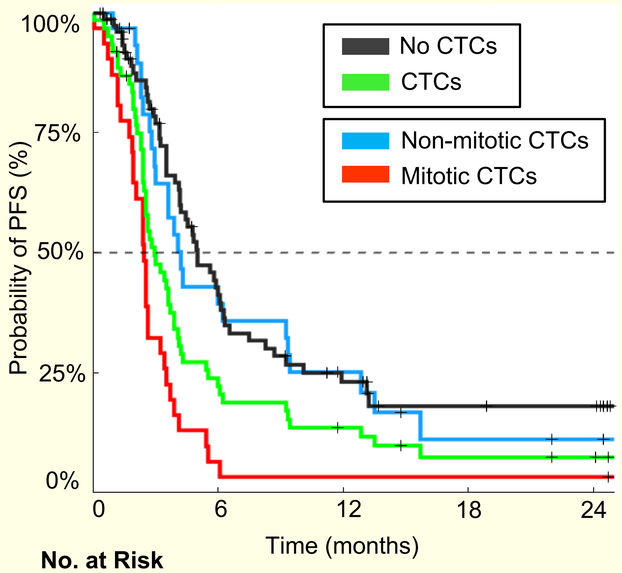
ABSTRACT

Circulating tumor cells (CTCs) are a well-known non-invasive blood biomarker which can stratify metastatic breast cancer (mBC) patients, especially those with highly aggressive subtypes. Initial pilot studies have characterized a distinct subtype of CTCs undergoing mitosis, whose presence correlates with worse survival outcomes than CTCs alone. However, their prognostic value and their influence in different therapeutic regimes remains unknown. In a multi-institutional prospective study, we isolated CTCs from n=138 mBC patients to categorize mitotic CTCs, evaluate their association with progression-free survival (PFS) & overall survival (OS) over 2 years, and how their response rates effect different therapeutic strategies.

MATERIALS & METHODS

Peripheral blood samples (7.5ml) were collected from n=138 mBC patients progressing on systemic therapies but prior to new systemic therapies (i.e. chemotherapy n=48, hormone therapy n=17, immunotherapy n=64, targeted therapy n=22). CellSieve microfilters isolated CTCs via size exclusion and cells fluorescently stained for CD45, Cytokeratin, and DAPI. CTCs were imaged, enumerated, and subtyped based on the presence of ≥1 mitotic CTC, using previously established visual indicators. PFS and OS were assessed over 2 years by censored univariate and multivariate analyses. Therapy efficacy was assessed by comparing median PFS (mPFS) and median OS (mOS) in the therapy categories.

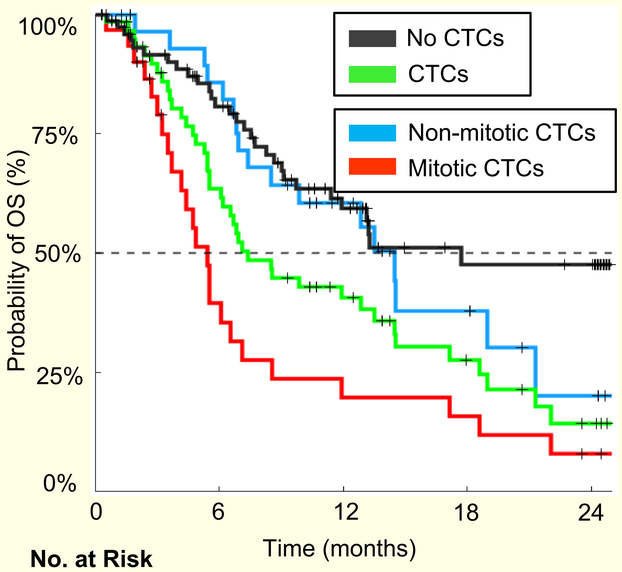
Figure 1. PFS of CTC Subtypes



No. at Risk

No CTCs	77	26	12	5	5
CTCs	61	13	7	3	2
Non-mitotic CTCs	30	11	6	2	1
Mitotic CTCs	31	2	1	1	1

Figure 2. OS of CTC Subtypes



No. at Risk

No CTCs	77	51	28	14	13
CTCs	61	34	18	9	3
Non-mitotic CTCs	30	24	13	5	2
Mitotic CTCs	31	10	5	4	1

Figure 3. Median PFS by Cell Group

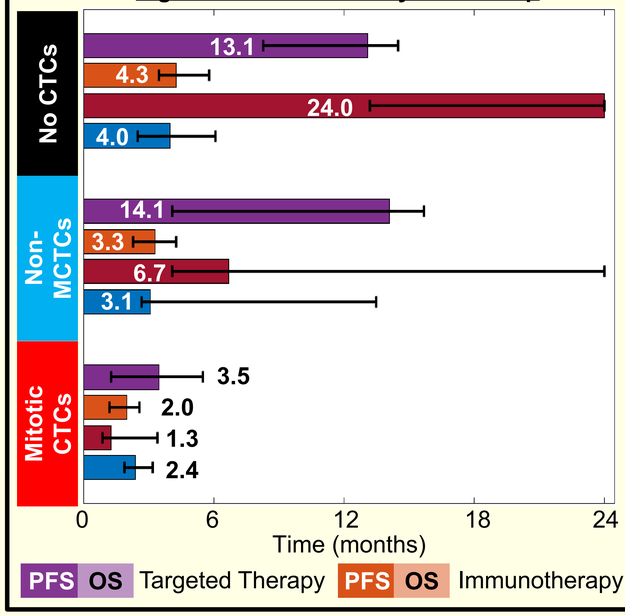
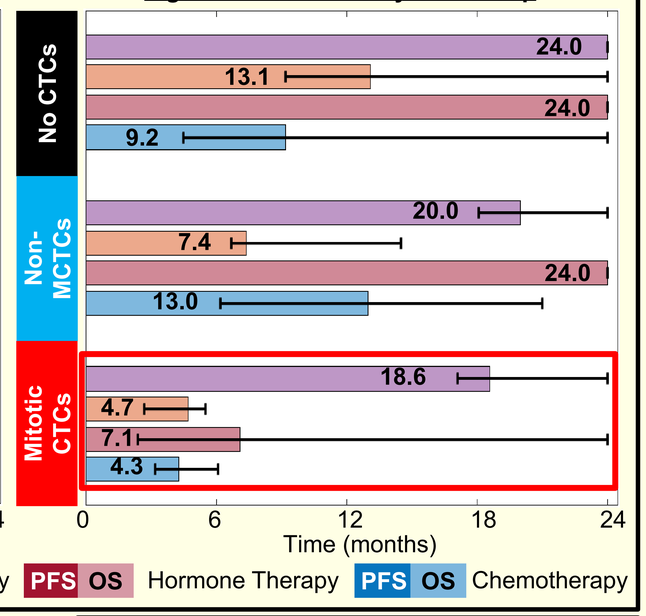


Figure 4. Median OS by Cell Group



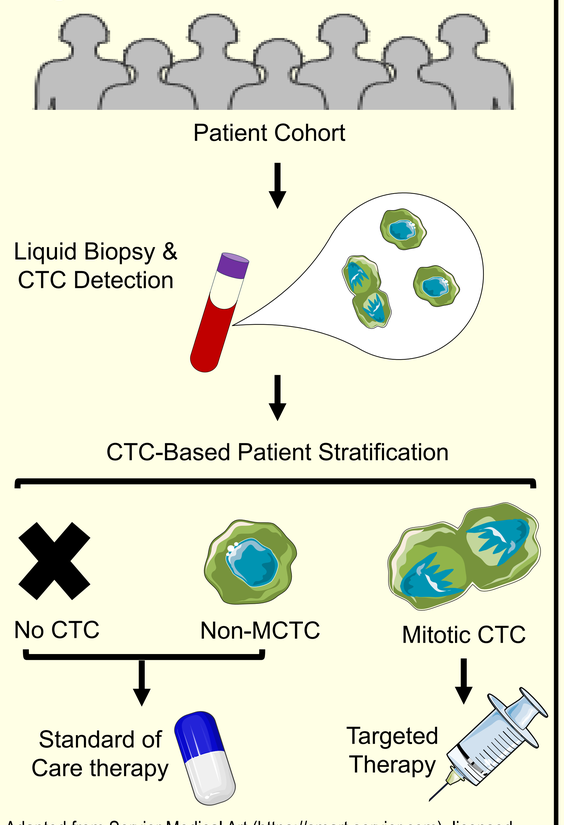
RESULTS

- Any CTC type was found in 44% of patients (n=61/138), Mitotic CTCs were identified in a subset, 51% (n=31/61)
- Any CTC type was associated with poorer PFS (HR=1.8, p=0.0064) & OS (HR=2.1, p=0.0035) vs without CTCs. Mitotic CTCs had significantly poorer PFS (HR=2.8, p=0.0009) & OS (HR=2.6, p=0.0068) versus non-mitotic CTCs. **(Fig. 1 & Fig. 2)**
- Both No CTCs & Non-mitotic CTCs have similar response and survival rates independent of therapy. **(Fig. 3 & 4)**
- Mitotic CTCs had poor PFS to all therapies but longer OS when treated with targeted therapy. **(Fig. 3 & 4)**

CONCLUSION

- While detection of any CTC type indicated poor outcomes in patients, CTCs undergoing mitosis appears to indicate highly aggressive disease with the poorest survival rates.
- No CTCs and non-mitotic CTCs has similar survival rates to the various therapy types.
- Mitotic CTCs appear to have superior survival benefit when treated with targeted therapy.
- CTC stratification could identify aggressive CTC populations who could benefit from specific therapy types allowing for improved outcomes. **(Fig. 5)**
- Larger studies are needed to expand upon and validate these preliminary findings.

Figure 5. CTC-Based Patient Stratification



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