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A Pooled Analysis of the Prognostic Relevance of Circulating Tumor Cells in Early Breast Cancer

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Background

While there is unequivocal evidence regarding the prognostic relevance of circulating tumor cells (CTCs) in peripheral blood of patients with metastatic breast cancer, less data is available for the prognostic relevance at time of primary diagnosis.

Methods

We conducted a pooled analysis with individual data of 3172 patients with non-metastatic (Stage I-III) breast cancer from five academic breast cancer units in Enschede (Netherlands), Houston (USA), Munich (Germany), Paris (France), and Tuebingen (Germany). Prevalence and number of CTCs in the peripheral blood were assessed at time of primary diagnosis using the FDA-approved CellSearch System (Veridex, USA). Patient outcomes were analyzed using univariate log-rank tests and multivariate Cox regressions. The median follow-up time was 61 months.

Results

At least one CTC was detected in 640 out of the 3172 (20.2%) of the patients. The presence of CTCs was associated with larger tumors, more axillary lymph node metastases, and higher histological tumor grade (all p < 0.005). No association was found between CTC prevalence and menopausal status, hormone-receptor status (HRS), or HER2 status.

The presence of CTCs was significantly related to poor progression-free survival (PFS, log-rank test, p < 0.001, hazard ratio [HR] 2.02, 95% CI 1.63 – 2.50; Figure 1a) and overall survival (OS, p < 0.001, HR 2.57, 95% CI 1.96 – 3.37; Figure 1b). Multivariate Cox regressions including tumor size, nodal status, histological tumor grade, hormone-receptor status, HER2 status, and CTC prevalence confirmed that the presence of CTCs was an independent prognostic factor for both poor PFS (HR 1.75, 95% CI 1.40 – 2.18, p < 0.001) and OS (HR 2.11, 95% CI 1.59 – 2.7, p < 0.001; Table 1).

Results

Figure 1: Kaplan-Meier survival plots of (a) progression-free survival and (b) overall survival according to CTC prevalence at the time of primary diagnosis.

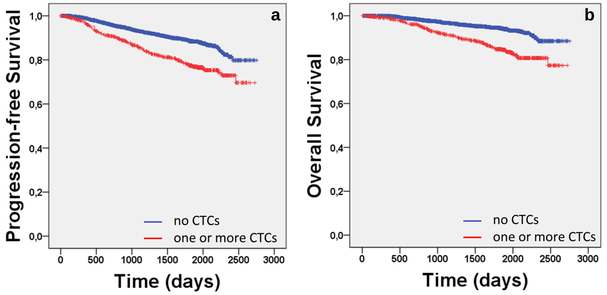
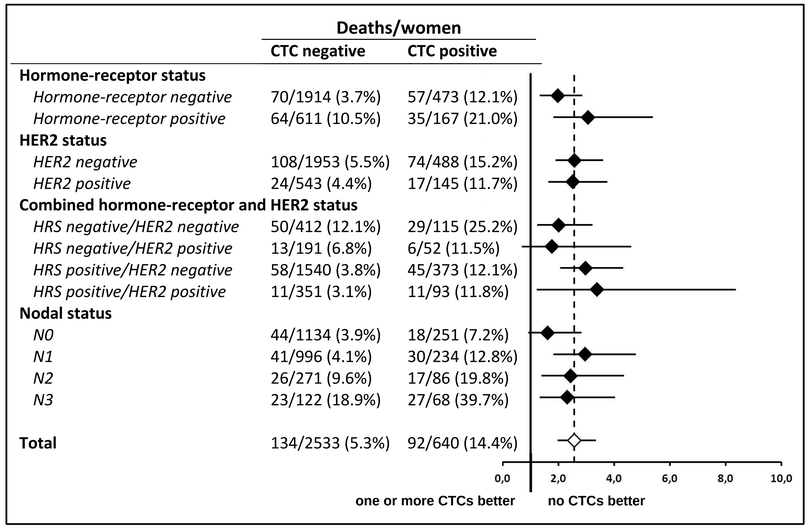


Table 1: Cox regression analyses of overall survival.

Variable	Hazard ratio	95% CI	P- value
CTCs			
pos vs. neg	2.108	1.594 – 2.788	< 0.001
Tumor grade			0.001
G2 vs. G1	1.073	0.489 – 2.354	0.861
G3 vs. G1	2.239	1.028 – 4.874	0.042
Histological type			0.389
lobular vs. ductal	1.320	0.865 – 2.015	0.198
other vs. ductal	0.898	0.498 – 1.620	0.722
Tumor stage			< 0.001
T2 vs. T1	1.853	1.301 – 2.638	0.001
T3 vs. T1	3.706	2.310 – 5.947	< 0.001
T4 vs. T1	3.538	2.014 – 6.218	< 0.001
Nodal stage			< 0.001
N1 vs. N0	1.547	1.081 – 2.213	0.017
N2 vs. N0	2.538	1.660 – 3.879	< 0.001
N3 vs. N0	3.824	2.471 – 5.918	< 0.001
Hormone receptor status			
pos vs. neg	0.402	0.294 – 0.550	< 0.001
HER2 status			
pos vs. neg	0.579	0.407 – 0.823	0.002
Menopausal status			
post vs. pre	1.370	1.023 – 1.834	0.035

Figure 2: Univariate subgroup analyses of overall survival for no CTCs versus one or more CTCs.



In the univariate subgroup analysis concerning overall survival (Figure 2), the hazard ratio for patients with positive HRS was 3.07 (p<0.001), and 1.98 (p=0.001) for patients with a negative HRS. The prognostic relevance of CTC status was similar for patients with HER2 negative and HER2 positive tumors (hazard ratios 2.58 and 2.51, respectively). A prognostic relevance of CTC status was shown for triple-negative patients (hazard ratio 2.01, p=0.003) as well as for patients with HRS positive/HER2 negative tumors (hazard ratio 2.97, p<0.001) and for patients with HRS positive/HER2 positive tumors (hazard ratio 3.4, p=0.003), while CTC prevalence was not significantly associated with prognosis in patients with HRS negative/HER2 positive tumors (hazard ratio 1.76, p=0.25).

Presence of CTCs significantly predicted overall survival independently from the cut-off value used (univariate analyses with log-rank test, all p<0.05; Figure 3).

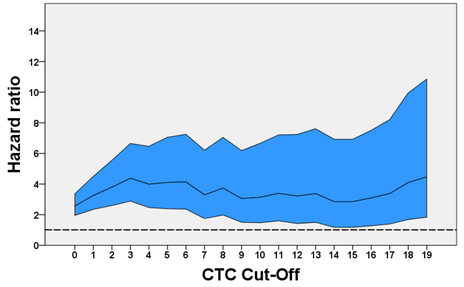


Figure 3: Hazard ratios (black line) and 95% confidence intervals (blue area) of univariate analyses of overall survival according to the presence of CTCs categorized using different cut-off values (Cut-off 0: 0 CTCs vs. higher; Cut-off 1: 0-1 CTCs vs. higher; Cut-off 2: 0-2 CTCs vs. higher, etc.).

Conclusions

In patients with early breast cancer, the presence of CTCs in peripheral blood is an independent predictor of poor progression-free and overall survival.

Acknowledgment

We would like to thank all patients for participating at this study and donating their blood samples for research purposes.