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Prognostic relevance of Circulating Tumor Cells across different molecular subgroups in the adjuvant SUCCESS-A Study

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Background

The prognostic value of circulating tumor cells (CTCs) has recently been confirmed for the adjuvant setting by the SUCCESS A Study (Rack et al. JNCI 2014). As breast carcinomas depend on partly different pathways for progression, the relevance of CTCs could differ between molecular intrinsic subtypes of breast cancer. Aim of this study was to analyze the prognostic impact of CTCs in molecular subtypes.

Methods

SUCCESS A trial is a large, randomized, open-label, 2x2 factorial design Phase III study in patients with high risk breast cancer (stage N1 or T2–T4 or grade 3 or age ≤ 35 or hormone-receptor negative). Patients were randomized to adjuvant chemotherapy treatment with 3 cycles of Epirubicin-Fluorouracil-Cyclophosphamide (FEC) followed by either 3 cycles of Docetaxel or 3 cycles of Gemcitabine-Docetaxel. CTC status before chemotherapy was assessed using the FDA-approved CellSearch System (Veridex, USA), and CTC positivity was defined as ≥ 1 CTC. Molecular subtypes were defined as triple negatives, HER2 positives, luminal A likes (hormone-receptor positive, grading 1 or 2), or luminal B likes (hormone-receptor positive, grading 3).
Overall survival (OS) was defined as the time interval from the date of diagnosis to the date of death or the date of censoring. Disease-free survival (DFS) was defined as the time from randomization to the earliest date of disease progression (distant metastasis, local recurrence, death from any cause) or the date of censoring. Initially, a mixed-effects Cox proportional hazards model was fitted with study center as random effect and the well-known predictors for survival as fixed effects: age, BMI, tumor stage, lymph node status, and molecular subtype. This basic model was compared with a mixed-effects Cox model with the same predictors and additionally CTC status (categorical; CTC = 0, CTC > 0) and the interaction between CTC status and molecular subtype using the likelihood-ratio test. In case of significance, the interaction model was compared with a reduced regression model where the interaction term was dropped using a likelihood ratio test again. A significant result here means that the influence of CTC on prognosis significantly differs among molecular subtypes. In that case the interaction model was used to present molecular subtype specific HRs for CTC > 0 versus CTC = 0 adjusted for the other well-known predictors. Crude survival rates for patient subgroups defined by molecular subtype and CTC status were estimated using the Kaplan-Meier product limit method. All of the tests were two-sided, and a P value of < 0.05 was regarded as statistically significant. Calculations were carried out using the R system for statistical computing (version 3.0.1; R Development Core Team, Vienna, Austria, 2013).

Results

A total of 1994 patients were included in the analysis. 98.3% of all patients had complete patient and tumor characteristics. The percentage of missing values in each variable was below 0.3% except for molecular subtype with 1.7% missing values. Missing values were imputed as described above. Patient characteristics according to CTC status are shown in Table 1. Median follow-up time for overall survival was 5.3 both in patients with no CTCs and in patients with at least one CTC. Median follow-up time for disease-free survival was 5.3 and 5.2 years respectively.

Table 1: *Patient characteristics according to CTC status*

Characteristic		No CTC Mean or N	No CTC SD or %	At least one CTC Mean or N	At least one CTC SD or %
Age		53.2	10.6	53.7	10.4
BMI		26.0	4.9	26.9	5.5
Tumor Stage	pT1	681	43.3	163	38.6
	pT2	797	50.7	226	53.6
	pT3	73	4.6	27	6.4
	pT4	21	1.3	6	1.4
Grading	G1	83	5.3	14	3.3
	G2	737	46.9	205	48.6
	G3	752	47.8	203	48.1
Nodal status	pN+	1036	65.9	293	69.4
	pN0	536	34.1	129	30.6
Tumor type	Ductal	1280	81.4	333	78.9
	Lobular	175	11.1	64	15.2
	Other	117	7.4	25	5.9
ER	Negative	534	34.0	139	32.9
	Positive	1038	66.0	283	67.1
PR	Negative	635	40.4	171	40.5
	Positive	937	59.6	251	59.5
HER2	Negative	1186	75.4	323	76.5
	Positve	386	24.6	99	23.5
Molecular Subtype	Her2 positive	386	24.6	99	23.5
	Luminal A likes	626	39.8	172	40.8
	Luminal B likes	257	16.3	71	16.8
	Triple Negative	303	19.3	80	19.0
Menopausal Status	Pre	910	57.9	253	60.0
	Post	662	42.1	169	40.0

Overall survival

CTC status significantly influenced overall survival in addition to well-known prognostic factors (p < 0.000001, likelihood ratio test comparing interaction model with basic model). Moreover, the influence of CTC status significantly differed among molecular subtypes (p = 0.04, second likelihood ratio test). Molecular subtype-specific HRs are shown in Table 2 and survival rates are presented in Table 3 and Figure 1.

Table 2: *Overall survival analysis, showing hazard ratios (HRs) with 95% confidence intervals for CTC > 0 versus CTC = 0 by molecular subtypes.*

Molecular Group	HR	p-value
HER2+	2.35 (1.04, 5.32)	0.04
Luminal A likes	3.57 (1.81, 7.03)	< 0.001
Luminal B likes	3.96 (1.93, 8.14)	< 0.001
Triple Negatives	1.18 (0.62, 2.24)	0.61

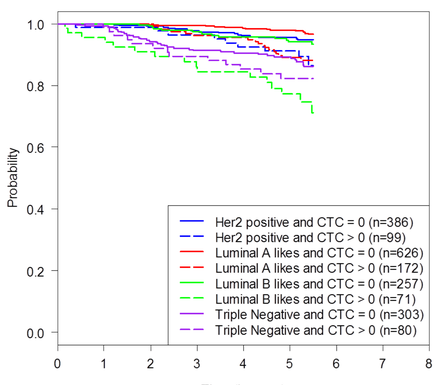

Figure 1: *Kaplan-Meier curves for overall survival according to molecular subtype and number of CTC before chemotherapy.*

Table 3: *Overall survival rates according to CTC status and molecular subtype with 95% confidence intervals in brackets.*

		At risk	Events	2-year rate	5-year rate
HER2+	CTC = 0	386	17	0.99 (0.98, 1.00)	0.96 (0.93, 0.98)
	CTC > 0	99	9	0.99 (0.97, 1.00)	0.91 (0.85, 0.98)
Luminal A likes	CTC = 0	626	16	1.00 (0.99, 1.00)	0.98 (0.97, 0.99)
	CTC > 0	172	18	1.00 (1.00, 1.00)	0.89 (0.84, 0.94)
Luminal B likes	CTC = 0	257	14	0.99 (0.98, 1.00)	0.94 (0.91, 0.97)
	CTC > 0	71	16	0.91 (0.84, 0.98)	0.77 (0.67, 0.89)
Triple Negatives	CTC = 0	303	35	0.94 (0.92, 0.97)	0.89 (0.86, 0.93)
	CTC > 0	80	13	0.94 (0.88, 0.99)	0.82 (0.74, 0.92)

Disease-free survival

CTC status significantly influenced disease-free survival in addition to well-known prognostic factors (p < 0.00001, likelihood ratio test comparing interaction model with basic model). Differences within molecular subtype could not be shown (p = 0.07). The HR across all patients for CTC > 0 versus CTC = 0 adjusted for the considered prognostic factors is 1.93 (95% CI: 1.48 to 2.52).

Conclusions

With regard to OS the prognostic effect of CTCs seems most prominent in patients with hormone receptor positive disease. It is still significant in HER2 positives, but not in TN breast cancer patients. Results with regard to DFS trended into the same direction, differences within subgroups could however not be shown, possibly due to power reasons.

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