ER, PR, HER2 was previously determined. IHC molecular subtypes were defined based on expression of these markers: Luminal A: ER+ and/or PR+, HER2− and Ki67−; Luminal B: ER+ and/or PR + and HER2+ and/or ki67+; ERBB2: ER−, PR− and HER2+; Basal-like: ER−, PR−, HER2− and EGFR+ and/or CK5/6+; Unclassified: ER−, PR−, HER2−, EGFR− and CK5/6−. IHC molecular subtypes were validated against gene expression defined molecular subtypes. Assessment of distribution and prognostic effect of molecular subtypes was stratified to age (<65 versus ⩾65 years).

Results: Validation of molecular subtypes determined by IHC against gene expression revealed a substantial agreement in classification (Cohen's kappa coefficient 0.77). A statistical trend to an association ($p = 0.056$) was found between molecular subtypes and age, where Luminal tumors were more often found in elderly patients, while ERBB2, basal-like and unclassified subtypes were more often found in young patients. Molecular subtypes showed a prognostic association with outcome in young patients concerning relapse free period (RFP) ($p = 0.03$) and relative survival (RS) ($p < 0.001$). No statistically significant prognostic effect was found for molecular subtypes in elderly patients (RFP $p = 0.7$; RS $p = 0.3$). Additional analyses showed that no molecular subtypes showed a statistically significant difference in outcome for elderly compare to young patients, apart from Luminal A tumor where elderly patients had a worse RS.

Conclusion: We have shown that molecular subtypes have a different distribution and prognostic effect in elderly compared to young breast cancer patients, emphasizing the fact that biomarkers may have different distributions and prognostic effects and therefore different implications in elderly compared to their younger counterparts. Our results support the premise that breast cancer clinical behavior is significantly affected by patient age, but we suggest that competing risks of death in elderly patients and ER-driven differences in biology are underlying these age-dependent variations in patient prognosis, rather than the general belief that elderly breast cancers are of a more indolent biological character.

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Survival in Early Breast Cancer Patients is Influenced by Circulating Tumor Cells

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Background: There is good evidence for Circulating tumor cells (CTCs) in the peripheral blood to be a predictor of shortened progression-free and overall survival in metastatic breast cancer patients. Now we evaluated whether the presence of CTCs in patients with early breast cancer before the initiation of systemic adjuvant chemotherapy increases the likelihood of subsequent relapse and death.

Methods: In 2,026 patients with early breast cancer, CTCs were analyzed using the CellSearch System (Veridex, USA) right after complete resection of the primary tumor and prior to the initiation of systemic adjuvant treatment. All patients were randomized in the SUCCESS A trial, which compared FEC-Docetaxel vs. FEC-Docetaxel-Gemcitabine and 5 vs. 2 years of treatment with zoledronic acid in primary breast cancer patients and node positive or high-risk node negative disease. Patients were followed for a median of 35 months (range 0 to 54 months). The prognostic significance of CTCs for disease-free and overall survival was assessed using the Cox regression models.

Results: CTCs were detected in 21.5% of patients (435 out of 2026; median 1.3, range 1–827). Axillary lymph node involvement was more prevalent in patients with CTCs ($p < 0.001$), but no association was found with tumor size, histopathological grading or hormone receptor status.

There were 114 events of recurrence and 66 patients died of their disease. The presence of CTCs before systemic treatment was an independent predictor of poor disease-free survival (DFS) ($p < 0.0001$), distant disease-free survival (DDFS) ($p < 0.001$) and overall survival (OAS) ($p = 0.0002$). Patients with at least 5 CTCs had the worst prognosis with a four-fold increased risk of recurrence and a three-fold increased risk of death (hazard ratio (HR) 4.0 for DFS and 3.1 for OAS).

Conclusions: This is the first study to prospectively evaluate in a large patient cohort with early breast cancer the relevance of CTCs observed in the peripheral blood prior to the initiation of systemic treatment to the prognosis of early disease recurrence. CTC detection may be a clinically useful tool for monitoring treatment and should be tested as an indicator for secondary adjuvant treatment interventions in clinical trials.

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Using the 21-gene Breast Cancer Assay in Adjuvant Decision-making in ER-positive (ER+) Early Breast Cancer (EBC) is Cost-effective: Results of a Large Prospective German Multicenter Study

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Background: The Onco*type* DX® Recurrence Score (RS) is accepted as a predictive marker of adjuvant chemotherapy benefit in patients (pts) with ER+ EBC. We performed a clinical study to evaluate the impact on treatment decisions when using the RS including a pharmacoeconomic assessment of cost-effectiveness of using the assay in Germany.

Materials and Methods: Pts with ER+, HER2-negative N0 and N+ (1−3 positive lymph nodes) EBC and no contraindication for chemotherapy were included. Treatment recommendations before and after knowledge of the RS and actual treatment data were recorded. A Markov model was developed to estimate the long term costs and life expectancy associated with chemotherapy decisions in ER+, N0 and N+ EBC including 3 health states (recurrence, no recurrence and dead). Transition from one state to another was based on published recurrence risk data. The model compared costs and life expectancy associated with treatment decisions either based on criteria currently used in German clinical practice or on the RS. The study was conducted in the perspective of German sick funds' and over a 30 year time frame. Costs and outcomes were discounted at 3% per year. One-way sensitivity analyses were conducted on key variables.

Results: Of the 366 evaluable pts 244 were N0 and 122 N+, 54.1% had low, 38.0% intermediate and 7.9% high RS values. Initial recommendation changed in 33.1% of all cases.

Prior to the RS 50.5% of low, 62.6% of intermediate and 75.9% of high RS pts were recommended chemotherapy. Net changes in chemotherapy use from the study were −18.9% for all pts, −36.9%, 1.4%, and +20.7% for pts with low, intermediate and high RSs. Using Onco*type* DX to guide chemotherapy decisions was associated with an increase in survival (4.83 life years) due to the high number of pts reclassified by the RS as likely to benefit from chemotherapy and an incremental cost of €757 per patient. Thus, using the test in Germany is expected to be cost-neutral to the sick funds (i.e. incremental cost-effectiveness ratio of €206/life year). Considering the societal perspective, the incremental cost-effectiveness ratio associated with the use of the test is €6/life year. One-way sensitivity analyses confirmed the robustness of the main results.

Conclusions: Onco*type* DX guided chemotherapy decision-making for ER+ EBC resulted in a significant reduction of adjuvant chemotherapy usage and was cost-neutral versus current clinical practice.

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Could the Axilla Be Managed Less Aggressively in Selected Node-positive Breast Cancer Patients?

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Background: With advances in staging, and increasingly effective systemic treatments, management of the axilla is becoming less aggressive. Until recently, when sentinel lymph node biopsy became the standard axillary staging technique, our institutional policy has entailed four-node sampling, with node-positive (<4) patients receiving axillary radiotherapy (ART) without axillary clearance. This has been retrospectively evaluated for outcomes of regional recurrence, in a consecutive cohort with over 10 years of follow-up. Our hypothesis is that this management protocol is efficient and associated with low risk of regional recurrence (RR), and that there is a difference based on the number of positive nodes.

Methods: The study population was selected from 2607 consecutive patients with operable cT1-T2 breast cancer at our institution between the years 1990 and 2000. Surgery and radiotherapy to breast or chest wall, and systemic therapy, were given according to standard local guidelines.