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Carcinoembryonic antigen (CEA), Cancer Antigen 15.3 (CA 15.3), and 18-FDG-PET in Early Breast Cancer Follow-up: Findings from the KRONOS Trial

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Introduction

Background: Current breast cancer (BC) follow-up guidelines for asymptomatic patients recommend only annual mammography and periodic physical exams, based on two trials published in 1994 (JAMA vol. 271). No subsequent randomized controlled trials (RCTs) have evaluated alternative strategies. Advances in BC biology, treatments, and diagnostic tools like 18-FDG-PET have transformed the landscape, prompting a need to reassess surveillance protocols. The role of serum tumor markers (CEA, CA 15.3) and 18-FDG-PET have never been validated in prospective RCTs..

Methods and Patients

The KRONOS trial for the first time over 30 years after the 2 old RCTs, compares standard follow-up (annual mammography and physical exam; control arm) with an intensified approach (standard plus quarterly serum CEA and CA 15.3, with 18-FDG-PET performed if markers rise critically; experimental arm). The primary endpoint assesses whether intensified surveillance detects recurrences earlier, measured by the difference in restricted mean survival time (RMST). Assuming a 20% five-year recurrence, a 3-month RMST reduction (diagnostic lead time ~10 months) was targeted. If early diagnosis of metastases is demonstrated, the impact on survival will be evaluated as the final endpoint. Secondary endpoints include marker predictive value, PET accuracy, and quality of life.
Eligible patients had stage I–III BC after adequate surgery, only very low-risk cases and rare histologic types were excluded. The study included two cohorts: newly starting follow-up (cohort 1) and those completing five years without relapse (cohort 2). Participants were randomized 1:1, stratified by nodal status, HER2, and ER status. Follow-up was planned for at least 10 years after surgery (figure 1). The mean diagnostic anticipation achievable in the experimental arm was assessed by calculating the difference in RMST between the 2 arms and testing such a difference non-parametrically by means of bootstrap resampling.

STUDY DESIGN

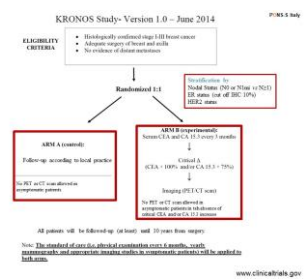


Figure 1 Study Design

Results

Between October 2014 and November 2021,1507 patients were randomized: 1047 in cohort 1 (515 to control arm, 532 to experimental arm) and 460 in cohort 2 (227 to control arm, 233 in experimental arm) . Median age was 56 years; 52% stage I, 34.9% stage II, 13.1% stage III. Tumor biology: 64.8% ER-positive/HER2-negative, 25.8% HER2-positive, 9.4% triple-negative. Median follow-up was 7 years. Overall 130 recurrences (8.6%) occurred—101 distant metastases (6.7%) and 29 locoregional relapses (1.9%).

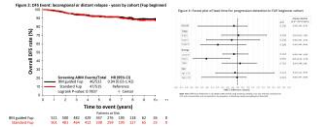
Additionally, 89 patients (5.9%) developed new non-breast primary cancers, and 20 (1.3%) died without recurrence

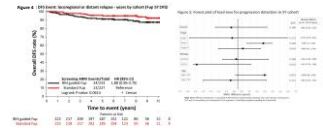
.In the overall population the RMST over 10 years was 7.7 years (experimental) vs. 8.3 years (control), indicating an anticipatory benefit of 7.4 months (95% CI -3.1-13.4). Overall survival was similar, with 97 deaths (6.4%) and no significant difference between groups

In cohort 1 (newly starting follow-up) 93 recurrences (8.9%) were observed -75 distant (7.2%) and 18 locoregional (1.7%).

The 10-year relapse-free survival in cohort 1 was 89% in the experimental arm vs. 88% in the control arm (figure 2). The median diagnostic anticipation was 4 months [0.34 years (2.5th-97.5th percentiles: -1.4;0.72)] , not significant (figure 3). In the pre-planned analysis of biological sub-groups a potentially clinically relevant diagnostic anticipation was observed only in HER2 positive patients: 3.03 years (2.5th-97.5th percentiles: -4.32; -0.74). The 10-year overall survival in cohort 1 was not different between the 2 arms (87% control arm and 89% experimental arm)

In cohort 2 (patients randomized after completing 5 years of follow-up without relapse) 37 recurrences occurred (8%) – 26 (5.6%) distant and 11 locoregional (2.4%) relapses. The 10-year relapse-free survival was 87% in the experimental arm vs. 92 % in the control arm (figure 4). The median diagnostic anticipation was 10 months [0.84 years (2.5th-97.5th percentiles: -2.9;3.78)].





Discussion and Conclusions

The recurrence rate (~8.6%) after a median follow-up of 7 years was lower than expected. Intensified follow-up did not improve overall survival in this unselected BC population. These findings support current standard surveillance, with no evidence of benefit from routine use of serum markers or 18-FDG-PET in asymptomatic patients.
However our data suggest a possible significant diagnostic anticipation in HER2 positive patients (in both cohorts) and in late relapses (cohort 2).
Given that the low number of events may have reduced the potency of the trial the study will continue until a minimum follow-up of 10 years from randomization and a higher number of events in order to confirm the results.

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