Title: Dynamic prediction in breast cancer: a way to provide information on how prognosis evolves over time

Authors: Azevedo, S.[1,2]; Sousa, L.[1,3]; Esteves, S.[4]

Affiliations:

1. Departamento de Estatística e Investigação Operacional, Faculdade de Ciências, Universidade de Lisboa
2. Exigo Consultores, Lisboa, Portugal
3. Centro de Estatística e Aplicações, Faculdade de Ciências, Universidade de Lisboa
4. Instituto Português de Oncologia de Lisboa, Francisco Gentil, E.P.E., Portugal.

Background: In breast cancer patients risk stratification at diagnosis is central for the decision on the initial therapeutic approach. However, these survival estimates may not provide accurate information on long-term prognosis. There is limited up-to-date data on the evolution of the relapse and survival probability as a function of disease-free elapsed time. Existing information mostly refers to old cohorts who have not been treated with current standard treatments and does not discriminate conditional survival in biological subgroups with different clinical behaviour (1). Understanding more about conditional disease-free survival (CDFS) after treatment may help the clinician to tailor the patient's follow-up plan according to the dynamic risk of relapse. We aimed to evaluate the disease-free survival conditional on the time lived without disease and assess the long-term prognostic significance of relevant prognostic factors at presentation in patients with early-stage breast cancer who received initial treatment according to current standard practices.

Methods: We conducted a non-interventional, single-center, cohort study with retrospective data collection. Patients potentially eligible for the study were identified from the National Cancer Registry database and comprised all consecutive female patients with stage I, II or III (AJCC) breast cancer diagnosed and treated in IPOLFG from January 2006 to December 2011. Data included age, disease stage, tumour grade, axillary lymph node status and immunohistochemistry (IHC) subgroups considering hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status (HR+/HER2-, HR+/HER2+, HR-/HER2+, HR-/HER2). These variables were selected based on their significance in initial prognosis, according to the existing literature. Disease free survival (DFS) was defined as time, in days, from surgery to recurrence of breast cancer or death from any cause. Observed 2-year and 5-year CDFS for all covariates were calculated using Kaplan-Meier method. CDFS was defined as the probability of remaining alive and disease-free for further 2 and 5 years, knowing that the patient is disease-free at 0, 1, 2, 3, 4 and 5 years after surgery. We assessed time-varying effects of specific covariates using a proportional baselines landmark supermodel (2). Landmark time points were established at every third month between 0 and 5 years after surgery. A prediction model

for 2-year and 5-year DFS at a specific time point is constructed by selecting the individuals at risk at that time point and incorporating the values of any covariate at that respective time point in a Cox proportional hazards model. Statistical analysis were performed using R, version 3.4.1.

Results: We analysed 4620 patients. Median age at diagnosis was 59 years (range: 23-95), the majority of patients (78%) presented with stage I/II and more than a half had intermediate histological grade (58%) and no axillary node involvement (59%). Most common IHC subtype was HR+/HER2+ (69%). Median follow-up time in patients still alive was 6.6 years (range: 0.2-12.1). Overall, 13.4% of the patients had a recurrence and 20% died. As expected, patients with stage III, high grade tumour, positive lymph nodes and HR-/HER2- showed worse initial DFS. The 5-year CDFS survival estimates for those who had been disease free for 0, 1, 2, 3, 4, and 5 years after surgery is 0.82, 0.82, 0.82, 0.81, 0.78, 0.63, respectively. Considering the disease stage, tumour grade and status of the lymph nodes, CDFS is almost constant regardless if the estimate is made at the time of the surgery or 5 years after it. In the opposite, we found that 2-year and 5-year CDFS showed a trend for a gradual increase in the HR-/HER2- and HR-/HER2+ subgroup and a gradual decrease in HR+/HER2- and HR+/HER2+. For instance, 5-year CDFS for HR-/HER2- subgroup at 1 year and 4 years after surgery was 0.77 and 0.84 respectively, whereas for HR+/HER2- is 0.87 and 0.83. Landmark supermodel analysis showed a significant decrease in the 2-year window (and a slight one at 5-year) in the hazard ratios in the following groups: HR-/HER2-, HR-/HER2+ and stage III; which suggests that the prognostic importance between these groups decrease as more time elapses since surgery.

Conclusions: Overall, there was a gradual decrease in 5-year CDFS over time. This was due to the occurrence of late relapses, which is in line with other studies showing a non-negligible risk of breast cancer recurrence as late as 5-20 years after diagnosis, and to the increased risk of death expected in an ageing cohort. More importantly, our preliminary results suggest a gradual increase in 5-year CDFS in the HR-/HER2- patients, a subgroup with poor prognosis at baseline. In fact, when considering the surviving patients with no recurrence at 4 years after surgery, 5-year CDFS was similar between all IHC groups. By contrast, the difference in 5-year CDFS observed within subgroups defined according to lymph node status, disease stage and tumour grade was minimally impacted by years already survived being disease-free. This was confirmed in the multivariable landmark supermodel analysis which showed a decrease over time of the prognostic significance of IHC groups and stage at diagnosis but not for the other evaluated variables. Further studies with long-term follow-up are needed to confirm our results. If confirmed, these findings are relevant to inform and counsel patients regarding the dynamic nature of their prognosis over time and should be considered in the patients' surveillance plans.

References:

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