## S5. LONGTERM PROGNOSTIC VALUE OF OESTROGEN RECEPTOR AND PROGESTERONE RECEPTOR IN EARLY STAGE BREAST CANCER

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**Introduction:** The prognostic value of oestrogen receptor (ER) and progesterone receptor (PR) in early stage breast cancer remains uncertain. To evaluate the prognostic role of the steroid receptors, a multivariate analysis should be used to include the effect of age and/or menopausal state and lymph node status on the survival, since they are important discriminators of their prognostic value [3]. Besides the need for newer statistical methods, a longer follow-up period and a homogeneous patient population seem important to detect non-proportional effects on hazards [3]. In 1998, Hilsenbeck stated that failure to recognise violations of proportional hazards might lead to over- and under-estimation of the effects of important prognostic factors [2]. We wanted to check the time-dependence of hazard ratios for steroid receptors in the Surveillance, Epidemiology and End-Results (SEER) patient population.

**Patients and methods:** Women aged between 25 and 95 years at diagnosis with histologically confirmed non-metastatic T1–T2, node-negative or – positive primary breast carcinoma, diagnosed between 1990 and 1997, who were treated curatively and underwent axillary dissection, were abstracted from the SEER Program [1]. ER- and PR-positivity were found in 43829 and 37907 patients, respectively. Event was defined as death from any cause. The follow-up cut-off date was December 31, 1999. Cox proportional hazards models were used for multivariate survival analysis. The time dependence of hazards was examined by performing diagnostic plots of residuals with length of follow-up time. Variables considered in the models were: tumour size, age and year at diagnosis, number of nodes examined and number of nodes involved, registry area, race, marital status, tumour topography, histological type and grade, steroid receptor status, type of primary surgery, and administration of post-operative radiotherapy. Subgroup analysis was performed by examining the interaction between ER and PR with nodal status. Significance level was set at $P < 0.006$ to adjust for the size of the data and multiple comparisons.

**Results:** The multivariate analysis resulted in the following values for Hazard Ratios for ER-positivity and PR-positivity for the overall patient population: 0.771 (0.732–0.811) and 0.890 (0.846–0.936), respectively. Subgroup analysis revealed a Hazard Ratio for ER-positivity of 0.796 (0.742–0.854) for the node-negative and 0.743 (0.689–0.800) for the node-positive subgroup. The Hazard Ratio for PR-positivity was 0.975 (0.911–1.045) and 0.799 (0.742–0.860), respectively. Thus, ER- and PR-positivity were both associated with a favourable outcome, but PR-positivity was not significant in the node-negative patients. A check of hazards constancy over time showed that the favourable effect of ER+ was constant only during the first 3 years, after that it decreased progressively, ER+ did not have a prognostic value after 6 years. The favourable effect of PR+ remained almost constant up to the maximum observed follow-up period of 10 years. This test confirmed a major departure from the proportional hazards assumption for ER+ ($P < 0.0001$), and a minor departure for PR+ ($P = 0.011$).

**Discussion:** Our data suggest that PR appears to have a more constant prognostic effect over time than ER. This result confirms the analysis done by Costa and colleagues [3] that revealed that PR appeared to be superior to ER in predicting the prognosis of primary breast cancer patients. However, subgroup analysis suggests the presence of interaction effects (PR was non-significant in node-negative patients). Further analysis of this data-set is warranted to investigate the interactions and influence of age and systemic treatment. In addition, more attention needs to be directed to the method and the cut-off level of the steroid receptor assays.

### References

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