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Title: Utility of the DCIS Biological Risk Profile for Predicting Recurrence Risk Compared to Standard Clinicopathologic Factors

Background: Identifying patients' DCIS recurrence risk after breast conserving surgery (BCS) is an important clinical need. Standard clinical pathologic (CP) factors are commonly used to help assess DCIS recurrence risk. The utility of a novel biologic risk profile was compared with weighted CP factors. The biologic risk profile was developed in two large female patient cohorts treated with or without radiation therapy (RT) after BCS and subsequently validated in an independent Kaiser Permanente Northwest (KPNW) population treated with BCS and optionally RT.

Material and Methods: The development cohorts included patients from Uppsala University Hospital (UUH) diagnosed with DCIS from 1986-2004, and patients from University of Massachusetts (UMass) diagnosed from 1999-2008. The subsequent independent validation study included KPNW members diagnosed with DCIS from 1990-2007. Biomarkers from FFPE tissue were assessed by board certified pathologists. Pathology and clinical data were collected from medical records. A biologic risk profile combined 7 biomarkers and 4 clinical pathology factors (age, extent, palpability, and margin status) to calculate a total risk score (0 to 10). Biologic risk profile scores (RS) were calculated using cross-validation for the development study, and generated prospectively for the KPNW validation study. Standard CP factors (patient age, family history, clinical presentation, tumor grade, tumor necrosis, tumor margin, and number of excisions) were combined using the MSKCC DCIS nomogram weights to calculate a CP score (0 to 200). Kruskal-Wallis analysis was used to assess if there was a ranked relationship between the RS and the CP score for each study; total recurrence risk predicted by the RS and CP score were assessed with multivariate Cox proportional hazards, respectively.

Results: The RS ranges (0-3) and (3-7) were independent of the CP score in all cohorts, as assessed by the Kruskal-Wallis anova. However, RS >7 increased with increasing CP scores in the development cohorts ($p<.001$) and subsequent KPNW validation study ($p=0.04$). Multivariate Cox proportional hazard analysis showed that recurrence risk increased with increasing RS (0-10) and decreased with radiation therapy, but was not significantly associated with the CP score.

Conclusions: The biological risk profile is prognostic for DCIS recurrence and provides utility beyond standard clinical pathology factors that can be used to personalize treatment decisions.

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