inferior outcome than ACT on univariate analysis (OS: HR = 2.3, $p < 0.0001$; DFS: HR = 1.9, $p = 0.0002$). Among patients who underwent NACT, 33% had pathological complete response (pCR) versus 67% patients with residual disease. Both OS and DFS were significantly better among patients achieving pCR than those with residual disease (OS: HR = 0.07, $p < 0.0001$; DFS: HR = 0.19, $p < 0.0001$). Patients receiving ACT or NACT with pCR had superior OS and DFS than patients receiving neoadjuvant with partial response ($p < 0.0001$). Presence of LVI, stage III and having Medicaid had significantly inferior OS and DFS outcome. Adjuvant radiation, type of chemotherapy, age, race, grade and year of treatment had no effect on OS or DFS. Results did not substantively change after multivariate adjustment for age, race, stage, surgery, chemotherapy, radiation, LVI, institution and insurance type.

Conclusions: This is a large triple negative breast cancer series showing survival outcome and various prognostic factors. Future studies are needed to improve the pathological complete response rate. More insight is needed to explore the relationship between different insurance types and outcome in this distinct breast cancer cohort.

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Identification and Validation of a Radiation Sensitivity Signature in Human Breast Cancer

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Purpose/Objective(s): The development of a specific radiation (RT) sensitivity signature to predict likelihood of response to RT in human breast cancer (BC) is an attractive goal. Previous BC signature development efforts have focused on prognosis or response to adjuvant chemotherapy. We hypothesized that pairing post-RT clonogenic survival data with gene expression data across a large spectrum of BC cell lines would generate a BC-specific RT sensitivity signature predictive for RT response in BC patients and allow identification of patients with tumors refractive to conventional therapy.

Materials/Methods: Using clonogenic survival assays, we identified the range of surviving fraction (SF) after 2 Gy of RT across 22 BC cell lines. Using SF as a continuous variable, the RT sensitivity score (RSS) was correlated to gene expression using Spearman's correlation method. Supervised hierarchical clustering identified differences in gene expression across resistant and sensitive cell lines to generate a radiation sensitivity (RS) signature. This signature was validated in a separate human breast tumor dataset (185 patients) containing early stage, node-negative patients treated with surgery and RT alone without adjuvant chemotherapy to assess the predictive effect of the radiation signature on recurrence risk after RT.

Results: Clonogenic survival identifies a range of radiation sensitivity in human BCC lines (SF 77%-17%) with no significant correlation (r value < 0.3) to the intrinsic BC subtype. Using Spearman's correlation method, a total of 126 genes were identified as being associated with radiation sensitivity (72 positively correlated, 54 negatively correlated). Supervised hierarchical expression discriminates gene expression patterns in the RT resistant and sensitive cell lines and is enriched for genes involved in cell cycle arrest and DNA damage response, including RAD51, TOP2A, BUB1 (enrichment p value 5.0 E-22). Application of this RS signature to an independent breast cancer dataset with clinical outcomes validates the signature and accurately identifies patients with decreased rates of recurrence compared to patients with high expression of the radioresistant signature (p value < 0.0001, misclassification error rate .31, 12 of 13 patients with locoregional recurrence accurately identified).

Conclusions: In this study, we derive a human breast cancer-specific radiation sensitivity signature (RSS) with biologic relevance from preclinical studies and validate this RSS for prediction of recurrence in a clinical data set. The RSS is not correlated to the intrinsic subtypes of human breast cancer and therefore represents "value added" information over traditional BC subtyping. This signature has the clinical potential to identify patients with tumors refractory to standard RT for whom other strategies or treatment intensification are needed.

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Cytosolic Mislocalization of BRCA1 Is Associated With Increased Metastatic Risk in Breast Cancer

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Purpose/Objective(s): To assess the relationship between subcellular mislocalization of BRCA1 to the cytosol and metastasis in patients with breast cancers.

Materials/Methods: Tissue microarrays were assembled from 106 patients treated from 1986-2006. These samples were analyzed for BRCA1 localization via immunofluorescence staining and categorized as "cytosolic," "nuclear-cytosolic," or "nuclear" BRCA1 localization. Wild type and BRCA1-sequestering mutant (BRCA1 5382insC) MCF-7 cells were subjected to in vitro invasion and migration assays. Tissue microarrays were assembled from 504 patients treated from 1970-2005. These samples were analyzed for BRCA1 localization via immunofluorescence staining and compared to recurrence-free survival (RFS) and distant metastasis-free survival (MFS). BRCA1 localization analyses were conducted via paired and unpaired t-test. Association of cytosolic BRCA1 RFS and MFS were analyzed via log-rank test using a Cox regression to adjust for other prognostic factors (age, tumor size, and lymph node, ER, PR, and Her2 statuses).

Results: Previous literature reported that breast cancer cells contain 8.2-14.8% cytosolic BRCA1. Tissue microarray analysis revealed that the cytosolic BRCA1 content of lung metastases ($\mu = 36.0\%$, 95% CI = [31.7%, 40.3%]) from patients with breast cancer was markedly higher. Intriguingly, lung metastases and their corresponding primary tumors were similarly rich in cytosolic BRCA1 in both unpaired ($36.0\% \pm 18.9\%$ vs $38.5\% \pm 10.5\%$, $p = 0.36$) and paired analyses ($35.8\% \pm 19.2\%$ vs $37.8\% \pm 12.3\%$, $p = 0.70$). In vitro studies demonstrated that genetically induced BRCA1 cytosolic sequestration increases the invasion efficiency of tumor cells (5.04% vs 1.24%, $p = 0.03$). Correlation of tissue microarray data with clinical outcomes indicated an inverse relationship between cytosolic BRCA1 and metastasis-free survival ($p = 0.07$), which was statistically significant in patients over age 40 ($p = 0.02$).

Conclusions: Enrichment of cytosolic BRCA1 in primary tumors may play a causative role in breast cancer metastasis development, making it a potential therapeutic target and biomarker for metastatic risk.

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Complementing Ipsilateral Breast Tumor Recurrence (IBTR!) Estimates With the 21-Gene Recurrence Score (RS) in Early-Stage, Hormone Receptor-Positive, HER2-Normal, Lymph Node-Negative Breast Cancers

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Purpose/Objective(s): The 21-gene RS quantifies the risk of distant recurrence in early-stage, hormone-receptor positive, lymph node-negative