Researchers Identify Genetic Markers for Response to Radiation Therapy and Prediction of Recurrence

For immediate release
October 10, 2019

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ASCO Perspective

"The ability to use gene signatures to predict the likelihood of response to radiation or recurrence after radiotherapy increases our understanding of an individual patient’s prognosis and may eventually allow us to modify the type, timing, and intensity of treatment to improve survival and quality of life for each patient. This is what precision medicine looks like. However, more studies will be needed in larger populations before gene signatures can be used this way in practice," said ASCO Expert Merry-Jennifer Markham, MD, FACP.

ALEXANDRIA, Va. – Genetic information could help identify patients likely to respond to radiation therapy and predict when disease recurrence following radiation is likely to occur. This could help clinicians better tailor treatment strategies to individual patients to boost efficacy, while minimizing unwanted side effects. The findings come from two studies that will be presented at ASCO Breakthrough: A Global Summit for Oncology Innovators, taking place October 11-13, 2019 in Bangkok.

Genomic Analysis Identifies a Gene Mutation Linked With Response to Radiation Treatment
In the first of these studies, researchers identified mutations in the ATM gene that appear to be associated with better response to radiation treatment for cancer. Predicting individuals who will benefit most from radiation therapy could improve disease response and extend survival. In addition, being able to identify patients in whom the risks of radiation treatment would likely outweigh the benefits could help eliminate unnecessary side effects and cost.

Researchers examined whole-genome screening results of patients in a prospectively collected radiotherapy registry. Of 134 patients, they identified 33 with mutations in the ATM (11 patients) and BRCA 1/2 genes (22 patients). In comparing response to radiation therapy with a group of closely matched patients (with similar histology and who received similar doses of radiation) who did not have the mutations, researchers found that mutations in the ATM gene were associated with better complete response (50% with ATM mutation vs. 8% without mutation), overall response (61% vs. 24%), and local control rates at targeted lesions (94% vs. 58%). Complete response means no evidence of disease; overall response includes complete and partial responses. Local control involves the disappearance of the primary tumor and any nearby lymph-node metastases. In addition, response to treatment lasted longer for patients with mutated ATM (median of 11 months vs. 3 months).

“Radiation works by damaging DNA strands. Therefore, a DNA damage-repair gene that is malfunctioning could mark a tumor as sensitive to radiation treatment. In this context, our study showed that the ATM gene (a DNA damage-repair gene) may serve as a novel mutation-based marker of radiosensitivity, which could be harnessed for personalized treatment in the future,” said author Jason Joon Bock Lee, MD, of the Yonsei Cancer Center.

**Gene Signature Could Predict Timing of Recurrence Following Radiation in Patients with Breast Cancer**

In a second study, researchers identified a gene pattern that could help predict which patients with breast cancer will have early or late disease recurrence following radiation therapy. The ability to predict the timing of recurrence could change — and improve — treatment strategies and determine the length of follow-up needed.

Previously the researchers had identified a gene signature linked with response to radiation therapy among patients with breast cancer. They expanded on these results using data from
two cohorts of patients who had undergone radiation therapy and breast-conserving surgery. One set of patients (n=119) was studied to develop a model correlating timing of recurrence with gene expression and another group (n=112) to validate the model. The resulting signature included 41 genes. Based on validation, sensitivity of the signature for accurately identifying early versus late recurrence was 75% and specificity was 100%.

“Historically, women who have breast cancer that comes back within the first 3 years have significantly worse outcomes, including much higher rates of death from breast cancer. If we can identify these patients before they develop early, aggressive recurrences, we may be able to more effectively treat these patients,” said lead author Corey Speers, MD, PhD, who is an assistant professor of radiation oncology at the University of Michigan.

Next Steps

“This work, while exciting and novel, is still premature and not yet ready for clinical adoption. Validation studies in prospective clinical trials are still needed,” said Speers.

This study was funded by the Breast Cancer Research Foundation (BCRF). Dr. Speers is also the recipient of a 2015 Young Investigator Award from Conquer Cancer, The ASCO Foundation.

Doctor-approved information for your readers from Cancer.Net:

- The Genetics of Cancer
- Understanding Radiation Therapy
- Guide to Breast Cancer

View the 2019 ASCO Breakthrough Summit News Planning Team and their disclosures.

ATTRIBUTION TO 2019 ASCO BREAKTHROUGH: A GLOBAL SUMMIT FOR ONCOLOGY INNOVATORS IS REQUESTED IN ALL NEWS COVERAGE
Abstract 130: Genomic analysis reveals somatic mutations of ATM gene in DNA repair confer exceptional target lesion response to radiation therapy.

Authors: Jason Joon Bock Lee, Andrew Jihoon Yang, Jee Suk Chang, Han Sang Kim, Hong In Yoon, Sang Joon Shin, Yong Bae Kim, Woong Sub Koom, Joong Bae Ahn; University of Ulsan, College of Medicine, Seoul, South Korea; Yonsei Cancer Center, Seoul, South Korea; Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Yonse Cancer Senter, Seoul, South Korea; Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, South Korea; Yonsei University College of Medicine, Seoul, South Korea; Department of Internal Medicine, Cancer Metastasis Research Center, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Somatic mutations of genes involved in DNA repair (e.g. ATM and BRCA1/2) may result in chemotherapy resistance and poor prognosis, but may confer sensitivity to radiation therapy. In this study, we aimed to the hypothesis that patients with such mutations may be more susceptible to radiotherapy. Methods: Using prospectively collected RT registry, we identified patients who underwent both RT to gross disease and NGS panel screening between 2013 and 2019 (N = 27,664). From a cohort of 134 patients, 33 patients with somatic mutation in ATM or BRCA 1/2 were identified and closely matched with 33 patients without mutation using propensity score based on radiation dose and histology. Results: Infield response rate was evaluated in 66 patients with 90 gross lesions (ATM mutation, 11 patients
and BRCA 1/2 mutation, 22 patients). The median tumor size and RT dose was 24 mm (3-140) and 40 Gy (12-66), respectively. Stark differences were seen in infield complete response rate, overall response rate, and local control rate at target lesions by ATM mutation (mutation vs. no mutation; 50% vs. 8%, 61% vs. 24%, and 94% vs. 58%, $P < .05$). Response duration was also longer ATM mutation (median 11 vs. 3 months, $P = .001$). However, RT-related toxicities were not different (17% vs. 11%, $P = .515$) and no severe toxicity occurred. **Conclusions:** ATM mutations confer exceptional responses to radiation therapy, even with palliative dose, which has potential therapeutic implications.

**Disclosures:** Jason Joon Bock Lee, MD, MS, Employment with DiNonA Inc.

**Research Funding Source:** No funding received

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**Abstract 112:** A signature predictive of early versus late recurrence after radiation (RT) for breast cancer that may inform the biology of early, aggressive recurrences.

**Authors:** Corey Wayne Speers, S. Laura Chang, Benjamin Chandler, Andrea Pesch, Anna Michmerhuizen, Kari Wilder-Romans, Shyam Nyati, Lori J. Pierce; University of Michigan Hospital, Ann Arbor, MI; University of Michigan, Ann Arbor, MI

**Background:** Unmet clinical needs in breast cancer (BC) management include the identification of patients at high risk to fail locally despite standard local therapy and an understanding of the biology of these recurrences. We previously reported a radiation response signature and here extend those studies to identify a signature predictive of timing of recurrence after RT. **Methods:** 2 independent patient cohorts were used for training (119 pts) and validation (112 pts). All patients received RT after BCS and systemic therapy as
appropriate. Spearman's rank correlation to correlate gene expression to recurrence time was used for feature selection. Significant genes were used to train a linear model which was locked before validation. Cox regression was used for both UVA and MVA. **Results:** Spearman's correlation identified 485 genes whose expression was significantly associated with recurrence time (+/-3 yrs). Feature reduction refined the list to 41 genes retained within the signature. In training, the correlation of score to recurrence time was 0.85, p-value < 1.3x10-31; AUC of 0.91. External validation in an independent BC validation set accurately identified patients with early vs. late recurrences (correlation= 0.75, p-value = 0.001, AUC = 0.92, sens.=0.75, spec.= 1.0, PPV = 1.0, NPV = 0.8). Unique associations of breast cancer intrinsic subtype to timing of local recurrence were found. In UVA and MVA the signature remained the most significant factor associated with recurrence. GSEA analysis of the 41 genes retained within the signature identified proliferation and EGFR concepts associated with early recurrences and luminal and ER-signaling pathways associated with late recurrences. Knockdown of genes associated with the early and late recurrences demonstrated novel effects on proliferation and clonogenic survival, respectively.

**Conclusions:** We report a BC gene expression signatures that may be useful in identifying patients unlikely to respond to adjuvant RT and may be used to predict timing of recurrences, with implications for potential treatment intensification and duration of follow-up for women with breast cancer treated with RT.

**Disclosures:** Corey Wayne Speers, MD, PhD, Stock and Other Ownership Interests with PFS Genomics; S. Laura Chang, Ph.D., Employment with PFS Genomics, Stock and Other Ownership Interests with PFS Genomics; Lori J. Pierce, MD, Stock and Other Ownership Interests with PFS Genomics

**Research Funding Source:** Breast Cancer Research Foundation

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