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News Release

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Radiation therapy outcomes better for African-American prostate cancer patients than Caucasian patients

Genetic analyses contrast assumptions about race and prostate cancer, pointing to increased sensitivity to radiation therapies in African-American men

SAN ANTONIO, October 22, 2018 — While popular beliefs and population data suggest that African-American men are at higher risk of dying from prostate cancer than Caucasian men, a new analysis of genetic data from a large prospective registry and clinical data from several randomized trials indicates that African-American patients may have comparatively higher cure rates when treated with radiation therapy. The study, which is the first report demonstrating improved prostate cancer outcomes for African-American men, will be presented today at the 60th Annual Meeting of the American Society for Radiation Oncology (ASTRO).

"Our findings suggest that African-American race is not *independently* associated with worse prostate cancer outcomes," said lead author Daniel Spratt, MD, an associate professor and Chief of the Genitourinary Radiotherapy Program at the University of Michigan Rogel Cancer Center. "When we started this project, we had the commonly-held assumption that African-American men harbor more aggressive disease that leads to lower survival rates. We were surprised, however, that they appear to be more responsive than Caucasian men to radiation therapy and have improved outcomes following this treatment."

Cancer registries have reported that African-American men appear to be at higher risk of dying from aggressive prostate cancer, with an incidence rate almost 60 percent higher and a mortality rate two-to-three times greater than Caucasian men. What remains unclear, however, are how socioeconomic versus biological factors contribute to these disparities.

The two-part study from Dr. Spratt's team examined biological factors that drive responses to prostate cancer treatment and may explain the disparity in outcomes. The team first investigated differences in how specific genes were expressed in tumor samples from 17,003 men (1,953 or 11.5 percent African-American) with prostate cancer, focusing on androgen receptor activity — a key driver of prostate cancer — and sensitivity to radiation, as well as outcomes following radiation therapy.

Tumors with low androgen receptor activity were significantly more likely to develop distant metastases within ten years (37 percent vs. 17 percent, p=0.008), and tumors from African-American men were

significantly more likely to have low androgen receptor activity ($p<0.001$). Low androgen receptor activity was an independent predictor of distant metastasis even after adjusting for Gleason grade, T-stage, PSA level, margin status after surgery, and lymph node invasion ($p=0.03$).

Tumors from African-American men also were more likely, however, to have indicators of increased sensitivity to radiation therapy: decreased expression of the double-strand DNA repair pathway ($p<0.001$), increased expression of immune pathways ($p<0.001$), and increased radiosensitivity as predicted by a 24-gene prostate cancer radiation sensitivity score developed by the research team. Increased radiotherapeutic sensitivity suggests that African-American patients have improved outcomes when treated with radiation.

"Differences in gene expression between African-American and Caucasian patients revealed that African-American patients had lower DNA repair and more immunogenic tumors, both of which have been shown to predict better responses to radiation therapy," said Dr. Spratt.

Next, researchers examined outcomes from 5,854 patients (19.3 percent African-American) in four large NRG Oncology/RTOG randomized prostate cancer trials (NRG-RTOG 9202, 9408, 9413 and 9910). This meta-analysis showed that African-American men treated with radiation therapy, compared to Caucasian men, were less likely to see their cancer return or spread.

Specifically, African-American patients in these trials had lower rates of biochemical cancer recurrence (hazard ratio (HR) 0.82, 95% CI 0.74, 0.92; $p=0.0005$) and distant metastasis (HR 0.70, 95%CI 0.57, 0.86; $p=0.0008$), even after controlling for age, performance status, PSA, Gleason grade, T-stage, N-stage and hormone therapy use.

Dr. Spratt, who also co-chairs the radiobiology and radiotherapy working group for the Prostate Cancer Foundation, said the team's findings, coupled with other recent analyses, confirm that the seeming racial disparities for prostate cancer are rooted more in societal causes than biology.

"Our results directly question previously held beliefs from population-based registry data that African-American men independently have worse prostate cancer outcomes than Caucasian men," he explained. "These findings strengthen the notion that most of the observed disparity found in population datasets regarding stage-for-stage outcomes between African-American and Caucasian men are reflective of social constructs and not rooted in biology."

"Not only did both groups generally have similar prognoses, but African-American men treated with radiation therapy actually had higher rates of cure and excellent outcomes. Patients should be treated irrespective of race," he added.

The abstract, "Androgen receptor activity and radiotherapeutic sensitivity in African-American men with prostate cancer: A large scale gene expression analysis and meta-analysis of RTOG trials," will be presented in detail during a news briefing and the plenary session at ASTRO's 60th Annual Meeting in San Antonio. To schedule an interview with Dr. Spratt and/or outside experts in prostate cancer, contact ASTRO's media relations team on-site at the Henry B. González Convention Center October 21 through 24, by phone at 703-286-1600 or by email at press@astro.org.

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Attribution to the American Society for Radiation Oncology (ASTRO) Annual Meeting requested in all coverage.

This news release contains additional and/or updated information from the study author(s).

Study Presentation Details

- News Briefing: Monday, October 22, 11:00 a.m. – 12:00 p.m. CT, Room 225-D, http://bit.ly/ASTRO18-2
- Plenary Session: Monday, October 22, 2:15 – 3:45 p.m. CT, Stars at Night Ballroom
- Abstract available on the final page of this release.

Resources on Prostate Cancer and Radiation Therapy

- Digital brochure: Radiation Therapy for Prostate Cancer; (Spanish version)
- Videos: Radiation Therapy for Prostate Cancer; (Spanish version), An Introduction to Radiation Therapy; (Spanish version)
- ASTRO's clinical practice statements and guidelines
- Additional brochures, videos and information on radiation therapy from ASTRO's patient site, RTAnswers.org

ABOUT ASTRO

The American Society for Radiation Oncology (ASTRO) is the world's largest radiation oncology society, with more than 10,000 members who are physicians, nurses, biologists, physicists, radiation therapists, dosimetrists and other health care professionals who specialize in treating patients with radiation therapies. The Society is dedicated to improving patient care through professional education and training, support for clinical practice and health policy standards, advancement of science and research, and advocacy. ASTRO publishes three medical journals, International Journal of Radiation Oncology • Biology • Physics, Practical Radiation Oncology and Advances in Radiation Oncology; developed and maintains an extensive patient website, RT Answers; and created the nonprofit foundation Radiation Oncology Institute. To learn more about ASTRO, visit astro.org or RTanswers.org, sign up to receive our news and follow us on our blog, Facebook and Twitter.

Androgen receptor activity and radiotherapeutic sensitivity in African-American men with prostate cancer: A large scale gene expression analysis and meta-analysis of RTOG trials

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Purpose/Objective(s): Population data suggests that African-American (AfA) men have an increased mortality from prostate cancer (PCa) compared to Caucasian (C) men. Socioeconomic variables contribute to this disparity, yet intrinsic biological differences remain plausible. Herein, we investigate the interplay of androgen receptor activity (AR-A) and radiotherapeutic sensitivity to provide a molecular rationale to help explain the disparity in outcomes for AfA men with PCa.

Materials/Methods: Transcriptome-wide expression profiles of FFPE tumor samples from 5,831 localized PCa patients were used. Tissue was obtained from a prospective population cohort (n=5,239) and two retrospective cohorts with long-term outcomes (n=592). Predicted radiation sensitivity was measured using the 24-gene post-operative radiotherapy (RT) outcome score (PORTOS). AR-A was defined from the pooled expression of nine canonical AR-target genes. Clinical radiosensitivity was validated using individual patient data from four RTOG trials (92-02, 94-08, 94-13, and 99-10), comprised of 6,011 patients (18.5% AfA). Competing risk adjustments were used for all survival analyses for biochemical recurrence (BCR) and distant metastases (DM).

Results: In men treated by surgery from the prospective cohort, low AR-A tumors were significantly more likely to develop DM (10-year rate: 37% vs 17%, p=0.008). On multivariable analysis after adjusting for Gleason grade, T-stage, PSA, margin status, and lymph node invasion, low AR-A remained independently prognostic for DM (p=0.03). After generating a matched cohort of AfA and C patients, AfA tumors were more likely to have low AR-A (p<0.001). However, AfA tumors had decreased double strand break repair pathway expression (p<0.001) and increased predicted RT sensitivity (p<0.001). This suggests that AfA men may have improved outcomes with RT. To clinically test whether AfA tumors are more radiosensitive, we leveraged four large RTOG trials of men treated with RT. On both unadjusted and propensity weighted cohorts (adjusting for age, performance status, PSA, Gleason grade, T-stage, N-stage, and use/duration of hormone therapy), AfA men had significantly improved outcomes compared to C men (BCR (HR 0.82 [95%CI 0.74, 0.92], p=0.0005) and DM (HR 0.70 [95%CI 0.57, 0.86], p=0.0008)).

Conclusion: Our data suggests that there are population level differences in AR signaling and DNA repair in AfA and C men's PCa, which transcriptionally suggest that AfA men may harbor more radiosensitive tumors. To our knowledge, this is the first report demonstrating that AfA men may have improved outcomes compared to C men treated with RT, which is consistent with our hypothesis regarding diversity in AR-A, and warrants further investigation.