

Embargoed until 3:15 pm ET, Sunday, September 25, 2016

Contact: Liz Gardner
703-286-1600
liz.gardner@astro.org

Nancy Mayes
Mayes Communications
703-772-2510
nancy@mayescommunications.com

Three novel intrinsic subtypes of prostate cancer identified

Results find two subtypes associated with response to post-operative RT, establish basis for further research on individualizing treatment

BOSTON, September 25, 2016 -- In the largest study of its kind to date, researchers have identified and validated three distinct molecular subtypes of prostate cancer that correlate with distant metastasis-free survival and can assist in future research to determine how patients will respond to treatment, according to research presented today at the 58th Annual Meeting of the American Society for Radiation Oncology (ASTRO). Findings represent a step toward the implementation of personalized medicine in prostate cancer care.

To diagnose and determine treatment for prostate cancer, clinicians consider many factors, including a digital rectal exam, the prostate specific antigen (PSA) level in a patient's blood and prostate tumor biopsy results. Molecular subtyping of tumor cells allows oncologists to individualize care and tailor treatment based on the actual biology of each patient's individual disease.

"Tumors that appear similar under a microscope can behave very differently, from a clinical standpoint," said Daniel E. Spratt, MD, lead author of the study and Chief of the Genitourinary Radiotherapy Program at the University of Michigan in Ann Arbor, Michigan. "One promise of genomic analyses is to elucidate subtypes of cancer based on the genetics of the tumor rather than merely how they look or what size they are."

To identify genomic profiles for prostate cancer, researchers analyzed RNA expression patterns in 4,236 samples from nine separate groups of men treated with radical prostatectomy for localized prostate cancer. In an effort to create "intrinsic" subtypes specific to the cancer itself rather than the associated surrounding tissue, data were refined to remove non-tumor genes from the training (i.e., identification

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

251 18TH STREET SOUTH • 8TH FLOOR • ARLINGTON, VA 22202 • PHONE: 703-502-1550 • FAX: 703-502-7852 • www.astro.org
ASTRO Press Office: press@astro.org • PHONE: 703-286-1600 • FAX: 703-286-1601

not validation) dataset. Through K-median clustering analysis, researchers identified three molecular subtypes of prostate cancer that could be characterized through a profile of 100 distinct genes, named the Prostate Cancer 100 (PC100) by study investigators.

“We were surprised to find that prostate cancer subtyped into only three very distinct subtypes,” said Dr. Spratt. “We knew that primary prostate cancer was a relatively quiet tumor, genomically, but similar cancers that are endocrine-driven, like breast cancer, have been shown to be able to be clustered into a finite number of subtypes.”

Researchers validated the subtypes across six additional retrospective cohorts, representing a variety of RNA sequencing platforms and tissue storage methods, and two prospective cohorts comprising 2,610 patients. The intrinsic subtypes were associated with androgen receptor (AR) activity, expression of the ERG oncogene and other known drivers of prostate tumor growth and progression, but researchers did not find a link from mutations or genetic rearrangements to the subtypes.

Rates of distant metastasis-free survival (DMFS) at ten years varied significantly among the three subtype groups. DMFS rates were 57.1 percent for subtype A, 64.4 percent for subtype B, and 73.6 percent for subtype C (B vs. A: Cox Hazard Ratio (HR), 1.31, $p = 0.02$; C vs. A: HR, 1.65, $p = 0.0001$). After controlling for clinicopathologic variables, the profile remained independently associated with DMFS (B vs. A: Cox HR, 1.31, $p = 0.026$; C vs. A: HR, 1.33, $p = 0.024$). Additionally, multivariate interaction analysis determined that subtypes B and C shared a significant correlation with response to post-operative radiation therapy (RT) (Wald $p = 0.0016$).

“We have discovered and independently validated a highly stable 100-gene intrinsic molecular profile of prostate cancer that is both prognostic and predictive for radiation therapy,” said Dr. Spratt. “We believe that these subtypes reflect truly distinctive underlying biology and that this work represents a significant advance in our understanding of prostate cancer biology. Moreover, our findings identify numerous genes and enriched biologically active pathways in prostate cancer that have been underappreciated to date but may be potential targets to improve cure rates in this disease by developing new targeted therapies.”

The abstract, “Identification and Validation of Intrinsic Subtypes of Prostate Cancer,” will be presented in detail during a scientific session at ASTRO’s 58th Annual Meeting at 3:15 p.m. Eastern time on Sunday, September 25, 2016. To speak with Dr. Spratt, please contact ASTRO’s media relations team on-site at the Boston Convention and Exhibition Center September 25 through 28, by phone at 703-286-1600 or by email at press@astro.org.

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

251 18TH STREET SOUTH • 8TH FLOOR • ARLINGTON, VA 22202 • PHONE: 703-502-1550 • FAX: 703-502-7852 • www.astro.org
ASTRO Press Office: press@astro.org • PHONE: 703-286-1600 • FAX: 703-286-1601

ATTRIBUTION TO THE AMERICAN SOCIETY OF RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING REQUESTED IN ALL COVERAGE.

This news release contains updated data from the study author(s). Full study abstract available on the final page of this release.

ABOUT ASTRO'S ANNUAL MEETING

ASTRO's 58th Annual Meeting, the nation's premier scientific meeting in radiation oncology, will be held September 25-28, 2016, at the Boston Convention and Exhibition Center in Boston. The 2016 Annual Meeting is expected to attract more than 11,000 attendees from across the globe, including oncologists from all disciplines and members of the entire radiation oncology team. Led by ASTRO president David C. Beyer, MD, FASTRO, the 2016 meeting will feature keynote addresses from Kathleen Sebelius, former U.S. Secretary of Health and Human Services; Thomas James Lynch Jr., MD, Chair and CEO, Massachusetts General Physicians Organization; and Jason Ragona, general manager, SMS and Safety Alliances, Corporate Safety, Security, and Compliance, Delta Air Lines, Inc. The Presidential Symposium, "Prostate Cancer: Defining Value and Delivering It," highlights the meeting's theme of "Enhancing Value, Improving Outcomes" and will feature recent practice-changing studies and current developments in value-based care for prostate cancer. ASTRO's four-day scientific meeting will feature a record number of abstracts, including 368 oral presentations, 1,760 posters and 180 digital posters in more than 50 educational sessions and 20 scientific panels for 20 disease-site tracks. For more information about ASTRO's 58th Annual Meeting, visit www.astro.org/AnnualMeeting. For press registration and news briefing information for ASTRO's 58th Annual Meeting, visit www.astro.org/AMPress.

ABOUT ASTRO

ASTRO is the premier radiation oncology society in the world, 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. As the leading organization in radiation oncology, 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 (www.redjournal.org), Practical Radiation Oncology (www.practicalradonc.org) and Advances in Radiation Oncology (www.advancesradonc.org); developed and maintains an extensive patient website, RT Answers (www.rtanswers.org); and created the Radiation Oncology Institute (www.roinstitute.org), a nonprofit foundation to support research and education efforts around the world that enhance and confirm the critical role of radiation therapy in improving cancer treatment. To learn more about ASTRO, visit www.astro.org.

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

251 18TH STREET SOUTH • 8TH FLOOR • ARLINGTON, VA 22202 • PHONE: 703-502-1550 • FAX: 703-502-7852 • www.astro.org
ASTRO Press Office: press@astro.org • PHONE: 703-286-1600 • FAX: 703-286-1601

Identification and Validation of Intrinsic Subtypes of Prostate Cancer

D. E. Spratt¹, S. G. Zhao¹, S. L. Chang¹, M. R. Cooperberg², N. G. Erho³, C. Speers⁴, R. Mera¹, Y. S. Niknafs¹, P. L. Nguyen⁵, R. B. Den⁶, A. P. Dicker⁶, E. A. Klein⁷, R. J. Karnes⁸, E. M. Schaeffer⁹, E. Davicioni³, P. Carroll², A. Chinnaiyan¹⁰, S. A. Tomlins¹, F. Y. Feng¹¹, and A. E. Ross⁹; ¹University of Michigan, Ann Arbor, MI, ²University of California, San Francisco, San Francisco, CA, United States, ³GenomeDx Biosciences, Vancouver, BC, Canada, ⁴Veteran Affairs Hospital Ann Arbor, Ann Arbor, MI, ⁵Brigham & Women's Hospital, Dana Farber Cancer Institute and Harvard Medical School, Boston, MA, ⁶Sidney Kimmel Medical College at Thomas Jefferson University, Sidney Kimmel Cancer Center, Philadelphia, PA, ⁷Cleveland Clinic, Cleveland, OH, ⁸Mayo Clinic, Rochester, MN, ⁹Johns Hopkins University, Baltimore, MD, ¹⁰The University of Michigan Cancer Center, Ann Arbor, MI, United States, ¹¹University of California at San Francisco, San Francisco, CA

Purpose/Objective(s): To identify the first ever intrinsic molecular subtypes of primary prostate cancer through unbiased high-throughput analyses.

Materials/Methods: RNA expression patterns captured from high-density microarrays and transcriptome sequencing were analyzed in 4,236 primary prostate cancer samples from nine independent cohorts. K-medoids clustering was used in training and validation sets to identify intrinsic subtypes. The subtypes were correlated with distant metastasis-free survival (DMFS). The Database for Annotation, Visualization and Integrated Discovery (DAVID) was used to identify biological functions enriched in the subtype genes. Mutation analysis was performed using the cBioPortal for Cancer Genomics.

Results: Clustering in the training dataset initially was strongly influenced by stromal genes, likely indicative of tumor content, as well as genes strongly associated with warm ischemia, likely indicative of elapsed time between specimen harvest and fixation. After these tumor extrinsic factors were removed, we identified three distinct groups based on 100 genes (PC100). These findings were validated in the remaining seven frozen or FFPE retrospective cohorts as well as in a prospective validation cohort of 2,113 patients. The intrinsic subtypes were associated with known drivers of prostate cancer, including *AR* and *ERG*, but do not appear to be driven by mutations or rearrangements. The 10-year rates of DMFS across the three subtypes were 73.6% (A), 64.4% (B), and 57.1% (C) (B vs. A: Cox HR=1.31 [95%CI 1.04-1.66], p=0.02, C vs. A: HR=1.65 [1.29-2.10], p=0.0001). The subtypes were independently associated with DMFS after adjusting for clinicopathologic variables (B vs. A: Cox HR=1.31 [1.03-1.65], p=0.026, C vs. A: HR=1.33 [1.04-1.71], p=0.024). Furthermore, on multivariate interaction analysis, subtype C was significantly associated with response to post-operative radiotherapy (Wald p=0.0016). Within the 100 genes, enriched biological functions relate to clusters of genes governing protein degradation, RNA processing, apoptosis, the cell cycle, ATP synthesis, and a large cluster of genes relating to protein localization.

Conclusion: We have identified three novel intrinsic subtypes of prostate cancer in the largest study of its kind, and validated our findings across sequencing platforms, storage methods, and within both retrospective and prospective cohorts. In defining unique biological clusters of disease, the PC100 represents a step towards personalization of prostate cancer care. Future work will focus on validating the predictive capacity of these subtypes to therapy such as radiation therapy.

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

251 18TH STREET SOUTH • 8TH FLOOR • ARLINGTON, VA 22202 • PHONE: 703-502-1550 • FAX: 703-502-7852 • www.astro.org
ASTRO Press Office: press@astro.org • PHONE: 703-286-1600 • FAX: 703-286-1601