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## **Unstable chromosomes linked to less favorable response to radiation therapy and surgery in prostate cancer patients**

Atlanta, September 25, 2013—Detailed evaluation of a prostate cancer tumor biopsy may predict treatment outcomes for image-guided radiation therapy (IGRT) or surgery for prostate cancer, according to research presented today at the American Society for Radiation Oncology's (ASTRO's) 55<sup>th</sup> Annual Meeting. The study results indicate that patients who have abnormal levels of breaks at common fragile sites (CFSs), sites within the chromosomes that are sensitive to DNA damage, are more likely to have their cancer to return—treatment failure. These CFS break abnormalities are usually associated with instability of the cell's DNA, a phenomenon that is particularly associated with cancer.

In this study, researchers assessed the outcomes of 280 prostate cancer (CaP) patients, and reviewed the DNA “fingerprints” of each patient's tumor (using the patient's initial diagnostic core biopsy) to determine if gene copy number alterations (CNAs), or breaks in CFSs, were related to a less positive response to treatment. Two groups were analyzed: 126 localized intermediate risk CaP patients who had received image-guided radiation therapy (IGRT) treatments, with a mean dose of

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74.6 Gy; and 154 localized intermediate and high risk CaP patients who had undergone radical prostatectomy (RP), which is the surgical removal of the entire prostate gland.

Utilizing an array comparative genomic hybridization (aCGH), DNA from frozen needle biopsies of the RT patients was analyzed for 13 previously characterized CFSs: FRA2G, FRA3B, FRA4F, FRA6E, FRA6F, FRA7E, FRA7G, FRA7H, FRA7I, FRA7K, FRA8C, FRA9E, FRA16D. The effect of having at least one CNA in any CFS was assessed using the Kaplan-Meier method and Cox proportional hazard models.

The data revealed a pattern in which the patients who failed treatment had abnormal levels of CNAs at CFSs. In the IGRT group, CNAs in CFSs occurred frequently, with 80 of the patients (64 percent) having a CNA in one or more CFS locations (median was 1, and the range was 0 – 10).

Each patient's biochemical relapse-free rate (bRFR) was gauged, because if a patient relapses biochemically, his prostate specific antigen level has risen significantly and this is a reasonable indicator that the cancer has recurred. Thus, a high bRFR is desirable. On univariate analysis, patients with a CNA in at least one CFS showed a decreased 5-year bRFR (64 percent), compared with the bRFR of patients without genetic alteration in CFSs (90 percent; HR = 2.13, 95% CI: 1.17-3.86,  $p = 0.011$ ). After adjusting for clinical factors in a multivariate model, a CNA in a CFS was determined to be a significant independent predictor of decreased response to radiation therapy and higher incidence of recurring cancer. (HR = 2.94, 95% CI: 1.51-5.75,  $P = 0.0016$ ).

The results of the 154 patients in the RP group were compiled using the publically available Memorial Sloan-Kettering Cancer Center (MSKCC) aCGH database of patients. CNAs in CFSs were also frequent in the RP group, with 81 patients (53 percent) having a CNA in one or more location (median was 1, and the range was 0 – 6). These results also correlated to decreased 5-year bRFR rates of 68 percent, compared to 82 percent for RP patients without genetic alterations in CFSs (HR = 1.79). Despite this strong trend, after adjusting for clinical factors in a multivariate model, a CNA in a CFS was not a statistically significant predictor of cancer recurrence (HR = 1.52, 95% CI: 0.77-3.02,  $P = 0.23$ ).

“We thought that patients who have CFS breaks might be more sensitive to radiation therapy-induced DNA damage,” said the lead author of the study, Robert G. Bristow, MD, PhD, a Professor within the radiation oncology and medical biophysics departments at the University of Toronto; and a Clinician-Scientist at the Princess Margaret Cancer Centre in Toronto. “We now think that the CFS breaks are a signal that the cancer cell has acquired numerous genetic changes that lead to more aggressive cancer cells that can spread early and outside the prostate gland. Our data suggest that the patients failing treatment are due to early metastatic (distant spread) disease. If we validate this study in similar, but larger groups of patients, we can develop a test based for CFS breaks; the results would allow us to place patients in one of two categories: those whose tumors do not have CFS breaks and who would likely do well with local treatment alone (e.g. radiotherapy or surgery); and, those patients whose tumors do have CFS breaks and would need a more complex treatment protocol, in addition to RT or surgery, to combat distant spread. ”

The abstract, “Genomic Instability in Common Fragile Sites (CFSs) is Associated with Less Favorable Outcome in Patients with Intermediate-Risk Prostate Cancer (IR-CaP),” will be presented in detail during a scientific session at ASTRO’s 55th Annual Meeting at 1:00 p.m. Eastern time, on Wednesday, September 25, 2013. To speak with Dr. Bristow, please call Michelle Kirkwood on September 22–25, 2013, in the ASTRO Press Office at the Georgia World Congress Center at 404-222-5303 or 404-222-5304, or email [michellek@astro.org](mailto:michellek@astro.org).

ASTRO’s 55<sup>th</sup> Annual Meeting, held in Atlanta, September 22-25, 2013, is the premier scientific meeting in radiation oncology and brings together more than 11,000 attendees including oncologists from all disciplines, medical physicists, dosimetrists, radiation therapists, radiation oncology nurses and nurse practitioners, biologists, physician assistants, practice administrators, industry representatives and other health care professionals from around the world. The theme of the 2013 meeting is “Patients: Hope • Guide • Heal” and focuses on patient-centered care and the importance of the physician’s role in improving patient-reported outcomes and the quality and safety of patient care. The four-day scientific meeting includes presentation of four plenary papers, 363 oral presentations, 1,460 posters and 144 digital posters in 70 educational sessions and scientific panels for

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19 disease sites/tracks. Keynote and featured speakers include: William B. Munier, director of the Center for Quality Improvement and Patient Safety at the Agency for Healthcare Research and Quality; Darrell G. Kirch, MD, president and CEO of the Association of American Medical Colleges; James Cosgrove, PhD, director of the U.S. Government Accountability Office; Otis W. Brawley, MD, chief medical officer of the American Cancer Society; and Peter Friedl, MD, PhD, of St. Radboud University Nijmegen Medical Centre at the University of Nijmegen and MD Anderson Cancer Center.

## **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 that 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 two medical journals, International Journal of Radiation Oncology • Biology • Physics ([www.redjournal.org](http://www.redjournal.org)) and Practical Radiation Oncology ([www.practicalradonc.org](http://www.practicalradonc.org)); developed and maintains an extensive patient website, [www.rtanswers.org](http://www.rtanswers.org); and created the Radiation Oncology Institute ([www.roinstitute.org](http://www.roinstitute.org)), a non-profit 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](http://www.astro.org).*

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**2013 American Society for Radiation Oncology (ASTRO) 55<sup>th</sup> Annual Meeting  
News Briefing, Wednesday, September 25, 2013, 8:15 a.m. Eastern time**

Scientific Session: Wednesday, September 25, 2013, 1:00 - 2:30 p.m. ET, Georgia World Congress Center

**305 Genomic Instability in Common Fragile Sites (CFSs) is Associated with Less Favorable Outcome in Patients with Intermediate-Risk Prostate Cancer (IR-CaP)**

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**Purpose/Objective(s):** 20-40% of patients with IR-CaP will fail radiotherapy (RT) or radical prostatectomy (RP). The genomic complexity of CaP emphasizes the need to find the genetic factors involved in progression and differential tumour response. CFSs have been established as sites of frequent chromosome breakage and rearrangements in cancer cells.

**Materials/Methods:** Using array comparative genomic hybridization (aCGH), we profiled the copy number alterations (CNAs) in 13 previously characterized CFSs; FRA2G, FRA3B, FRA4F, FRA6E, FRA6F, FRA7E, FRA7G, FRA7H, FRA7I, FRA7K, FRA8C, FRA9E and FRA16D using tumor DNA from frozen needle biopsies derived from 126 IR-CaP patients (T1-T2, GS < 8 and PSA < 20 ng/mL) who underwent RT (Mean dose: 76.4 Gy). The effect of having at least one CNA in any CFS was assessed using the Kaplan-Meier method and Cox proportional hazard models.

**Results:** CNAs in CFSs occurred frequently in our cohort: 80/126 (63.5%) patients had a CNA in one or more CFS loci (median: 1, 0-10). CNAs in CFSs were significantly associated with increased genetic instability manifested by higher percent genome alteration (PGA;  $P < 0.0001$ ). Allelic losses and gains were observed predominantly at FRA16D (31.7%), FRA6F (19.8%) and FRA8C (21.4%), FRA7I (11.9%), respectively, and were significantly associated with increased genomic instability. 55 patients experienced biochemical relapse (Median follow-up: 7.8 years (0.8-12.2)). On univariate analysis, a CNA in at least one CFS was associated with decreased 5y-bRFR compared with patients without genetic alteration in CFSs (64% vs. 90%; HR = 2.13, 95% CI: 1.17-3.86,  $P = 0.011$ ). After adjusting for clinical factors in a multivariate model, a CNA in a CFS was a significant independent predictor (HR = 2.94, 95% CI: 1.51-5.75,  $P = 0.0016$ ). Univariate and multivariate analyses both showed statistically significant decreased 5y-bRFR with FRA8C gain. Results were validated using publically available MSKCC aCGH database from patients treated by RP. CNAs in CFSs were also frequent in RP cohort (95/171; 55.6%, median: 1, 0-7), and were associated with decreased 5y-bRFR (60% vs. 82%; HR = 2.19, one-sided lower 95% CI: 1.34,  $P = 0.0036$ ). After adjusting for clinical factors in a multivariate model, a CNA in a CFS was a significant independent predictor (HR = 1.90, 95% CI: 1.04-3.50,  $P = 0.038$ ). Losses at FRA6F (28.7%) and FRA16D (23.4%), and gains at FRA7I (12.9%) were the most frequent found genetic changes in CFSs.

**Conclusions:** This is the first report on CFSs status as a general class in patients with CaP. Our data show that genomic instability in CFSs is a common event in CaP and is associated with less favorable clinical outcome. The genetic changes in these loci are likely to underlie progression of CaP and act as prognostic markers for clinical outcome.

**Author Disclosure Block:** **A. Fotouhi Ghiam:** None. **G. Zafarana:** None. **L. Emilie:** None. **J. Sykes:** None. **W.L. Lam:** None. **A. Meng:** None. **P.C. Boutros:** None. **M. Milosevic:** None. **T. van der Kwast:** None. **R.G. Bristow:** None.