Unstable chromosomes linked to less favorable response to RT and surgery in prostate cancer patients

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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) 55th 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 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."

More information: 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.

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