Impact of a Genomic Classifier of Metastatic Risk on Postprostatectomy Treatment Recommendations by Radiation Oncologists and Urologists

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OBJECTIVE To evaluate how a genomic classifier (GC) that predicts the risk of metastasis after prostatectomy would impact adjuvant treatment recommendations made by radiation oncologists and urologists. The 2 specialties often disagree about postprostatectomy adjuvant treatment recommendations.

MATERIALS AND METHODS Twenty-six radiation oncologists and 20 urologists with genitourinary oncology expertise reviewed de-identified clinical results from 11 patients after radical prostatectomy and made adjuvant treatment recommendations. The same cases were later randomized and reassigned, and treatment recommendations were made using the clinical information and GC test results together.

RESULTS Using clinical information alone, observation was recommended in 42% of decisions made by urologists vs 23% by radiation oncologists ($P < .0001$). The GC test results altered 35% and 45% of treatment recommendations made by radiation oncologists and urologists, respectively. Multivariate analysis showed GC risk was the strongest factor influencing treatment recommendations by both specialties, with an adjusted odds ratio of 4.17 (95% confidence interval [CI], 2.26-7.70) and 6.51 (95% CI, 4.29-9.88) for radiation oncologists and urologists, respectively. GC results indicating high metastatic risk resulted in intensification of treatment, whereas low metastatic risk resulted in less aggressive recommendations. The GC results increased interdisciplinary agreement in treatment recommendations, as the odds of a recommendation for adjuvant treatment by urologists vs radiation oncologists increased from 0.27 (95% CI, 0.17-0.44) to 0.46 (95% CI, 0.29-0.75) after results of the GC test were available.

CONCLUSION The GC test significantly influenced adjuvant postprostatectomy treatment recommendations, reduced disagreement between radiation oncologists and urologists, and has the potential to enhance personalization of postprostatectomy care. UROLOGY 86: 35–40, 2015. © 2015 Elsevier Inc.

The American Urological Association (AUA) and the American Society for Radiation Oncology (ASTRO) released a joint statement in 2013 recommending that adjuvant radiation be discussed as a possible treatment option for men with pathologic T3 (pT3) or margin positive disease (SM+) after radical prostatectomy (RP). However, urologists and radiation oncologists often differ in their recommendations regarding adjuvant radiation.[1] The results of a large, national survey of physicians found that radiation oncologists were significantly more likely to recommend adjuvant radiation, whereas urologists were more likely to advocate for observation, followed by early salvage radiation (if needed).[2] This disparity has the potential to create confusion and uncertainty for patients regarding their treatment options.

Although 3 phase III trials have demonstrated that adjuvant radiation decreases the risk of recurrence in patients with positive surgical margins or pathologic T3 disease,[3-5] radiation oncologists and urologists looking at the same standard clinical variables have not come to convergence on what constitutes the appropriate use of

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postprostatectomy adjuvant therapy.[2] Among other factors, concerns regarding the potential of overtreatment of some patients to benefit others have prevented widespread adoption of adjuvant radiation.[6] Thus, there is a need to identify subsets of patients at even higher risk for disease progression to guide recommendations regarding adjuvant treatment.

Several previous studies have shown that genomic features in the primary tumor provide a quantitative measure of biological potential for disease progression and metastasis.[7-9] Recently, a ribonucleic acid (RNA)—based genomic classifier (GC) test (Decipher; GenomeDx Biosciences, San Diego, CA), which uses 22 markers derived from paraffin-embedded prostatectomy tissue, has been validated as a significant independent predictor of early metastasis after RP.[10-13] In 1 cohort study, the GC test had an area under the curve of 0.79 for predicting metastases. In the same study, the GC test outperformed all clinical variables and other published gene signatures.[12] As adjuvant radiation was reported in the 2006 *JAMA* publication of the Southwest Oncology Group 87-94 randomized trial to significantly reduce the risk of distant metastases, precise information about a patient's risk of distant metastasis from the GC test could be very helpful to clinicians trying to formulate adjuvant treatment recommendations after prostatectomy.[4] We sought to determine whether information from the GC test influenced adjuvant treatment recommendations made by radiation oncologists and urologists and whether the GC results reduced disagreement in treatment recommendations between the 2 specialties.

MATERIALS AND METHODS

Study Design

A multicenter, prospective, decision impact study was developed to evaluate the influence of GC results on adjuvant treatment recommendations after RP among US board-certified radiation oncologists (n = 26) and urologists (n = 20). Participants meeting eligibility criteria reviewed 11 de-identified case histories from actual postprostatectomy patients and were asked to make recommendations for further treatment. Case histories were obtained from a prior clinical validation study.

Participants were first provided with a patient case history including only clinical variables (without GC results). To minimize the risk of recall bias, the case histories were reordered and resent to participants with the GC results added; they were then asked to provide treatment recommendations using both the clinical variables and the GC results. Clinical variables provided were as follows: age at surgery, preoperative prostate-specific antigen, pathologic stage, biopsy and surgical Gleason score (sGS), presence of seminal vesicle invasion or extraprostatic extension (EPE), surgical margin (SM) status, and lymph node involvement. Treatment recommendations were reported as "observation with regular clinical follow-up," "adjuvant radiation therapy alone," "adjuvant radiation therapy plus hormone therapy," "adjuvant hormone therapy alone," and "other (please specify)." The study was conducted in accordance with the Declaration of Helsinki and the Belmont report and was reviewed and approved by an independent institutional review board (Quorum Review Inc., Seattle, WA). This study is registered on Clinicaltrials.gov (NCT02034812).

Participant Eligibility Criteria and Recruitment

Radiation oncologists who self-identified as genitourinary specialists were identified using the ASTRO directory. A total of 50 e-mail invites were sent to physicians meeting these criteria. Among them, 26 (52%) were responders who met additional inclusion criteria in that they reported providing consultations to at least 80 new patients with prostate cancer per year. These participants were then sent enrollment packages, which included a cover letter, an educational primer on the GC test, a confidentiality agreement, a Web link to the study's informed consent form, and electronic case report questionnaires. The educational primer included information on test development and validation, data about its performance characteristics, and information on how to read the test reports. Specifically, it states that the test has been shown to outperform clinicopathologic features in a 2013 validation study[12] and can provide an accurate prediction of the risk of metastatic disease from genomic analysis of the tissue, with an area under the curve of 0.79 for discriminating between patients who did vs who did not develop metastases 5 years after RP.[12]

Urologists were identified using the AUA membership directory. A total of 50 e-mail invites were sent. Only those who reported they had performed at least 40 RPs in the following year and provided written consent for study participation were enrolled into the study as previously described.[14]

Statistical Methods

All statistical tests were 2 sided using a 5% significance level. The chi-squared or Fisher exact test was used to determine the association (contingency) between different kinds of classification. Exact binomial confidence intervals (CIs) were constructed to measure the changes in treatment without and with GC results. Mixed-effect linear models were considered to account for physician-specific behavior in determining treatment recommendation changes. Univariate and multivariate regression models were used to assess the impact of the GC and clinical variables in relation to treatment recommendation and intensity without and with knowledge of the GC results. Linear models were used to determine the association of years in practice (continuous), region (categorical), and practice setting (academic vs community) on treatment recommendation change percentage of physicians. Categorization of GC risk for some analyses into high- and low-risk groups was based on a prespecified cut point reported in a previously reported study. sGS was dichotomized into ≤ 7 and >7, considering small number of cases with sGS <7. EPE (positive vs negative), SVI (positive vs negative), and SM (positive vs negative) were treated as binary variables.

Generalized linear mixed-effect models were used to measure the importance of physician type (urologist or radiation oncologist) as a variable in treatment recommendation (treatment vs observe) without and with GC results with patients as random effects while adjusting for GC risk. Furthermore, Fleiss' kappa was considered to measure the agreement in treatment recommendation between the urologists and radiation oncologists and see if an improvement in agreement was observed in the results without and with GC.

Statistical analyses were performed using R v3.0 (R Development Core Team, 2010).