Editorial

Genetic signatures on radical prostatectomy specimens: clinical implications

Christopher B. Anderson, G. Joel DeCastro

Department of Urology, NewYork-Presbyterian/Columbia University Medical Center, New York, NY, USA

Correspondence to: Christopher B. Anderson, MD. Columbia University Medical Center, 161 Fort Washington Avenue, New York, NY 10032, USA. Email: cba2125@cumc.columbia.edu.

Submitted Dec 08, 2017. Accepted for publication May 18, 2018.
doi: 10.21037/tcr.2018.07.16
View this article at: http://dx.doi.org/10.21037/tcr.2018.07.16

Introduction

Prostate cancer is the most common non-dermatologic cancer in the United States, with an estimated 3.3 million men in the United States living with the disease in 2016. In 2017, an estimated 161,000 new cases and 26,000 deaths are expected (1,2). The majority of incident cases diagnosed are organ-confined. While active surveillance is often an appropriate management strategy, many patients with newly diagnosed prostate cancer undergo some form local treatment with curative intent. Radical prostatectomy (RP) remains the most common treatment modality for men under 65 years of age, though decreases with age (1).

Survival outcomes after RP are generally excellent, but between 30–40% of men will suffer biochemical recurrence after surgery (3). Predicting which patients are most likely to recur is essential. While there are clinical tools that take into account preoperative variables to estimate risk of disease recurrence after surgery, its predictive accuracy is improved if pathologic information is available from the prostatectomy specimen. Several studies have consistently demonstrated that three adverse pathologic findings—extra-prostatic extension (EPE), positive surgical margins (PSM), and seminal vesicle invasion (SVI)—are the most closely associated with disease recurrence and progression.

Three randomized trials—SWOG 8794, EORTC 22911, and ARO 96-02—have demonstrated reduced biochemical recurrence in patients with high-risk pathologic features who underwent adjuvant radiotherapy (RT) after RP as compared to surveillance (4-7). Meta-analysis of these results shows a hazard ratio of 0.48 (P<0.00001, 95% CI: 0.42–0.56) favoring adjuvant RT (8). The data for reduced clinical progression and improved survival is less clear. SWOG S8794 was the only study to demonstrate that adjuvant RT reduced clinical progression (P=0.05), and improved overall survival (74% *vs.* 66%) and metastasis-free survival (71% *vs.* 61%) (4,9). The AUA and ASTRO guidelines published in 2013 recommend that adjuvant RT after RP should be offered (8).

Alternatively, there is a survival benefit for salvage radiation over surveillance at the time of biochemical recurrence, particularly if given at a low prostate-specific antigen (PSA) (10). This approach avoids the potential morbidity of early RT and avoids over treating approximately one-half of patients with adverse pathologic features who would have been cured with surgery alone. Additional arguments against the use of adjuvant radiation are the persistent debate regarding any survival benefit, and the significant genitourinary and rectal toxicities stemming from radiation. The degree of postoperative stress urinary incontinence, as well as the time required to recover functional continence after prostatectomy, is worsened by adjuvant radiation (5,11). Indeed, there is evidence that increasing the time between prostatectomy and RT—i.e., opting for possible salvage versus more prompt adjuvant treatment—may reduce the local toxicities of radiation (12). Perhaps in part as a result of the above, and despite the AUA/ASTRO guidelines, there has been a measurable decline in use of adjuvant RT in patients with adverse features at prostatectomy (13).

Given the risks of adjuvant radiation and the significant number of patients for whom would be eligible to receive it, accurate patient selection becomes increasingly important. There have been several attempts to improve risk stratification for disease recurrence after prostatectomy using clinical nomograms derived from a combination of

pre- and post-prostatectomy data.

In 2005, Stephenson and colleagues published a nomogram using both pre- and post-operative pathologic data after RP to predict the risk of disease progression, defined as a PSA ≥0.4ng/mL; local recurrence confirmed on biopsy; development of distant metastasis; disease specific mortality; or initiation of androgen deprivation or RT (14). In addition to PSM, extracapsular extension (ECE), and SVI, the nomogram incorporates preoperative PSA, pathologic Gleason score, lymph node involvement (LNI), and year of surgery. Using these variables, their nomogram had a concordance index of 0.79 to predict disease progression.

Similarly, the CAPRA-S nomogram, first published by Cooperberg and colleagues in 2011, utilized data from about 4,000 patients enrolled in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database (15). It also employed preoperative PSA, along with PSM, ECE, SVI, pathologic Gleason score, and LNI. When combined, the concordance index for the nomogram was 0.77 for prediction of recurrent prostate cancer.

The use of these and other nomograms does appear to influence treatment decisions, and may decrease overtreatment with adjuvant radiation (16). However, there has been a push to identify biomarkers to improve postoperative risk stratification. Here we review two such tests: the Decipher genomic classifier (GC) (GenomeDx Biosciences), and Prolaris cell cycle progression (CCP) score (Myriad Genetics).

Prolaris® (CCP score)—Myriad Genetics, Salt Lake City, Utah

Genes that regulate CCP are upregulated during tumor proliferation and have previously demonstrated prognostic value in breast cancer (17). In a 2011 study, the prognostic value of CCP genes was first tested in cohort men with prostate cancer treated with RP (18). Tumor RNA was extracted from 410 archived prostatectomy specimens obtained between 1985 and 1995. A CCP score was derived based 31 CCP genes which were normalized using 15 housekeeping genes. Each 1 unit change in CCP score represented an approximate doubling of the level of CCP gene expression. After a median follow-up of 9.4 years and 148 (36%) of men experiencing a biochemical recurrence, the CCP score was significantly associated with time to biochemical recurrence (adjusted HR 1.74, 95% CI: 1.39–2.17; P<0.001). Importantly, the CCP score was independently associated with biochemical recurrence accounting for PSA, Gleason score, stage and margin status. The CCP score was only weakly correlated with clinical variables, and there was heterogeneity of CCP score within each Gleason score group. This study also observed that the CCP score was independently associated with prostate cancer-specific mortality among 337 men diagnosed on TURP who were conservatively managed.

These findings were validated in a 2013 study of 413 prostatectomy patients treated at a large, academic center (19). RNA was extracted from the dominant tumor focus of archived RP tissue and the CCP score was generated. The authors examined the independent prognostic information of the CCP score over the CAPRA-S score. Most patients (67%) were CAPRA-S low-risk and nearly 20% experienced a biochemical recurrence after a median follow-up of 85 months. The CCP score was modestly but significantly correlated with CAPRA-S (r=0.21, P<0.001) and there was significant CCP heterogeneity within each CAPRA-S risk group. On multivariate analysis, the CCP score was significantly associated with biochemical recurrence after adjusting for CAPRA-S score (HR 1.7, 95% CI: 1.3–2.3; P<0.001).

The CCP score can also be derived from a prostate biopsy and is independently associated with biochemical recurrence (20,21) and death from prostate-cancer (22,23). In summary, the CCP score significantly improves the ability to predict recurrence after prostatectomy independent of the clinical variables that have been classically used to estimate post-operative risk of recurrence.

Decipher® (GC)—GenomeDx Biosciences, Vancouver, British Columbia

The Decipher test has emerged as a method to improve the ability to estimate the risk of postoperative metastasis and identify candidates for adjuvant therapy. A 2013 study first identified and internally validated a GC to predict metastasis after RP for men who experienced a rising PSA (24). The authors used formalin-fixed paraffin embedded tissue from 545 RP specimens obtained at the Mayo Clinic from 1987–2001 to extract RNA from the dominant tumor focus. Using a case-control design, the cases included 213 RP patients who experienced metastasis after having a rising postoperative PSA and controls included patients who were without evidence of disease or had an elevated PSA but no evidence of metastasis within 5 years postoperatively. Among over 1 million candidate RNA features, the authors

identified 22 that were differentially expressed between cases and controls. These included both coding and non-coding RNAs that were related to a variety of cellular processes such as proliferation, structure, motility, cell cycle progression, immune response, and androgen signaling. Based on these 22 markers, a GC score was developed that ranged from 0 to 1, with higher scores indicating a higher risk of metastasis. There was heterogeneity of GC scores within Gleason score category such that patients with Gleason 7 disease and a high GC score were more likely to metastasize, and patients with Gleason 8 and higher disease with a low GC score were less likely to metastasize. The GC score outperformed prediction models that included clinical variables only (AUC 0.75 *vs.* 0.69), and on multivariable analysis the GC was the only variable significantly associated with metastasis (OR 1.36, 95% CI: 1.16–1.60; P<0.001) after adjusting for all relevant clinical and pathologic characteristics. The GC also outperformed all other known genomic markers associated with prostate cancer progression, including the CCP score.

The GC was validated on a separate cohort of RP patients treated at the Mayo Clinic from 2000–2006 (25). Among 219 patients with high-risk pathologic features, 69 developed metastases over a median follow-up of 6.7 years. On multivariable analysis predicting time to metastasis, GC score was the only significant variable (HR 1.51, 95% CI: 1.29–1.76; P<0.001) when controlling for pathologic variables (Gleason score, preoperative PSA, seminal vesical invasion, surgical margins status, LNI, ECE) and use of adjuvant therapy. When categorizing the GC into low (GC <0.4, 60% of cohort), intermediate (GC 0.4–0.6, 20% of cohort), and high risk (GC >0.6, 20% of cohort), the 5-year risk of metastatic disease was 2.4%, 6% and 22.5%, respectively. There was again significant heterogeneity of GC scores within each Gleason score category: 60% and 36% of men with Gleason 7 and ≥8, respectively, were GC low risk and unlikely to develop metastatic disease. This observation suggests some men with higher grade tumors may be spared adjuvant therapy.

The performance of the GC was then examined in a large RP cohort in which no patient received adjuvant therapy (26). RP specimens were obtained from 1992–2010 and all patients with a postoperative PSA <0.2 and high-risk pathologic features were included. Using a case-control study design, 260 patients were included of whom 99 developed metastatic disease. On multivariable analysis, the GC score was independently associated with time to metastatic disease (HR 1.26, 95% CI: 1.08–1.47; P<0.01) after adjusting for individual clinical factors and models including both clinical factors and GC score outperformed models that included clinical only or GC only. Other models adjusted for CAPRA-S score and a nomogram-predicted probability of metastasis, and the GC remained significant in both models. In attempting to identify which patients benefit most from having a GC score, patients with a low predicted risk of metastasis based on clinical factors (CAPRA-S <3) rarely experienced metastasis (8%), while those with a high predicted risk (CAPRA-S >5) had a relatively high rate of metastasis (39–72%). The authors propose that the GC was most useful in patients with an intermediate risk of metastasis based on clinical factors (CAPRA-S 3–5) who had a range of metastasis from 4–17% based on GC score.

The GC score was tested in another large cohort of RP patients with high-risk features who did not have any adjuvant therapy (27). Patients had RP from 1987–2008 and all were pathologic N0 with an undetectable PSA, a median follow-up of 7.8 years, and a median Decipher score of 0.35. The primary outcome was development of rapid metastasis (within 5 years of RP). The authors observed moderate correlation of the GC score with Gleason score and CAPRA-S score. Among CAPRA-S high-risk patients, 32% were classified as GC low risk and only one of these patients developed rapid metastasis. The prediction model that included the GC score plus the nomogram-estimated risk performed better (AUC 0.79) than models using the nomogram only (AUC 0.75), CAPRA-S (AUC 0.72) and GC only (0.77). On multivariable analysis, GC score was the only predictor of rapid metastasis (OR 1.48 per 0.1 unit increase, 95% CI: 1.07–2.05; P=0.018) when controlling for CAPRA-S in one model and the nomogram predicted risk in another. Finally, the GC score outperformed 19 other known predictive genetic markers of prostate cancer risk.

There was a recent meta-analysis that combined 855 patients from five studies to determine the performance of the GC to predict metastasis after RP (28). There were 82 metastatic events and median GC score was 0.37. There was modest but statistically significant correlation of GC with Gleason score (r=0.27), extraprostatic extension (r=0.20), seminal vesical invasion (r=0.19), and lymph node invasion (r=0.13) but no correlation with margin status or PSA. When classified by GC risk category, 60.9% of patients were low risk (<0.45) and had a 5-year risk of metastasis of 2.4%, 22.6% were intermediate risk (0.45–0.6) with a 5.8% risk of metastasis, and 16.5% were high risk (>0.6) with a 15.2% risk of metastasis. On multivariable

analysis, GC score was independently associated with time to metastasis (HR 1.3 for each 0.1 unit increase, 95% CI: 1.14–1.47). The c-index of the predictive model with clinical variables only was 0.76, which improved to 0.81 after addition of GC score.

Several of these studies also incorporated a decision curve analysis and determined that risk prediction models that incorporated the GC had improved net clinical benefit compared to clinical models only, due to fewer false-positive results that would have been unnecessarily treated with adjuvant radiation (25-27).

As the GC score has prognostic value and can improve postoperative risk stratification, two studies have evaluated the ability of the GC to predict which high-risk patients are best suited for adjuvant radiation versus observation and salvage radiation. The first study included 186 men from the GenomeDx prostate cancer database who had high-risk features after RP and had a Decipher test (29). Median follow-up after RP was 10 years, 51% were treated with adjuvant radiation, and 19 patients developed metastatic disease. As demonstrated in prior studies, the GC improved the ability to predict metastatic disease over clinical models, and 43% of clinically average- and high-risk patients were reclassified as GC low risk. Each 0.1 unit increase in GC was significantly associated with an increased risk of metastatic disease (HR 1.9). When stratifying patients according to low (<0.4) and high (>0.4) GC risk, there was no significant difference in risk of metastasis among low-risk patients treated with adjuvant (0%) or salvage (0%) radiation. However, patients with a high GC score had a lower risk of metastasis after adjuvant radiation (6%) compared to after salvage radiation (23%). The authors concluded that outcomes after adjuvant and salvage radiation were similar for GC low risk patients, but GC high risk patients were best treated with adjuvant radiation. These findings reinforce GC as a prognostic marker of metastasis after RP, and the authors note that GC "*may be a predictive marker that can help determine which patients will benefit from [adjuvant radiation] as opposed to [salvage radiation]*".

A second study included 512 RP patients from four academic institutions in the GenomeDx prostate cancer database of whom 21.9% received adjuvant radiation, 42% were treated with initial observation and salvage radiation, and 58% were observed (30). All adverse pathologic features at RP and an undetectable postoperative PSA. Sixty-two men (12.1%) experienced a clinical recurrence, defined as a biopsy-proven local recurrence or radiographic metastasis. On multivariable analysis, high (>0.6) versus low (<0.45) Decipher score (HR 2.93, 95% CI: 1.58–5.55; P<0.01) and use of adjuvant radiation (HR 0.34, 95% CI: 0.11–0.82; P=0.01) were independently associated with time to clinical recurrence after adjusting for pathologic characteristics. The coefficients from this multivariable model were converted into a simple risk score that included ≥ pT3b, pathologic Gleason score 8–10, LNI and high Decipher score. Stratification by risk score was associated with 10-year risk of clinical recurrence (5.6% for score of 0 up to 57.4% for score of 4). Patients with a risk score <2 had similar 10-year risks of clinical recurrence whether they were treated with adjuvant radiation (3.5%) versus initial observation (9.3%, P=0.18). However, patients with a risk score of ≥2 had lower risk of recurrence if treated with adjuvant radiation (10.1%) compared with initial observation (42.1%, P=0.012). As approximately 75% of the patients in this cohort had a risk score of <2, the authors hypothesize that many patients can be spared adjuvant radiation and that "*it might not be prudent to withhold [adjuvant radiation] in favor of an initial observation approach*" for patients with a risk score ≥2.

In addition to predicting the risk of prostate cancer-specific mortality after RP (31) and the development of metastatic disease after receipt of salvage radiation (32), modelling studies have also shown that the GC score can improve postoperative decision-making (33). Finally, results of the GC test help physicians make postoperative treatment recommendations. One study surveyed 26 radiation oncologists and 20 urologists about 11 RP cases without and with GC results (34). Adding GC results changed treatment recommendations for 35% and 45% of patients for radiation oncologists and urologists, respectively, without increasing the total number of people referred for radiation. The results of the GC also helped improve agreement in treatment recommendations between radiation oncologists and urologists.

The PRO-IMPACT study published in 2017 was a multi-center study testing the ability of the GC to impact treatment recommendations for patients being considered for adjuvant and salvage radiation (35). Among 150 patients with high-risk features after RP who were candidates for adjuvant radiation, 32% had high-risk GC scores and the addition of the GC score lead to an 18% change in treatment recommendations. Among 114 patients being considered for salvage radiation therapy, 41.7% had high-risk GC scores and the addition of the GC score led to a 32% change in treatment recommendations. The higher the GC score generally led to more intensive therapy

recommendations. In addition, the integration GC score was associated with less decisional conflict and less patient anxiety.

Cost effectiveness data for post-prostatectomy genetic testing is limited, but there have been some attempts at incorporating this information into decision making (36). Using a Markov model, Lobo and associates analyzed the cost effectiveness of using the Decipher GC score to select patients for adjuvant radiation (37). They compared the estimated differences in cost based on a Quality of Life Years (QALY) model between administering adjuvant RT according to GC risk stratification and two control groups: use of adjuvant RT in all post-prostatectomy cases and for those according to existing patterns of care (i.e., in the case of adverse pathologic findings). Assuming an assay cost of $4,000, using adjuvant RT according to GC risk stratification was less costly than when used in all post-prostatectomy patients, and was also associated with greater QALY. When compared to patients with adverse pathology, treatment based on GC risk stratification was similarly cost-effective: there was an improvement in QALY, and an estimated reduction in expected incidence of metastasis at 5 and 10 years.

In summary, the GC score is prognostic of metastasis and death after RP for men with high-risk features and can reclassify many patients from clinical risk alone. The two studies performed to date suggest that patients with a low GC risk score could be spared adjuvant radiation therapy, whereas those with a high GC risk score should be considered for adjuvant radiation. While these studies suggest the potential role for Decipher as a predictive biomarker for response to adjuvant versus salvage radiation, they are limited by their retrospective design and prospective studies are required to validate these findings.

Discussion

The role of clinical nomograms remains important in predicting disease recurrence after prostatectomy, but the addition of genetic markers appears to add useful information. However, given the added cost of testing, and the limited additional utility, it is important to identify the best candidates for these additional tests.

Patients at highest for recurrence—that is, those with multiple pathologic risk factors and high scores on the various nomograms—may not benefit much from additional genetic data. Existing information about the patient's disease is likely to be sufficient to reliably predict recurrence, and allow for a strong recommendation on the part of the consulting physician. Indeed, in his recent study using the National Cancer Database, Sineshaw *et al.* noted that while there is an overall decline in the use of adjuvant RT, those with the highest pathologic risk factors were most likely to undergo treatment (13). However, the majority of patients who undergo RP do not fall in the highest risk groups. For example, of the 3,800+ patients analyzed in the CaPSURE database for the creation of the CAPRA-S nomogram, those with scores >5 made up <7% of the entire patient sample (15). For the majority of low and intermediate risk patients, where recommendations are less clear, the utility of additional testing may prove most useful. In attempting to identify which patients benefit most from having a GC score, Ross *et al.* found that patients with a low predicted risk of metastasis based on clinical factors (CAPRA-S <3) rarely experienced metastasis (8%), while those with a high predicted risk (CAPRA-S >5) had a relatively high rate of metastasis (39–72%). The largest effect size for adding a GC score was for intermediate risk patients based on clinical factors (CAPRA-S 3–5), leading the authors to conclude that the GC was most useful in this group.

While there is ample evidence to demonstrate the utility of genetic markers in decision making, the available clinical studies are limited by their retrospective nature, and cost effectiveness data is limited by statistical models that may differ from real world data. Further studies will help improve patient selection in order to maximize the impact of adjuvant radiation while minimizing cost and potential side effects.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Israel Deutsch, James McKiernan, Charles Drake) for the series "Prostate Cancer: Current Understanding and Future Directions" published in *Translational Cancer Research*. The article did not undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.07.16). The series "Prostate Cancer: Current Understanding and Future Directions" was

commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

References

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271-89.
2. Cancer Facts & Figures. American Cancer Society. 2016. Available online: https://www.cancer.org/cancer/prostate-cancer/about.html
3. Punnen S, Freedland SJ, Presti JC Jr, et al. Multi-institutional validation of the CAPRA-S score to predict disease recurrence and mortality after radical prostatectomy. Eur Urol 2014;65:1171-7.
4. Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 2007;25:2225-9.
5. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380:2018-27.
6. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol 2014;66:243-50.
7. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009;27:2924-30.
8. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 2013;190:441-9.
9. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181:956-62.
10. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008;299:2760-9.
11. Suardi N, Gallina A, Lista G, et al. Impact of adjuvant radiation therapy on urinary continence recovery after radical prostatectomy. Eur Urol 2014;65:546-51.
12. van Stam MA, Aaronson NK, Pos FJ, et al. The Effect of Salvage Radiotherapy and its Timing on the Health-related Quality of Life of Prostate Cancer Patients. Eur Urol 2016;70:751-7.
13. Sineshaw HM, Gray PJ, Efstathiou JA, et al. Declining Use of Radiotherapy for Adverse Features After Radical Prostatectomy: Results From the National Cancer Data Base. Eur Urol 2015;68:768-74.
14. Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2005;23:7005-12.
15. Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer 2011;117:5039-46.
16. Ross AE, Yousefi K, Davicioni E, et al. Utility of Risk Models in Decision Making After Radical Prostatectomy: Lessons from a Natural History Cohort of Intermediate- and High-Risk Men. Eur Urol 2016;69:496-504.
17. Sotiriou C, Wirapati P, Loi S, et al. Gene expression profiling in breast cancer: understanding the molecular basis of histologic grade to improve prognosis. J Natl Cancer Inst 2006;98:262-72.
18. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol 2011;12:245-55.
19. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol 2013;31:1428-34.
20. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol 2014;192:409-14.
21. Tosoian JJ, Chappidi MR, Bishoff JT, et al. Prognostic

utility of biopsy-derived cell cycle progression score in patients with National Comprehensive Cancer Network low-risk prostate cancer undergoing radical prostatectomy: implications for treatment guidance. BJU Int 2017;120:808-14
22. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. Br J Cancer 2012;106:1095-9.
23. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. Br J Cancer 2015;113:382-9.
24. Erho N, Crisan A, Vergara IA, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS One 2013;8:e66855.
25. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol 2013;190:2047-53.
26. Ross AE, Johnson MH, Yousefi K, et al. Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men. Eur Urol 2016;69:157-65.
27. Klein EA, Yousefi K, Haddad Z, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. Eur Urol 2015;67:778-86.
28. Spratt DE, Yousefi K, Deheshi S, et al. Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease. J Clin Oncol 2017;35:1991-8.
29. Den RB, Yousefi K, Trabulsi EJ, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol 2015;33:944-51.
30. Dalela D, Santiago-Jimenez M, Yousefi K, et al. Genomic Classifier Augments the Role of Pathological Features in Identifying Optimal Candidates for Adjuvant Radiation Therapy in Patients With Prostate Cancer: Development and Internal Validation of a Multivariable Prognostic Model. J Clin Oncol 2017;35:1982-90.
31. Cooperberg MR, Davicioni E, Crisan A, et al. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. Eur Urol 2015;67:326-33.
32. Freedland SJ, Choeurng V, Howard L, et al. Utilization of a Genomic Classifier for Prediction of Metastasis Following Salvage Radiation Therapy after Radical Prostatectomy. Eur Urol 2016;70:588-96.
33. Lobo JM, Dicker AP, Buerki C, et al. Evaluating the clinical impact of a genomic classifier in prostate cancer using individualized decision analysis. PLoS One 2015;10:e0116866.
34. Nguyen PL, Shin H, Yousefi K, et al. Impact of a Genomic Classifier of Metastatic Risk on Postprostatectomy Treatment Recommendations by Radiation Oncologists and Urologists. Urology 2015;86:35-40.
35. Gore JL, du Plessis M, Santiago-Jimenez M, et al. Decipher test impacts decision making among patients considering adjuvant and salvage treatment after radical prostatectomy: Interim results from the Multicenter Prospective PRO-IMPACT study. Cancer 2017;123:2850-9.
36. Lobo JM, Stukenborg GJ, Trifiletti DM, et al. Reconsidering adjuvant versus salvage radiation therapy for prostate cancer in the genomics era. J Comp Eff Res 2016;5:375-82.
37. Lobo JM, Trifiletti DM, Sturz VN, et al. Cost-effectiveness of the Decipher Genomic Classifier to Guide Individualized Decisions for Early Radiation Therapy After Prostatectomy for Prostate Cancer. Clin Genitourin Cancer 2017;15:e299-309.

Cite this article as: Anderson CB, DeCastro GJ. Genetic signatures on radical prostatectomy specimens: clinical implications. Transl Cancer Res 2018;7(Suppl 6):S704-S710. doi: 10.21037/tcr.2018.07.16

