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PCa Commentary

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***** We are excited to celebrate our 100th issue *****

The PCa COMMENTARY began with Volume 1 in October 2002 and we want to thank all of our readers and medical colleagues for their valuable contributions over the years.

DECIPHER: A Useful Tool in Post-Prostatectomy Treatment Planning?

The timing and the choice of men to receive radiation following a prostatectomy has received extensive analysis, but is still controversial. The explanation for this lack of clarity lies in the inherently complex genetic heterogeneity of prostate cancer, particularly in intermediate and high-risk disease.

Prostate cancer management is steadily moving into the genomic age, providing more accurate predictions of outcome than the various combinations of tumor stage, PSA, and Gleason score. "Decipher," (GenomeDx Biosciences, San Diego, CA) is a validated genomic classifier designed to assist in selecting the optimal choice of management for men with adverse pathological features who might benefit from post-surgery radiation therapy. Adverse features are defined in the current NCCN guidelines as extracapsular extension, seminal vesicle involvement, positive surgical margins, or "detectable" post-op PSA of $\geq$ 0.2 ng/ml [or, in some studies, $\geq$ 0.01 ng/mL].

"Decipher" is an RNA expression-based signature of 22 genes designed to predict the ten-year risk of metastatic cancer based on tissue obtained from the surgical specimen or prostate biopsy. The assay provides prognostic information independent of usual risk factors. Based on a validation study at the Cleveland Clinic, "Decipher was the only predictor of metastases when adjusting for age, preoperative PSA, and biopsy Gleason," Klein, Kattan, Stephenson *et al.*, Urology 2016 April. Decipher reports the assay results on a scale of 0 - 1 in which each 0.1 unit increase predicts greater cancer aggressiveness. A score of .45 or less is considered low risk; .45 - .6, intermediate risk; and > .6, high-risk for metastases.

Adjuvant (immediate) or Salvage (delayed) Radiation for high-risk patients?

The NCCN guidelines rather generally offer two options for management after surgery — i.e., radiation therapy or observation —in men with the adverse features listed above. "Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent," (NCCN guidelines). Adjuvant radiation refers to treatment as soon as a man has recovered from the surgical procedure, *despite* an "undetectable" PSA. Delayed — or salvage —radiation awaits the development of the changes referred to in the NCCN guidelines.

An argument for adjuvant therapy.

In "Predominant Treatment Failure in Post-prostatectomy Patients Is Local: Analysis of Patterns of Treatment Failure in SWOG 8794" Crawford, Messing, Ian Thompson, *et al.,* JCO. 2007 make the case for adjuvant radiation. Their contention is that the biologic behavior of high-risk cancer is early spread to the periprostatic region and that all men in the high risk category benefit from adjuvant radiation.

The Southwest Oncology Group trial 8794 randomized 431 men to adjuvant radiation or observation. With a median follow-up of 10.2 years, compared to observation, "… [in] patients with a post-surgery PSA of ≤ 0.2 ng/mL radiation was associated with reductions in the 10-year risk of biochemical failure (72% to 42%), local failures (20% to 12%), and distant failures (12% to 4%)."

A rationale for delaying radiation:

Despite the findings of the SWOG study and others, in current clinical practice there is reticence to uniformly prescribe radiation for all high-risk men. This reticence is understandable. "Only 50% of patients with adverse pathological features treated with surgery alone will develop biochemical failure, approximately 10% may never develop metastases," Den *et al.,Int J Radiat Oncol Biol Phys* Radiation.2014 Aug. Radiation therapy carries a risk of significant adverse effects: rectal inflammation and bleeding, urinary stricture, and incontinence. Hence, it is common practice to observe this cohort of men and offer delayed ("salvage") radiation before the PSA exceeds 0.5 ng/mL or if the PSA doubling time is less than 3 months, or possibly 6 months.

This practice is a compromise. It is based on the uncertainly resulting from the inherent genetic heterogeneity of prostate cancer. It weighs concern for adverse effects of radiation against the acknowledged benefits of radiation.

But can we do better?

Can a genomic classifier sensitive to the nuances of the genetic differences among cells offer better guidance for whom to treat and for whom to hold fire? The Decipher score offers a validated prognostic estimate as to the likelihood of future metastases and can inform the decision as to which cancers merit early radiotherapy.

Results of studies based on the Decipher Score:

1) "Genomic Classifier Identifies Men With Adverse Pathology After Radical Prostatectomy Who Benefit From Adjuvant Radiation Therapy," Den *et al. JCO* 2015 Mar, a prototype for analysis of Decipher for guiding radiotherapy timing after surgery. The study, based on data from the Mayo Clinic and Thomas Jefferson University, followed 188 men and analyzed for clinical metastases (regional or distant) at 5 years after surgery based on tissue from the surgical specimen. All men had either extracapsular extension, seminal vesicle involvement, or positive surgical margins. Radiation was considered adjuvant if started at PSA ≤ 0.2, and salvage when the PSA was > 0.2ng/mL. The median radiation dose was 66 Gy, inappropriately low by current standards, but was the customary dose during the earlier portion of the study period, 1990 - 2009.

   Their findings: "The cumulative incidence of metastases at 5 years after RT was 0%, 9%, and 29% for low [Decipher score < .4], average [.4 - .6], and high [> .6] genomic classifier scores (GC), respectively." For men with low scores the 5-year outcome was not different between adjuvant and salvage radiotherapy. Among this high-risk group of 188 men, 34 had GC scores of <0.4; 77, .4 - .6; and 77, >.6. These data led the authors to conclude that significant down-staging of risk exists in this high-risk category allowing the avoidance of radiation, reducing overtreatment, and gaining cost savings. Conversely, the data suggests in whom adjuvant radiation should not be deferred.

2) "Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastases Risk," by Klein, Kattan, Stephenson, *et al., Urology.* Jan 2016, utilized the prostate biopsy specimen to predict the cumulative occurrence of metastases at 10 years with an 80% accuracy. The GC prediction was validated by a median 8-year follow-up post-surgery of 57 men with a pre-op PSA of >20 ng/mL, stage pT3 disease, positive surgical margins, or Gleason score ≥ 8. The median Decipher score was 3.8 units, which was associated with a 6.5% risk of metastases. Each 0.1 unit increase in the score multiplied the risk by 1.72.

3) "Tissue-based Genomics Augment Post-Prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men," Ross, Partin, *et al., European Urology* 2016, presents retrospective data on 260 high-risk men, 99 of whom experienced metastases by 10 years. No additional treatment was given until the diagnosis of metastases. "At 10 yrs after RP the cumulative incidence of metastases was 12%, 31%, and 47% … among patients with low (>0.45), intermediate (0.45- 6.0), and high (>0.6) Decipher scores.

Information from GenomeDx: The Decipher test is covered by Medicare. GenomeDx will submit a charge to private insurance companies, and if not covered, the out-of-pocket cost to the patient is $100.

BOTTOM LINE: Decipher is validated genomic classifier that predicts for metastases at 5 and 10 years following radical surgery. Although adjuvant radiation is a strongly supported recommendation for men with adverse pathology, therapy is often deferred for valid conservative reasons. The Decipher score can offer guidance in the decision of which men benefit from immediate therapy and in whom therapy can be safely deferred.

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