HIGH-RISK PROSTATE CANCER: Can the Definition Be Improved To More Accurately Predict Risk of PSA Recurrence and Prostate Cancer-Specific Mortality?

Dr. Anthony D'Amico and colleagues deserve recognition as the first to combine three categories of data into a staging system: biological (PSA), pathologic (Gleason score), and anatomical (T stage). This original concept was presented in their article "Biochemical outcome after radical prostatectomy, external beam radiotherapy, or interstitial radiation therapy for clinically localized cancer," JAMA. Sept.16, 1998. The purpose of establishing categories of risk based on these parameters was to devise a common foundation for the comparison of the time to biochemical progression for three modes of radiotherapy with recurrence data following radical prostatectomy.

Hence, emerged the well-recognized high-risk grouping of clinical "stage T2c or PSA level >20 ng/ml or Gleason score 8-10." This is the system accepted by the AUA. The National Cancer Cooperative Network (NCCN) substituted T3 for T2c as their chosen surrogate for extent of cancer. Of the three D'Amico elements, the Gleason score is the most powerful predictor of prognosis, followed by PSA, and T stage. Risk of recurrence increases as 1, 2 or all of the subcategories are present.

The current (2012) Partin Tables (with calculator) subdivide PSA into 5 subcategories, the highest >10 ng/ml and make the appropriate distinction between Gleason 3+4 and 4+3 (http://urology.jhu.edu/prostate/partin_tables.php?lk=Partin). These tables predict likelihoods for organ confined disease, extra capsular extension, and positivity for cancer involving the seminal vesicles and lymph nodes.

The Prostate Cancer Nomogram calculator is found at http://nomograms.mskcc.org/Prostate and predicts progression-free probability for both prostatectomy and brachytherapy. This nomogram includes data on number of positive and negative biopsy cores.

The Han Tables (based on Partin data) estimate recurrence probability at 3, 5, 7, and 10 years, preoperatively and postoperatively (http://urology.jhu.edu/prostate/han_tables.php?lk=Han). None of these tables group predictions into categories of low-, intermediate-, or high-risk.

The volume of cancer, i.e. extent, is a strong predictor of recurrence and outcome. The clinical T stage, determined by the digital rectal examination (DRE) is the weakest contributor to predictions based on the classic triad of Gleason score, PSA, and T stage. It is meant to serve as surrogate for the extent of cancer. However, it is often subjective and unrepresentative of the true volume of cancer.

Formulations are evolving to attempt to more accurately represent the extent of cancer: i.e., adding the % of positive cores, the total amount of cancer in all the cores, the zonal distribution of the positive cores, and the maximal extent of cancer on any one core.
HIGH RISK Prostate Cancer continued:

It is likely that in the near future that a well-executed, expertly interpreted multiparametric MRI will be the final clinical arbiter of the volume and location of the cancer.

The 7th edition of the AJCC's section on clinical staging is beginning to accept imaging data in defining a T Stage:

"All information available before the first definitive treatment may be used in clinical staging. Imaging techniques may be valuable in some cases." This allowance opens the possibility that accurate estimates of tumor volume and location by imaging may eventually be incorporated into staging nomograms resulting in improved predictive power.

What benefits would accrue to clinical management decisions from more accurate predictive and prognostic information?

- The selection of optimal candidates for active surveillance would benefit from more accurate predictions about the volume and grade of cancer, the likelihood of upgrading at surgery, and the risk of progression.

- Surgical management decisions would be fortified or amended based on optimal information of the risk of lymph node involvement; and the likelihood and extent of extracapsular extension, seminal vesicle spread, positive surgical margins, and PSA recurrence risk. With this information surgeons can better estimate for a patient the likelihood of the need for post-operative adjuvant radiation and be more explicit about the possibility of preserving one or both neurovascular bundles.

- The radiotherapeutic decision regarding treatment of a pelvic field could be informed by an accurate estimate of lymph node involvement.

- The best available estimation of the risk of recurrence would inform the decision regarding the use and duration of androgen suppression.

- Consideration of the extent of serious co-morbidity in older patients is an essential component in the decision regarding. "Death from other causes" begins to exceed prostate cancer-specific death in older men with significant concurrent illness. The Charlson Comorbidity Scoring System is a well validated tool for aiding in evaluating the risks of dying from "other causes" against which the clinician can evaluate the expected gains from treatment. The scoring system can be found at http://touchcalc.com/calculators/ccj_js. A Charlson score of >3 is a red flag prompting thoughtful consideration.

Percent Positive Biopsy Cores as a Surrogate for Tumor Volume.

The importance of taking into account the number of positive cores was stressed by Walsh, Partin, and Epstein (BJU International. Oct 2012) in their analysis for recurrence after surgery: "More positive cores are correlated with less organ-confined disease (P<0.001), positive margins (P<0.012), increasing RP grade (P<0.001) and increased seminal vesicle/lymph node involvement (P=0.012)." They correlate the number of positive cores between 1 and >10 with a 75% likelihood of freedom from PSA recurrence at 10 years.

The UCSF-CAPRA (Cancer of the Prostate Risk Assessment) scale (Cooperberg, Carroll, et al. J Urol. 2005 June) is a well-validated risk assessment tool for predicting recurrence following surgery for clinically localized cancer. The scale range is from 0 to the highest risk at 10. The total score is built on the PSA divided into five subranges; the Gleason grade, 1-3 vs 4-5; T-stage, cT1-T2 vs cT3a; percentage of positive cores, <34% vs >34%; and age, <50 vs >50 years. Predictions are presented for estimated 5-year recurrence rate and 5-year survival.
HIGH RISK Prostate Cancer continued:

The confounding heterogeneity inherent in prostate tumors that are designated "high-risk" is highlighted by Cooperberg in the comparison of CAPRA scores with the total score utilized in the Kattan nomogram and the three risk categories of D'Amico. A Capra score of 4 captures 39% of men designated "high-risk" in the D'Amico system; a score of 5 adds 44% more for a total of 73%; and by CAPRA score 6 and >7 100% of men designated high-risk by D'amico are included. This overlapping between CAPRA and D'Amico likely results because a global designation of "high-risk" does not indicate which of the three categories has been met nor whether one, two, or all three of D'Amico elements are present. This ambiguity may argue for using the CAPRA system and also points up the need for even more exclusive predictive models.

Cooperberg concludes that the CAPRA model has "predictive accuracy for biochemical recurrence comparable to the Kattan nomogram, and is significantly easier to calculate and apply for clinical and research purposes." But, "We further recognize that biochemical recurrence is not an ideal proxy for either disease-specific or overall mortality." Tombol and colleagues agrees that "biochemical failure is not a true surrogate for overall survival." Their article provides an excellent discussion of the entire subject: "Can we improve the definition of high-risk, hormone-naive, non-metastatic prostate cancer?," British Journal of Urology.

Surely Yogi Berra had high-risk prostate cancer in mind ... "It's tough to make predictions, especially about the future!"

Clinical management decisions and expectations especially about high-risk cancer require accurate knowledge of the extent of cancer and the most representative Gleason score. To address this issue emerging research on biologic markers and genomic signatures promise to be helpful in predicting the future behavior of individual cancers. Examples of currently available candidates to improve risk predictions include:

1. Biomarkers for greater cancer aggressiveness: loss of tissue expression of the tumor suppressor PTEN; tissue over-expression KI-67 (an indicator of cellular proliferation); over-abundance in the urine of evidence of the fusion gene TMPRSS2:ERG (frequently combined with the measurement of the gene product of the cancer-related gene, PCA3).

2. Patterns of genetic signatures predicting biologic behavior:
   - Oncotype DX, a commercially available and validated test utilizing a 17-gene predictive signature combining information on the amount of RNA expressed by those genes to predict an individual's risk of progression. The test predicts cancer aggressiveness and may improve the selection of patients for active surveillance. OncotypeDx "does add independent information which increases predictive power of nomograms based on clinicopathologic variables, and predictive power was improved across all traditional risk categories (Society of Urologic Oncology 2013 - Session Highlights, Matthew Cooperberg.)
   - Prolaris, a commercially available RNA expression signature based on 31 genes operative in cell cycle proliferation (CCP ). The score predicts for disease, biochemical recurrence and cancer related death. It was evaluated in biopsy specimens in men with clinically localized prostate cancer and was shown to be useful identifying low-risk patients who could be safely managed by active surveillance. (Cuzik J 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 Mar).
HIGH RISK Prostate Cancer continued:

"The panel is predictive of outcome across all risk stratifications from both biopsy and radical prostatectomy tissue and is independent of other clinicopathologic data" (SUO 2013-Session Highlights, Michael Brawer).

- Many other formulations are in the pipeline such as the 5-gene signature for lethal cancer under development at the Fred Hutchinson Cancer Research Center in Seattle, or a 32-gene prognostic index for prostate cancer progression being developed at MGH and Harvard Medical School.

This rapidly expanding field of biomarkers and genomic signatures is in its development phase and all systems need extensive validation to establish their proper fit in guiding clinical management.

**BOTTOM LINE:** The venerable standard predictors of risk of recurrence and outcome (Gleason score, PSA, T Stage) are being further sharpened to identify subgroups with unique biological behaviors. Greater accuracy in estimating the volume of cancer can currently be achieved by consideration of the percentage of positive biopsy cores (and variations thereof) and imaging with multiparametric MRI. The evolving sophistication in assessing an individual patient's cancer with biomarkers and genomic profiles will likely contribute additional predictive power.

TESTOSTERONE RECOVERY After Six Months of Androgen Suppression: What can be learned from recent studies?

In standard current practice androgen suppression (AS) is administered for two months preceding and four months during radiation therapy to the prostate. The purpose served by this regimen is to potentiate radiation damage to cancer cells. In the PCa Commentary volume #85 [working on link] new information was offered about the biology of this interaction, i.e. lowered testosterone (T) prevents cellular recovery from radiation-induced double stranded breaks. Some escalated-dose radiotherapy regimens are now achieving excellent results without radiosensitization with androgen suppression.

Following surgery when the risk of cancer recurrence is high, androgen suppression is offered "adjuvantly" for six months (or longer) to address potential residual cancer or as a "down-payment" against microscopic spread.

Information about the median time to testosterone recovery (TTR) following 6 months can serve several purposes:

- This knowledge allows clinicians to inform patients when they might expect to be free of the adverse effects of T suppression, but modifying the estimate by considering factors that influence that duration, i.e older age; higher Gleason score; higher baseline serum T levels and baseline PSA levels.

- The duration of suppression after 6 months of AS predicts for prostate cancer specific mortality -- longer suppression following the cessation of therapy is associated with longer survival.

The term "testosterone recovery" requires definition. It can refer to a rise of T above the arbitrary "castrate level," i.e. 50 ng/dL (although actual castration in 75% of patients yields T levels <20 ng/dL).
TESTOSTERONE RECOVERY continued:

Or the term can refer to a rise above one of the accepted T levels that separate hypogonadal from normal levels, i.e. approx. >230 ng/dL. Additionally, it many refer to a patient's return to his baseline serum T level.

THE GOAL OF THIS ANALYSIS is to establish two easily remembered representative thresholds.

1) The first threshold is of functional significance. As T rises above the highly suppressed values of (say) 30 - 50 ng/ml AR signaling progressively returns and progressively promotes cellular proliferation. Therefore the time to achieve "supracastrate" levels of T has relevance as to when prostate cancer regrowth resumes after the cessation of T suppression. [This formulation does not take into account the even more functionally significant intraprostatic T and DHT levels. But measuring the rise and fall of these levels would require serial prostate biopsies]

2) The second threshold is of symptomatic significance. The testosterone deficiency symptoms associated with AS progressively abate as T levels rises above the hypogonadal levels. By knowing the median time to achieve T levels in the low 200 ng/dl range a clinician can predict when the deficiency symptoms will lessen.

A Brief Summary of Findings from Recent Articles:

Functional recovery: Recovery of serum T level to >50 ng/dl in the study by Dai (1) was achieved by 98% of men in 3 months. In a study by Gully (4) supracastrate levels were regained by 90% of men at 13 weeks. In another study by Murthy (5) supracastrate levels were achieved in 100% at 12 weeks.

"Therefore it is not difficult for PCa patients to recover supracastrate levels after short-term ADT therapy, because more than 90% patients could achieve this goal within 3 months (1)."

Symptomatic recovery: In the Dai study 66% of men reached a T level >230 ng/dl in 6 months and 92% were >230 ng/dl by 12 months. In Gully 80% exceeded 212 ng/dl by 6 months; and by that time in the Murthy study 89% were above 173 ng/dl. Combining these findings suggests the median recovery time to above hypogonadal levels is about 6 months.

The 2007 report by D'Amico the median time to exceed a level of 280 ng/dl was 15 months. He found that T recovery slower in men beyond 65 years who have low baseline T levels. For men <60 the median recovery was in 12 months; for men 61-64, 14 months; and for men >65, 16 months.

The difference between the median 6 month recovery reported by Dai, Gully, and Murthy and D'Amico's 15 months may possibly be explained by the greater time required to achieve 280 ng/dl, the value chosen by D'Amico.

A comment by Murthy summarizes the generalization: "After LHRHa treatment [6 months] and radiotherapy, the testosterone levels in most men had recovered to normal by 18-24 weeks after the last LHRHa injection."

SLOWER TESTOSTERONE RECOVERY REDUCES RISK OF PROSTATE CANCER-SPECIFIC MORTALITY.

D'Amico (2) reported on the association of the time to T recovery (TTR) to within 10% of baseline in 102 men with localized unfavorable-risk cancer following radiation and 6 months of ADT.
TESTOSTERONE RECOVERY continued:

Of these, 56% (with no or minimal comorbidities) had a time to recovery >2 years and none had died at a median follow-up of 7.6 years. Whereas the estimated PCSM at 8 years was 6% for those whose TTR was <2 years.

MAINTENANCE OF SERUM TESTOSTERONE BELOW 30 ng/dl SIGNIFICANTLY LOWERS RISK OF DEATH.

Bertaglia (6) studied 99 men with high-risk localized disease who experienced biochemical progression after surgery or radiation. They "assessed the relationship between serum testosterone after 6 months of LHRHa therapy and disease outcome." The median level of T suppression for the group was 39 ng/dl. Serum T was <20 ng/dl in 16.3%, between 20 to 50 in 45%, and above 50 ng/dl in 38.6%. Those whose T levels were suppressed to <30 ng/dl showed a 45% reduction in the risk of death as compared to higher levels. They stressed the importance of monitoring T levels during therapy to insure achieving a level <30 ng/dl.

BOTTOM LINE: For ease of memory I'll suggest approximate median times for T recovery after 6 months of androgen suppression: 3 months to rise above "castrate level" and progressively stimulate cancer growth; 6 months for T to rise above hypogonadal levels and progressively lessen testosterone deficiency symptoms.

REFERENCES:


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