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SPECIAL ISSUE: PSA DOUBLING TIME (PSADT) – CLINICAL APPLICATIONS

PREDICTING OUTCOME OF PRIMARY TX: PSA Doubling Time Predicts Survival After Biochemical Relapse Following Primary TX

Prostate-Specific Antigen doubling time (PSADT) has emerged as a strong independent predictor of risk of disease recurrence after primary therapy and prostate cancer specific survival. Application of this information can be useful in decisions about the timing of therapeutic interventions with chemotherapy and/or androgen deprivation for patients with a high risk of disease progression. Additionally, PSADT needs to be incorporated into the stratification schema of clinical trials, since categorization by PSADT has often been found to better explain outcome results than the effects of the different treatments under comparison.

An early review of this topic was presented by Walch, Partin and Pound in UROLOGY 62 (Suppl 6B), 2003: "Prostate-specific antigen doubling time in the identification of patients at risk for progression after treatment and biochemical recurrence for [clinically localized] prostate cancer". They studied 304 men post surgery who were followed without additional therapy after relapsing with a PSA value of > 0.2 ng/mL and analyzed for metastatic disease. At 5 and 10 years after relapse 50% and 75% respectively of those whose PSADT was faster than 10 months developed clinical metastasis, respectively, compared to 15% and 55%

for those with PSADT > 10 months (P <0.001). They argued that the calculation of the doubling time based on only the first two PSA values (separated by at least 3 months) after progression [less than the three or four values that are considered optimal] "provided useful information 6 to 12 months sooner in the course of recurrent disease" allowing an earlier decision regarding intervention. "The actuarial systemic progression-free survival for patients with a PSADT of >0.5 year, 0.5 to 1.0 years, 1 to 9.9 years, and $\geq$ 10 years was 64% $\pm$ 12%, 93% $\pm$ 12%, 95% $\pm$ 3%, and 99% $\pm$ 1%, respectively." On multivariate analysis PSADT was the "sole factor in prediction of the likelihood of systemic progression after biochemical recurrence", although on univariate analysis the Gleason score was also significant.

A succinct review of this issue in Clinical Prostate Cancer, March 2003, confirmed the predictive correlation between PSADT and clinical failure. In a group of 1289 men with post RP biochemical failure (set as PSA > 0.4 ng/mL), a PSADT of greater or less than 12 months was the "only factor with significant association with clinical failure (P <0.0001), e.g.: approximately 80% of men were free from clinical recurrence at 5 years for a PSADT of longer than 12 months compared to about 60% for PSADT less than12 months.

Several ASCO abstracts from the 2004 and 2005 meetings addressed PSADT as a predictor of prostate cancer-specific survival (PCSS):

1) In #4555 (2004) Walsh, Partin et al. reported that in 825 men post RP whose PSA values exceeded 0.2 ng/mL the PCSS was 98% and 85% at 5 and 10 years for PSADT longer than 10 months and 90% and 47% for a shorter PSADT.

2) In #4549 (2005) Sandler, Shipley et al. analyzed the PSADT values for 1514 men with T2C-T4 PC and PSA <150 ng/mL in the RTOG protocol 92-02, which compared EBRT with and without androgen deprivation. A PSADT of < 12 months was a surrogate endpoint for prostate cancer specific mortality, and importantly, categorizing outcomes as to PSADT < or > 12 months *better predicted survival outcome* than whether androgen deprivation was or was not given (RR 6.17 for PSADT < 12 months vs longer compared to a RR of 1.59 for AD vs. no AD)

3) In #4546 (2005) Partin, Walsh, Eisenberger et al. analyzed cancer-specific mortality in 5096 men post surgery for localized PC with a median follow-up of 10.3 years after BCR. They presented a table integrating three predictors: PSADT ($\geq$ 15, 9.0-14.9, 3.0-8.9, and < 3 months), BCR before or after 3 years following RP, and Gleason sum < or $\geq$ 8. The 15 year survival for any combination was distinctly worse if it included a PSADT of less than 8.9 years. Example: the 15 year survival was 86% for the favorable combination of PSADT 9.0-14.9, combined with BCR of > 3 years and Gleason < 8. But in this example by changing only the value of PSADT to 3.0- 8.9 survival fell to 59%, and fell further to 19% when the PSADT value was faster than 3 months.

4) In #4548 D'Amico et al. reported the now well known data that prostate cancer-specific mortality (PCSM) at 5 years following RP or RT in men with a PSADT of < 3 months was significantly worse (P = 0.0001) than those with longer doubling times, particularly if the Gleason score was $\geq$ 8: 31% for those with PSADT $\geq$ 3 months compared to 1% for those at PSADT less than 3 months. For men post RT with both PSADT less than 3 months *and* Gleason score 8 or greater the PCSM at 5 years was 75% vs. 35% for those with PSADT > 3 months and Gleason score $\leq$ 7. They suggested this data would help identify men who might benefit from additional therapy.

The aggregate implication from all these studies suggests that a significant decrement takes place in the prognoses for metastases-free survival and overall survival at the breakpoint of a PSADT of less that 10 to 12 months. The relevant question is whether intervention based on this awareness alters outcome.

ANDROGEN INSENSITIVE DISEASE: PSADT Predicts Survival In Hormone Refractory Prostate Cancer

PSADT continues to reflect the biology of the disease in HRPC because the rate of growth of malignancy remains essentially constant (log linear) during this period. It can serve as a guide in the usually difficult decision regarding intervention, which always involves a tradeoff between the toxicity of the treatment versus its benefit.

In the review cited above from Clinical Prostate Cancer the data also allowed a prediction for prostate cancer-specific survival in men with AIPC. PSADTs of <3, 3-6, 6-12, and >12 months were associated with survival times of 12.6, 38.4, 71.2 and 107.5 months.

Three ASCO abstracts addressed this issue:

1) #4631 (2005) presented the Stanford data on 90 men. 82% had objective metastases and 60% were symptomatic. They reported that those with PSADT >3 months *respond better to chemotherapy and had a superior survival*. A PSADT of < 1 month predicted for the early development of symptoms.

2) #4551 (2005) reported data on 202 metastatic HRPC patients and correlated the PSADT during the three months *prior to* chemotherapy with overall survival. The median PSADT for the entire group was 44 days and a faster value was associated with survival of 14.3 months compared to 25.6 months for a longer DT.

3) #4504 (2004) presents an analysis by Crawford et al. of data from 499 men in the SWOG 99-16 trial comparing mitoxanthrone/ prednisone with docetaxel/estramustine based on a determination of the PSADT *during the first three months* of chemotherapy. Their findings: categorization by PSA velocity [a measure of PSA dynamics related to PSADT] best predicted mortality: "After adjustment for PSA velocity, treatment was no longer associated with mortality"..."with odds of failing nearly quadrupling with each unit of increase of PSA velocity."

An important implication to be drawn from these data is that the PSADT needs to be considered in the design and interpretation of clinical trials.

BASIC SCIENCE & BIOLOGY: PSADT: Biology And PSA Dynamics

"We dance around in a ring and suppose, But the Secret sits in the middle and knows."
- "The Secret Sits" by Robert Frost.

It's easy enough to plug in a series of PSA values and their respective dates into the program available at Nomograms.org and get a straightforward answer. But accurately modeling the biological dynamics of PSA is an elusive goal because of a variety of subtle reasons. PSADT is very much a derived calculation based on assumptions and compromises.

It has become a cannon of prostatology that the numerical value of PSA is proportional to the volume of prostate cells - benign and malignant, and that by converting a sequence of PSA values to their natural logarithms a log-linear function emerges. This suggests an exponential pattern of growth. This relationship was first described by Stamey, McNeal, and Schmidt in CANCER, 1993 in which they proposed that in untreated patients "One gram of cancer on average produces 3.5 ng/mL of PSA" ... and that one gram of BPH tissue "elevates the PSA levels at an average of 0.3 ng/mL". When PSA was measured sequentially "there was an exponential (log-linear) increase in PSA with time in **86%** [emphasis mine] of 43 patients we followed up, a linearity that allowed us to calculate a doubling time for PSA". This generalization has been criticized by some as not fully reflecting the complexity of the dynamics. The critics suggest that not all

examples follow the first order kinetics growth pattern that is the assumed basis for calculation of PSADT and could lead to a loss of accuracy in some instances.

That PSA is proportional to prostate cancer volume is generally accepted, but a specific PSA value does not indicate a *specific* volume. In the untreated patient the contribution of PSA arising from BPH introduces a confounding variation. This issue may explain why PSADT in the pretreatment period has been much less informative than in post treatment measurements. Malignant cells produce PSA at 10 or more times their benign counterparts, and cells in the transition zone produce less PSA than those in the peripheral zones (presumably because of a lesser density of androgen receptors). Hence, a 70 year old cancer free man with a PSA value of 3 ng/mL will have a an estimated gland of 50cc3, whereas a 50 year old with the same PSA has an estimated gland size of 40 cc3 because of the greater amount of BPH tissue in the older man. Interpretation of the PSADT is complicated by this issue. In some models there is an effort to negate the effect of BPH derived PSA on PSADT by subtracting the estimated contribution of the BPH derived PSA using a formula: gland volume multiplied by 0.066 equals the amount of benign PSA from BPH.

Inoue, a U of W biostatistitian, using metaanalysis data identified a transition point in the pattern of rising total PSA at which the faster rising PSA produced by the malignant cells becomes dominant and emerges from the shadow of the PSA derived from underlying BPH. This inflection was termed the "change point" and his analysis placed this acceleration of PSA increase at a point prior to the identification of biochemically suspected disease - somewhere earlier than a PSA value of 4 ng/mL. This biologic insight introduces an aspect of non-linearity in this range of PSA that has implications for the interpretation both of PSA screening results and calculations of pretreatment PSADT.

Scardino, Wheeler et al. (J Urol. June 1994 - "Prostate specific antigen and Gleason grade: an immunological study of prostate cancer"), investigated the relation of Gleason grade to PSA. By carefully mapping the grade(s) of cancer in 86 prostatectomy specimens and using an immunological detection of the density of cellular PSA staining they identified a "strong inverse correlation between Gleason grade and the PSA content of prostate cancer". "Serum PSA levels correlated with total tumor volume, but the PSA levels per cm3 decreased with increasing grade." "While many grade 4 (found in 79% of specimens they studied) and grade 5 (49%) cells were positive, the intensity of staining was weak".

It follows that each tumor, with its own heterogeneous mix of cellular differentiation, produces a total amount of PSA that is a composite reflecting the diversity of grades of cellular differentiation uniquely represented in that particular tumor.

Despite these shortcomings the PSADT is proving to be clinically useful, although our incomplete understanding of prostate cancer biology limits the PSADT to be only the "best guide currently available".

HORMONE INTERVENTION: PSADT And Androgen Deprivation

Can the PSADT provide much needed guidance to the vexing decision as to the optimal timing for initiation of androgen deprivation (AD) after failure of primary and salvage therapy - a judgment that often is an ill defined tradeoff between psychology and biology?

This issue was addressed at the 2005 ASCO Prostate Cancer Symposium by Dr. Philip Kantoff, Chief, Division of Solid Tumor Oncology, Dana Farber Cancer Institute: "Biochemical failure - The case for Androgen Deprivation Therapy", and Dr. Kantoff kindly forwarded his slides to me for review. A major focus was on the predictive utility of PSADT, which he regarded as a "dominant determinant of outcome in this population" [exhibiting a rising PSA after BCR].

He illustrated the large difference in outcomes for PSADT calculations resulting from small differences at low PSA values by comparing two situations: #1) PSA 0.04, 0.3, and 0.5 at 12, 15, and 18 months - PSADT 2.6 months; #2) PSA 0.09, 0.3, 0.4 at 12, 15, and 24 months - PSADT 13.4 months. His

conclusion: “Measuring PSADT in an individual in real time can be fraught with error particularly with limited values and lower numbers”. [Some studies have even extended consideration of PSADT measured in the range only reflected in the “ultrasensitive postprostatectomy PSA” determination.]

Dr. Kantoff maintained that the hypothesis of benefit for the ***early*** application of AD was established in two well recognized major randomized trials: (1) the “Bolla” study comparing RT alone vs RT + 6 months AD in early high-risk cancer. The overall survival for the combination was 78% at 5 years vs. 62% for RT alone; and (2) the “Messing” study comparing immediate, sustained AD vs. delayed AD for node-positive men post RP. Early and sustained AD led to an overall survival of ~ 88% at 5 years vs. ~76% for delayed AD, and this superiority increased with time.

The success of early AD in these studies of high-risk men suggests the possibility that some parameter of PSA might be identified in the pattern of PSA rise in men showing only biochemical failure that would guide a beneficial initiation of androgen deprivation.

D’Amico’s analysis of prognosis in patients with ***a rising PSA*** (JNCI, April 7, 2004) was presented. His study found that PSADT values of 3, 6, 9, 12 months were associated with: 1) a median time to metastases of 2, 4, 6, 8 years, respectively; and, 2) median survivals of 6, 8, 10, and 12 years, respectively.

The only randomized study addressing this question was carried out by the British Medical Research Counsel in which 938 men with locally advanced and M+ prostate cancer were treated with immediate or delayed AD. A survival advantage was found for early AD, but methodological deficiencies flawed the study. In the absence of randomized prospective trials studying the timing of AD in the setting of early biochemical failure following primary and salvage therapy, any recommendations are essentially inferential.

In Dr. Kantoff’s conclusion he summarized: 1) “PSA velocity is the dominant determination of outcome in this population” [i.e. men with biochemical failure]; 2) “Measuring PSADT in an individual in real time can be fraught with error particularly with limited values and lower numbers”. Lastly, he acknowledged the need for “greater refinement” of guidance data. However, in his opinion if a patient’s PSADT was < 12 months he would “strongly consider intervention with ADT or a clinical trial of ADT plus other agents such as chemotherapy.”