SEATTLE PROSTATE INSTITUTE

PCa Commentary
Vol. 18: March 2004

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DIAGNOSTICS: Interpreting The Results Of PSA Testing

(Data assistance from Dr. David Corwin, Director, Clinical Division, Dynacare Laboratory, Swedish Hospital, Seattle)

Like Heisenberg's electrons, PSA test results are subject to a bit of uncertainty. A clinician's desire is that the test consistently and accurately represent the serum PSA level proportional to the aggregate mass of prostatic tissue, benign and malignant, so that he can make valid comparisons among sequential tests. Consider a case in point: postoperative values of .1 ng/mL on 9/03; .3 on 12/03; .3 on 1/04 and .6 on 2/04. Is the accuracy of the test in this low range sufficiently accurate to permit the calculation of a reliable PSA doubling time (actual calculation: 2.13 months)? The Dynacare Laboratory at Swedish Hospital, using the Beckman Access II test (traceable to the Hybritech method), reports an analytic imprecision (% coefficient of variation at the 95% level) of approximately 8% for PSA values in the range of .07 to 1.0 ng/mL, and <5% for values in the range 1.0 to 10 ng/mL. As the PSA values become considerably higher the figure increases from 5% to 8%.

Using a coefficient of variation of 8%, the fourth test report above could be reported .6 ng/mL (with a .05 to .07 ng/mL 95% confidence interval) This is sufficiently accurate for a reliable PSA doubling time calculation. Considering that an important clinical decision might be made based on this calculation of PSA doubling time, and also considering that the .6 ng/mL value is the major element affecting the rapid DT figure, a re-measurement of this crucial value would be prudent.

The circadian variation of PSA is minimal to the point of being clinically insignificant so intra day fluctuation doesn't complicate interpretation. One investigator found little change in the PSA values of 14 men tested q 4 hours over 32 hours. (Serum testosterone, however, has a marked circadian rhythm: highest in the early AM and lowest in the late evening, but this is muted in older age.) When a clinician compares two PSA values separated by many days, a compound variation representing both analytic and biologic variations must be taken into account, and this combined variance at minimum is in the range of 11 to 12%. However, the biologic fluctuation over days varies considerably. The Price review (see reference below) gives an 18% figure for the total variance, analytical plus biological, based on an average of 5 studies of men without cancer. Other factors that affect the PSA value include the effect of DRE, which causes a probably insignificant variation of .4 ng/mL. or less, and ejaculation, prostate instrumentation and, of course, prostatitis. Considering that the half life of PSA is approximately 2 to 3 days (2.3 days) and the half life of free PSA, 110 minutes, sufficient time should be allowed for the perturbations to return to baseline. It is suggested that 6 weeks should be allowed before measuring the PSA following a prostate biopsy or TURP.

Eastham et al. presented cautionary information in the article, "Variation of Serum Prostate-Specific Antigen Levels: An Evaluation of Year-to-Year Fluctuations in a Well Defined Cohort of Men", Am J Urologic Review, Jan 2004. They analyzed the yearly PSA values of 972 apparently healthy men (median age 62) participating in a colonic polyp evaluation study. Each man was tested yearly for more than five years and the test results were referenced against five different standard criteria of PSA abnormality, ones which often provide guidance as to the need for a biopsy: PSA > 4; PSA > 2.5; age-specific PSA; and free PSA ratio, < 25%; and PSA velocity, >.75 ng/mL/year. Result: during the course of the study 361 men (37%) had an abnormal test with regard to one of these criterion and of this group, regardless of which PSA criterion was exceeded, approximately 30% had a normal value for that marker at the next test (1 year). The mean PSA values for PSA in the age group 50 - 59 was 1.5; 60 - 69, 2.3; and 70-79, 2.8 ng/mL.

The establishment of age-specific PSA ranges is a important contribution to a more focused interpretation of the test. The most commonly quoted data comes from Oesterling et al. (JAMA 1993 Aug 18) based on 537 randomly chosen apparently healthy men seen at the Mayo Clinic and evaluated by a detailed clinical examination that included a PSA test, a DRE, and a prostate U/S. They wrote, "For a healthy 60 year old man with no evidence of prostate cancer, the serum PSA increased by approximately 3.2% per year (0.04 ng/mL per year)". Their well known guidelines for the upper limits of the "normal" PSA range for various age groupings of white men are: age 40 to 49, < 2.5; 50 to 59 < 3.5; 60 to 69 < 4,5; 70 to 79, < 6.5. However, certainty in this area remains a rare commodity. Setting the upper limits for an age group involves an arbitrary decision as what sensitivity to employ. A 99% sensitivity will embrace all but 1% of the "normals". But by reducing the sensitivity to the 97.5th centile the "normal" upper levels are different: age 40-50, <1.81; 50-60, <3.36; 60-70, <6.16; and 70-80, <4.33. At the 95% percentile of normal reference values, the upper limit values are 1.3, 1.6, 2.6, 5.6 for the same age "bins". The age "bin" can be changed, i.e. for age group 45-55 the upper limit is <2.93. The average PSA values are, of course, considerably lower: for age 41-50, 1.2; 51-60,

1.7; 61-70, 2.2; and for 71-80, 3.8. Partin (J Urol 1996 Apr) pointed out that by adherence to the suggested upper limits of age-specific PSA ranges, prostate cancer detection for men older than 60 years was decreaed by 22%.

This entire topic is extensively examined in the review article by Price et al., "Pre- and post analytical factors that may influence use of serum prostate specific antigen and its isoforms in a screening program for prostate cancer", Ann Clin Biochem 2001: 38: 188-216.

Bottom Line: To successfully accommodate the uncertainties associated with the interpretation of the PSA test a clinician needs sufficient information, ... and a good measure of clinical judgment.

PREDICTING OUTCOME OF PRIMARY TX: Mike Kattan Updates The MSKCC Prostate Nomograms - And Makes It Easier To Download Them

The previously available nomograms from MSKCC have been updated. The basic pretreatment nomogram calculates a prediction for 5 year freedom from PSA progression based on the pretreatment PSA, clinical stage, and Gleason score, and, the planned dose of radiation therapy. The nomogram queries whether neoadjuvant androgen suppression or neoadjuvant radiation therapy will be given. The resulting predictions estimate the pathologic factors related to organ confinement and address the outcome from surgery, external beam radiation therapy and brachytherapy. A postoperative nomogram calculates predictions for bPFS at 2, 5, and 7 years after a radical prostatectomy based on the actual pathologic findings. Another nomogram addresses predicted survival for patients with hormone refractory disease based on factors of age, performance score, hemoglobin, PSA, LDH, alkaline phosphatase and albumin, and gives estimates for one and two year survival probabilities and median survival in months. Urologists may find useful a calculator for prostate volume. There is a convenient calculator for PSA doubling time, and a calculator for life expectancy, an important factor when choosing treatment for older men.

In the past I have found it difficult to download this data onto my MAC and Palm Pilot, but the new offering is extremely easy to obtain: go to www.mskcc.org/nomograms/prostate; then, when asked to "select nomogram topic" choose "download software". You will be asked to enter your e-mail address and will quickly get a return e-mail from MSKCC with download instructions for MACs, Windows, and various type of "Palm Pilots". The icon remains on your desktop for easy usage. And MSKCC will automatically send you any new nomograms they develop. One forthcoming nomogram calculates predictions for outcomes from salvage radiation therapy post PSA failure after a radical prostatectomy.

PRIMARY TX UPDATES: Hormone and Radiation as Post - RP Adjuvant Treatment (Journal Review)

"Use Of Neoadjuvant and Adjuvant Therapy To Prevent Or Delay Recurrence Of Prostate Cancer In Patients Undergoing Surgical Treatment For Prostate Cancer," Gomella, Zeltzer, and Valicenti, UROLOGY Vol 62 December 29, 2004. (Contained in “The Conundrum Of Rising Prostate-Specific Antigen: Prevention and Treatment”, a special supplement to Vol. 62 edited by Ken Pienta) .

Please treat the reviews below as "Cliff Notes" that carry a "caveat emptor" - for the full story read the source articles.

Surgical treatment of pathologic stage pT2N0 yields long term biochemical control of 84% to 90%, whereas capsular penetration or positive surgical margins, pT3, degrades the outcome to

37% to 70%. Men with high risk features, (D'Amico - stage T2c, PSA >20 ng/mL, or Gleason ≥ 8) have a 14.2 X relative risk of cancer-specific mortality.

Does evidence based information exist to guide a decision to intervene with various adjuvant therapies to attempt to reduce this risk? This article reviews the options.

NEOADJUVANT HORMONAL THERAPY: At a follow-up period of 3 and 4 years there is no evidence of benefit for 3 or 8 months of neoadjuvant androgen deprivation, except as reported in the Canadian study, which found a significantly reduced risk of PSA recurrence at 4 years in the subgroup of intermediate-risk disease.

RADICAL PROSTATECTOMY WITH ADJUVANT HORMONAL THERAPY: Two studies address this issue. Wirth and Froehnew, 1999, reported improved progression free survival at 4 years in pT3 patients receiving flutamide 250 mg tid vs control of 90% vs 69%, P = 0.0029. The second study is the 2002 interim report (median follow-up 3 years) of the European Early Prostate Cancer Trial comparing Casodex 150 mg/day to control for post RP patients with Gleason >7, PSA >10 (regardless of T stage), which showed a 42% superiority in progression free survival for the Casodex group. Survival information requires further follow-up.

ADJUVANT EXTERNAL BEAM RADIATION THERAPY (administered within 3 to 6 months after RP): "The clear benefit of adjuvant EBRT in radical prostatectomy has not been established in a prospective study. It is controversial whether early adjuvant EBRT improves survival in men with pT3 disease with or without positive surgical margins." However, there are 5 retrospective "matched pair" studies which compare EBRT to control for advanced stage PC. The Anscher trial (1995) of 159 men with T3/4 disease at 10 year follow-up showed a benefit in bPFS for EBRT over no treatment: 55% vs 37% at 10 years, and 48% vs 33% at 15 years. The Valicenti report of 72 T3N0 patients whose post-op PSA was undetectable (36 treated vs 36 controls) showed a 5-year bPFS of 89% for EBRT vs 55% control. The other three studies also showed a benefit for EBRT. Schild presented data in support of improved outcome with an irradiation dose of ≥64 Gy. Forthcoming studies addressing this issue in pT3N0 men are the phase III randomized SWOG/INT0086 trial, which is completed and in follow-up, and the active EROTC 2291 trial.

Available evidence for benefit for EBRT in patients with pathologic seminal vesicle invasion is mixed at best. A study by Schild (1994) found no benefit from EBRT in this disease state; a Valicenti study (1998) found benefit only if the PSA was undetectable at 3 months post op. EBRT is associated with a poor outcome in men with SV involvement if the PSA is >.3 ng/mL at 6 weeks. Valincenti reported EBRT in stage pT3b was associated with only a 36% bPFS at 4 years, and a 20% bPFS when the PSA was persistently elevated post surgery.

ADJUVANT EXTERNAL BEAM RADIATION THERAPY WITH HORMONAL THERAPY: There are no reported prospective randomized trials in this area. The schema for the active RTOG 0011 trial compares EBRT + androgen blockade vs EBRT alone after RP in men with capsular penetration, Gleason score ≥7, positive surgical margins, or seminal vesicle invasion. Eligibility requires that the postop PSA levels are <.2 ng/mL. The RTOG 85-31 (1999) studied post RP pT3 men and compared the combination of RT and immediate androgen suppression therapy to immediate RT with androgen suppression only upon relapse. A retrospective analysis found a slight improvement in long term PSA control in the early androgen suppression group, but no clear comparative benefit in local control or overall survival. Until RTOG 0011 is reported there is no definitive answer to this issue.

Bottom Line: In the important area of adjuvant treatment to improve outcome in surgically treated men with high risk prostate cancer there is a need for well supported evidence based guidelines.

DIET & PREVENTION: Strong Support For A Provocative Thesis: Obesity Is Associated With Increased Prostate Cancer Aggressiveness And Poor Treatment Outcome

Currently in the United States about 1.8 million men are survivors of prostate cancer treatment. Obesity in the US is on a steep increase. If the above thesis is correct, then there may be a useful counseling message for clinicians to pass on to obese PC survivors. Two studies regarding this thesis appear in the JCO, February 1, accompanied by a thoughtful editorial (www.jco.org/cgi/content/full/22/3/395?etoc).

Although no consistent relationship as yet has been found between obesity and prostate cancer incidence, these two studies demonstrate that obesity, expressed in terms of body mass index (BMI ≥ 35 Kg/m2 in Freedland, and ≥ 30 Kg/m2 in Amling), is associated with an increase in prostate cancer mortality. Obese men present with higher Gleason scores at diagnosis and have a shortened PSA recurrence-free survival post radical prostatectomy.

Freedland et al. studied the clinicopathological and biochemical outcome post radical prostatectomy of 1106 men and found that a BMI ≥ 35 kg/m2 "significantly predicted biochemical failure [median follow-up 33 months] after RP (P = .012). "Obese patients had higher biopsy and pathological grade tumors (P < .001)." In their study, PSA, Gleason score, and BMI were each independent predictors of time to PSA recurrence. They noted that obesity doubled in their RP patients in the past 10 years.

mling et al. studied 3162 men post prostatectomy and compared the 19% obese men (≥ 30 kg/m2) with those having a lower BMI and also found that "obesity is associated with higher grade cancer [P < .001] and higher recurrence rates after RP [P = .003]". They argue that their data supports the hypothesis that "obesity is associated with the progression of latent to clinically significant prostate cancer". Both studies found that "black men have higher recurrence rates and greater BMI than white men".

The accompanying editorial cites the Cancer Prevention Study II finding that "men with BMI ≥ 30 kg/m2 had a 20% to 34% increased risk of prostate cancer death compared with men with BMI 18.5 to 24.9 kg/m2." They further conjecture that basic science gives the JCO study findings plausible theoretical basis by pointing out that obesity is associated with higher insulin and insulin-like growth factor 1 levels (both are mitogens); and that the lower testosterone levels in obese men may be a cause of higher grade prostate cancer.

How should we clinicians use this information? To date no human studies have shown that weight reduction post diagnosis and treatment slows the rate of prostate cancer progression. (A recent study of mice reported in Cancer Research, Feb 2004, however, did find evidence that a low fat diet prolonged tumor latency to 18 vs. 9 weeks and prolonged survival compared to a standard diet.) Until, and if, human studies find that weight reduction after diagnosis improves outcome, advice to our prostate cancer patients to lose weight is an expression of faith. But many life style decisions are based on speculations less convincing than may be inferred from these studies. Since maintaining a proper body weight promotes good overall health, it seems there is little to loose and possibly something to gain in the control over prostate cancer progression from reducing obesity.

[An easy to use table for calculating BMI can be found at http://www.consumer.gov/weightloss/bmi.htm]

Bottom Line: These findings showing the adverse influence of obesity on prostate cancer outcome and can be useful in counseling our prostate cancer patients, especially if we have a print out of the BMI table at hand.