SEATTLE PROSTATE INSTITUTE

PCa Commentary
Vol. 61: Jan.-Feb. 2010

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DIAGNOSTICS: PCA3 URINE TEST: An Affirmation ... and a Modest Retraction.

A PCA3 urine test was performed in a 72 year old man whose PSA values were stable around 4 ng/mL (7/03, 3.6; 7/05, 4.0; 7/06 3.3; 3/09, 4.8; 8/09, 4.0). The prostate was palpably normal and estimated by U/S at 50 cc. The test result was 127. A subsequent 16 core biopsy was positive for adenocarcinoma. Two cores were positive; one on the left with 1 focus <1mm, and one on the right with 2 foci, each <1mm, 3% and 5% of core length. Gleason score 3+3=6; PSA density 0.08 mg/cc.

First - the affirmation: The PCA3 urine test is a validated tool that assesses the risk of diagnosing cancer on an initial biopsy, or on re-biopsy after an negative first biopsy. A PCA3 test result of >35 is the threshold set for suspicion of underlying cancer and the predicted risk of diagnosing cancer increases with higher values. A value >35 has a 74% specificity and 58% sensitivity for cancer detection; and a result >100 carries a 69% prediction of a positive biopsy (See PCa Commentary, Vol.54, Nov/Dec 2009 indexed under "Diagnostics" as "PCA3 Urine Test: Increasing Applications.") For this man the test performed credibly, i.e. cancer was diagnosed as predicted by the PCA3 result.

This case is notable because the conventional predictors for underlying cancer - PSA velocity, PSA value in relation to accepted age-range norms (approximate range for ages 60-69, <4.5; 70-79, <6.5; and estimates vary), cT2 features, and PSA density (suspicious for cancer when >0.15ng/cc) - would not have prompted a prostate biopsy. Nomograms addressing risk of a positive biopsy abound. The popular calculator based on the Prostate Cancer Prevention Trial (http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp) predicts a 35% likelihood of a positive biopsy.

By Epstein's criteria this cancer would be predicted to be of low volume (<0.5cc); would likely exhibit an indolent growth pattern; and would allow this man to reasonably consider active surveillance as a management option.

And now,... the modest retraction:

The PCa Commentary of Nov/Dec 2009 (see above) featured two articles confirming the usefulness of a PCA3 test in indicating the risk of a positive biopsy, (J.Urol, Nov 2008, Whitman EJ; J.Urol, May 2008, Nakanishi H). However, the *new findings* reported in these articles suggested that PCA3 values above 47 indicate a high risk of extracapsular extension (94% specificity, positive predictive value, 80%). Additionally, the Nakanishi analysis suggested that even higher scores pointed to the possibility of Gleason scores >6, indicative of more aggressive cancer and greater tumor volume.

Considering the findings in these two articles, a high PCA3 value of 127, as in this case, raises concern that this man's prostate harbors more cancer than would be suggested by conventional clinical and biopsy data, and that this case *would not adhere* to Epstein's criteria for predicting "insignificant" cancer (i.e. Gleason score $\leq$6, PSAD <0.10, <3 cores positive and none >50% involved, and optimally <3 mm cancer/core). The implication based on these two articles suggests that management with active surveillance would not be an appropriate choice.

The analytic basis of the PCA3 test is the measurement of the ratio of transcripts of mRNA from the PCA3 gene in relation to mRNA transcripts of PSA. In the presence of cancer there may be many more mRNA transcripts for the PCA3 gene than for PSA. In fact, the highest ratio value at the Bostwick Lab was 700!

The interpretive conflict presented by this discrepancy: i.e a high PCA3 result set against the customary assessment of low volume/likely indolent cancer led to a personal communication with two pathologists, one with the Oppenheimer Lab where the test was performed, and a second conversation with Dr. Jungi Qian, Director of Molecular Diagnostics at the Bostwick Lab. Each pathologist was clear in his opinion. Their current experience did not support drawing conclusions from the test result other than indicating the risk for finding cancer on biopsy.

Active surveillance is a serious and potentially consequential management decision. Dr. Leonard Marks, MD, Professor of Urology at UCLA, who very kindly reviewed this case, agreed that he would not exclude the option of active surveillance based on the relatively high PSA3 value alone. However, he cautioned that before making a final management decision the man should be re-biopsied (to guard against the risk of Gleason upgrade) and he would attempt to confirm low volume, organ confined disease with an Diffusion Weighted MRI with Dynamic Contrast Enhancement using a 3T coil trans-abdominally or an Endorectal coil.

BOTTOM LINE: A PCA3 test result >35 remains a validated indication of a probability of cancer risk sufficient to warrant a prostate biopsy. In everyday clinical practice, however, further extrapolation of the results to reflect the volume, extent, and aggressiveness of cancer appears to require further validation.

PRIMARY TX OUTCOMES: ACTIVE SURVEILLANCE: Encouraging Outcomes from a Large National Study

In considering active surveillance, an increasingly practiced management strategy, ***the*** crucial question is whether by opting to postpone immediate treatment morbidities a patient sacrifices an outcome as good as might have resulted from initial intervention.

The Health Professionals Follow-up Study offers an encouraging answer to this question. The report (Journal of Clinical Oncology, October 2009) presents outcome data from the prospective nationwide study of 51,529 men, 3331 of whom were diagnosed with prostate cancer. Of this group 342 (10.3%) initially deferred treatment (DT). Of these, 174 (51%) remained ***untreated*** throughout a mean of 7.7 years of follow-up.

Key findings: the rates for developing metastases were similar (7.2 v 8.1 per 1000 person-years); and there was *no difference* in prostate cancer mortality (2.4 v 2.6 per 1000 person-years) in the DT cohort compared to immediate primary treatment.

Details: The mean age of study participants was 68.4 years; 51.7% were clinical Stage 1 and 41.4% Stage 2. The median PSA at diagnosis was 7 (<4 ng/mL, 11.8%; 4 to 10, 58.8%; and 10-20, 20%). Biopsy Gleason score was <6 in 21.2%; 6 in 4.6%; 7 in 25%; and 8+ in 8.2%. "Compared with those undergoing active treatment, DT patients at diagnosis had a significantly lower Gleason score (P=.002), had lower clinical stage (P=.0001), had lower PSA at diagnosis, [and] were 4.8 years older ...".

DT patients who then received treatment did so at an average of 3.9 years after diagnosis. The rate of treatment over 5 years was 38% in the low-risk group; 39% for intermediate-risk; and 60% for those at high-risk as categorized by the D'Amico criteria. Significant predictors of eventual active treatment after 1 year were younger age, higher clinical stage, higher PSA, higher Gleason score, and worse prognostic risk category.

To offer perspective, the authors refer to 2000-2002 SEER data that indicated that nationwide among men with low-risk cancer 55% underwent initial curative therapy, while 45% were managed expectantly or received only primary androgen suppression. This data suggests that there likely is a considerably larger pool of low-risk patients who might reasonably consider active surveillance.

BOTTOM LINE: The authors concluded: "Rates of PCa metastases or death among those men with low-risk cancer who opted for DT were similar to the rates of those who were initially treated, suggesting that appropriately selected patients may safely defer treatment for many years."

PRIMARY TX OUTCOMES: ACTIVE SURVEILLANCE: Dr. Peter Carroll, Professor and Chair of the Department of Urology, UCSF, Reports the Details and Outcome of Studies at UCSF

This article summarizes a video of Dr. Carroll's presentation at The Prostate Cancer Conference, 2008: "Prostate Cancer Over-Detection and [over]-Treatment. An alternative Strategy: Over-detection but Selective Treatment - Active Surveillance."

When Dr. Peter Carroll, self-described as "possibly one of the busiest surgeons in the US" encourages active surveillance [AS] as an option for men with low-risk prostate cancer, it is worth noting. He views this strategy as an antidote to the downside of the over-detection of prostate cancer that is an inevitable result of active PSA screening.

A combination of factors has increased the pool of potential candidates for AS: 15% percent of cancers are diagnosed in men with a PSA less than 4 ng/mL; thresholds for biopsy are being lowered - often to PSA values ≤2.5 ng/mL; the total number of biopsies performed and number of cores taken are increasing, with the result that currently the majority of cancers are low-grade and low-volume. When categorized according to risk of recurrence, 45.8% of cancers in 2004 were low-risk, 29% intermediate, and 25.1% of high-risk. (In the period 1990-94 only 27.% were low-risk.) Dr. Carroll is unsatisfied that in the period 2000-2004 only 8% of "ideal" candidates for deferred initial treatment received supervised expectant management.

As of 2006 at UCSF 120 men yearly were enrolled for AS and a total of 620 men were under study - average age 63 years, mean PSA 6.5 ng/mL, and 92% with Gleason score 6.

In Dr. Carroll's opinion the characteristics of the "ideal" candidate for AS are: PSA <10 ng/mL, no Gleason grade 4 or 5, cT1c, PSA density <0.15, <33% of cores positive and none with >50% (optimally none >33%) cancer. He repeatedly stressed the prime importance of a *well-performed biopsy by an experienced clinician*. Because of the known risk of sampling error, a repeat biopsy before embarking on AS was recommended.

Repeat biopsies in men whose initial biopsies were performed at UCSF resulted in an upgrade from Gleason 6 in <10% of cases (usually to Gleason 3+4), but in men rebiopsied after referral to UCSF the upgrade rate was 26%. Adherence to a schedule of sequential biopsies at yearly intervals after commencing AS is important. In men at UCSF on an AS study with less stringent entry requirements, biopsies performed at <1 year resulted in upgrade in 23%; biopsies done between 1 -2 years, 28%; and after 2 years Gleason upgrade was seen in >50% of men. An increase in Gleason score on re-biopsy was by far the most common reason for initiating treatment. PSA velocity of >0.75 ng/ml/yr as the second most common reason. Anxiety, unaccompanied by subclinical progression, occurred in ~10% of men, and a counseling program is directed at reducing this number.

What about comparative outcome, which is *the crucial* issue when considering AS vs initial intervention? Dr. Carroll was very focused on avoiding missing the opportunity of identifying and treating significant disease in a timely fashion

For a cohort of men who met *all* five of Dr. Carroll's criteria defining an "ideal" AS candidate, 24% underwent surgery by 3 years. In that group the surgical pathology showed pT2 cancer in 86%; T3a, 14%; and T3b, in 0%. No change in Gleason score was seen in 67%, and 24% were upgraded to Gleason 7, usually to Gleason 3+4. There was *no difference* in outcome at a follow-up of 3.9 years between immediate and delayed intervention. (He acknowledged that longer follow-up was essential.)

Dr. Carroll left no doubt that he was a strong proponent of surgery for the treatment of prostate cancer, but felt it should mainly be reserved for men with intermediate- and high-risk disease where he believed it could prolong survival and cure.

BOTTOM LINE: Based on UCSF experience, Dr. Carroll concluded, 1) in well selected patients on AS there is a low rate of disease progression, and 2) delayed intervention appears to be effective in well-defined patients on active surveillance.

HORMONE INTERVENTION / ANDROGEN DEPRIVATION: INTERMITTENT HORMONE THERAPY: Confirmation of Its Effectiveness

Intermittent hormone therapy (IHT) has gained increasing acceptance as a strategy for addressing a rising PSA after primary therapy, and for the treatment of metastatic disease. It should be reassuring to clinicians prescribing some variety of this type of regimen to have support from a major review that includes some basic guidelines as a framework.

"Intermittent hormone therapy and its place in the contemporary endocrine treatment of prostate cancer," a review in Surgical Oncology 18, 2009, by Shaw and Oliver, St. Bartholomew's Hospital, London, concludes: "Thus far *no difference* in survival has been demonstrated between IHT and continuous hormone therapy despite large numbers and prolonged follow-up."

Points of special interest from the review:

1. "The principle of IHT is that when a predetermined PSA nadir is reached hormone treatment can be stopped." A meta-analysis showed that there was no additional benefit from continued hormone suppression after a PSA response to <1 ng/mL. "A PSA nadir below 1 ng/mL has been shown to be the best determinant of when it is safe to stop treatment." This nadir can usually be achieved within 3

months in 95% of non-metastatic patients. Based on multiple studies, the authors suggest a standard of care: e.g. the duration of hormone therapy should be "no more than 3 months for patients with locally advanced disease and 8 months for those with metastatic disease."

"A rapid and complete PSA response indicates a good prognosis both in terms of the likelihood of time off treatment and overall survival." Meta-analyses have shown that anti-androgen monotherapy is sufficient for treatment of PSA recurrence after radical therapy, whereas combined blockade yields superior results for objective clinical disease.

2. The current thorny - and as of now unresolved - question for clinicians regards the proper timing of restarting androgen deprivation after a "therapy holiday." After extensive comparative analysis, Shaw concluded "Restarting treatment when the PSA rises to 15 ng/mL prolongs survival."

   "Patients in whom the PSA rises to over 15 have a 1.3x risk of developing AIPC and a relative risk of 1.6x for death."

   Periods of testosterone resurgence occur at the end of the off period. "Studies show that 90% of patients who have been treated with 3 months of LHRH recover a normal testosterone level with 18 weeks," which is far shorter than the usual off-treatment duration.

3. "Interpretation of PSA levels in the absence of contemporaneous testosterone [levels] is of limited value." The basis of this caution is that a rising PSA in the face of castrate testosterone levels is evidence of androgen insensitive disease.

4. "Phase II trial data suggests that that addition of finasteride prolongs the off-therapy period" [in one study, a doubling compared to no finasteride], but this observation needs further confirmation.

A recently published study of intermittent hormone therapy (IHT) from the South European Uroncological Group, Calais da Silva, et al., European Urology 55 (2009), focused on men with locally advanced and metastatic prostate cancer. The result: *no difference* in survival between men treated continuously vs IHT.

This study reported the comparison of outcomes for 625 men whose PSA dropped to <4 ng/mL after 3 months of combined androgen blockade who then were randomized between continuous and intermittent therapy. Androgen deprivation was restarted in the IHT cohort when the PSA rose to ≥20 ng/mL (in men with no symptoms).

The optimal outcomes occurred in those men without metastases, having Gleason scores of 6 - 7, and whose PSA after three months induction was <2ng/mL (median 1.2). For the 197 men who met this criteria, the median time off therapy was 74 weeks. When therapy was restarted, this group "had a median of 14 weeks of treatment followed by a second period off therapy (median 70 wk)." "Patients with a PSA level of <2 ng/mL spent a median of 82% of their time receiving no therapy." The men in the IHT cohort experienced no meaningful impairment of quality of life and reported better sexual activity."

BOTTOM LINE: Until an alternative to hormone therapy with LHRH analogues is accepted, intermittent hormone therapy offers an equally effective method of addressing biochemical recurrences and treating selected men with metastatic disease providing the added advantage of preserving quality of life and reducing costs.