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DIAGNOSTICS: What's New In Testing For Prostate Cancer?: "Upm3, A New Molecular Urine Test For The Detection Of Prostate Cancer."

The "rate of positive biopsies in men with PSA levels between 2.5 and 4.0 ng/mL is 20% to 23%" and "over half these are clinically organ confined aggressive cancers". The overall accuracy for cancer detection using tPSA in men with PSA $\geq$ 2.5 is 43%, leaving ample room for improvement. In early evaluation the new uPM3 urine test has shown an 81% overall detection accuracy.

The performance of the uPM3 test was evaluated at five institutions in 517 men and reported in Urology, August 2004. The test is a "molecular cytology" that identifies cancer cells expressed in the first 20 - 30 cc. after a 15 - 20 second "attentive" prostatic massage. The

specific molecular targets are “PSA mRNA as a marker of prostate cells and mRNA expressed by the PCA3 gene, “one of the most prostate-cancer specific genes described so far, with over expression in 95% of cancers tested and a median 66-fold upregulation compared to adjacent non-neoplastic tissue. In this early evaluation 86% of men produced assessable specimens. Subsequent to the testing the men underwent prostate biopsies, and the correlation of the uPM3 results, the total serum PSA, and the outcome of the biopsy was the subject of the report.

The most promising and potentially clinically useful information arises from the evaluation of the group of 95 men whose PSA levels were < 4.0 ng/mL, where the new test had a 74% sensitivity and a 91% specificity. The authors suggest that the test “may be particularly attractive in identifying those at high risk of cancer in the large population of men with a PSA level between 2.5 and 4 ng/mL” and may provide guidance in the decision to rebiopsy men whose initial biopsies were negative. Among 91 men whose initial biopsy was negative, the uPM3 test had a 74% sensitivity and a 87% specificity for identifying those men who were positive on rebiopsy. Additionally, a positive uPM3 test may be a better indicator of risk than “prostate biopsy features considered to [indicate] high risk such as HGPIN or atypia.”

Bottom Line: If confirmed in further evaluation, the uPM3 test, with its capacity to identify a very few malignant cells in urine, may offer “an overall accuracy twofold greater than the tPSA assay.”

QUALITY-OF-LIFE ISSUES: What The Media Is Saying About Us ... Actually About What Was Released Regarding The September 15 Jnci Article, “Five-Year Outcomes After Prostatectomy Or Radiotherapy For Prostate Cancer: The Prostate Cancer Outcomes Study.”

The “MEMO TO THE MEDIA” accompanying this quality-of-life report begins with:“Five years after prostate cancer diagnosis, patients treated with radical prostatectomy continue to experience worse urinary incontinence and erectile dysfunction compared to those treated with radiotherapy. However, patients in both groups have similar overall sexual function, mostly because of declining function among radiotherapy patients between 2 and 5 years after diagnosis...”

Although there are numerous credible reports in our specialized journals about quality-of-life after treatment which may differ from the JNCI findings, those assessments do not reach the public as this report has.

The JNCI study updated its previously published 2 year findings and was based on “patient self-reports as well as reviews of inpatient and ambulatory medical records of men 55 - 74 years old (901, surgery; 286, external beam radiotherapy) treated for clinically localized prostate cancer between 1994 and 1995. The six collaborating institutions include the Division of Cancer Control, NCI, and the Fred Hutchinson. The full report indicates the researchers’ meticulous effort to consider, and adjust for, many factors that might influence the accuracy of the findings. Of particular interest were trends that were seen during the interval between the years 2 and 5. Their major focus was on post treatment urinary incontinence, and dysfunctions in bowel and sexual areas. In the five year report a separate category was added which analyzed symptoms described as “bothersome”, and each area of concern was queried in great detail, considerably more extensively than reported below. Brachytherapy was not evaluated.

In brief, the major findings:

1) Urinary incontinence (defined as “having no control or frequently leaking urine”) at five years: 14.4% surgery, 4.9% radiotherapy. “Incontinence and overall bother” was 4 - 6 times more frequent in surgical patients (13.9 vs 3.0%). When “bother” was evaluated in terms of ”slow or difficult urination and urgency”: RP - 11.6% vs 23.9% RT. The outcomes at five years did not change significantly from the 2 year findings.
2) 2) Bowel urgency: RP 17,7% vs 33.4% RT; painful hemorrhoids, 11% RP vs 15.7% RT. Diarrhea: RP 23.3% vs. 28.8% RT.
3) 3) Sexual function: “Both groups reported substantial decrements in sexual function at 5 years after diagnosis.” The query focused on the categories: “achieving and maintaining erections; and frequency of sexual activity, and sexual interest. Whereas at 2 years impotence after RP was reported at 82.1%, at five year it was nearly unchanged at 79.3%. However, impotence worsened over time for RT; 50.3% at year 2, 65% at year 5. On the specific area of “erection insufficient for intercourse” at 5 years: 76.9% RP; 73.1% RT. No mention was made regarding results of nerve sparing surgical techniques. The analysis was adjusted for the use of androgen deprivation and erectile enhancing measures, and these issues did not affect the results. Androgen deprivation was utilized at 2 years in the RP group in 6% of men increasing to 8% at five years; in the RT group it was 3% increasing to 10%.

An accompanying editorial by Ian Thompson took note of “the growing evidence of substantial and long-lasting side effects from prostate cancer treatment”. He acknowledged that we have “good evidence of treatment outcomes but poor evidence of treatment benefit”. The potential extent of the impact of these quality-of- life issues is implied in his observation that “92% of men screened for prostate cancer have PSA levels less than 4.0 ng/mL, ... and of this group ”15% had prostate cancer [data from the Prostate Cancer Prevention Trial], and “of these, 15% had high grade disease”. He concludes “We need to develop better ways to identify those men for whom the benefits of treatment outweigh the harm.”

Bottom Line: The current treatments for localized prostate cancer carry significant morbidity. We clinicians need to know what the public is learning about the long term consequences of our treatments and strive for improvement in quality-of-life outcomes.

DIET & PREVENTION: Statins For Prostate Cancer Prevention?

A 56% reduction in risk of prostate cancer resulting from statin usage was reported in abstract form at 2004 ASCO Annual Meeting based on a pilot study conducted at the Oregon Health & Science University. The case controlled study compared 47 men with prostate cancer with 147 PSA normal clinic controls. Higher dosages and longer usage, > 3 years, of any type of statin were risk lowering. The mechanism of action is thought to be different from that which lowers cholesterol and probably involves unexpected interaction in an unsuspected signaling pathway. The evidence for risk reduction in prostate cancer is in line with a major 2004 ASCO report from researchers at the University of Michigan based on their Molecular Epidemiology of Colorectal Cancer Study which found that *any* type of statin medication used for a minimum of five years was associated with a 51% reduction in the risk of colorectal cancer. The results from these studies will certainly lead to follow-up.

HORMONE INTERVENTION: Six-Months Androgen Suppression Plus Radiotherapy - Strong Support For An Overall Survival Benefit In Men With Clinically Localized Intermediate And High Risk Prostate Cancer.

D'Amico et al reported (JAMA, August 2004) a randomized controlled trial that compared androgen suppression therapy (AST) with an LHRH agonist plus Flutamide 250 mg TID given for 2 months prior to, during, and after 70.35 Gy 3D-CRT (102 men) to RT alone (104 men). The RT covered the prostate plus a 1.5 cm. margin and included the seminal vesicles. Patients were stratified into four groups: 1), PSA 20 - 40 ng/mL; 2), biopsy Gleason score of at least 7; 3), PSA 10 - 20 *and* a biopsy Gleason score of 6 or less; and 4), low risk patients in whom an MRI showed seminal vesicle invasion or extra capsular extension. Bone scans were negative and lymph nodes were assessed as normal by MRI or CT. PSA failure was defined as a "PSA > 1.0 ng/mL, and increasing by more than .2 ng/mL on 2 consecutive measurements". Upon PSA failure, AST "salvage" was either restarted or initiated at an unstandardized point but "at a PSA level of approximately 10 ng/mL". The median follow-up was 4.52 years.

Results: "Estimates of overall survival were significantly longer for patients who were treated with 3D-CRT plus AST compared to patients receiving only 3D-CRT": estimated 5 year survival was 88% vs 78%. In the RT only group there were 6 prostate cancer deaths and none in the combined treatment group. Survival at five years *without* AST salvage (ie survival without progression) was significantly longer in the combined therapy groups, 82% vs 57%.

[Editor's note: The generalization claiming accrued benefit in this small study is supported by the essential similarity of the characteristics of the subjects in the two study arms. There was a slight difference in number of men in the cT1b, cT1c, and cT2b categories: 3D-CRT 41, 25, and 33 vs 3D-CRT+AST 54, 20, and 27. However, practical clinical application of the findings of this study would have been better facilitated (if there had been sufficient cases) by separate outcome comparisons within the 4 categories of enrollees, particularly since there was not a clear-cut "intermediate-risk group" as conventionally defined. As reference, Kupelian has reported (Radiation and Oncology, 2004, pp. 29-33) an approximate 80% five year freedom from biochemical recurrence for cT1-T2 staged men treated with EBRT (n = 340) and permanent seed brachytherapy (n = 733) and an overall 7-year estimated survival of approximately 95% for both treatment modalities.]

In an accompanying editorial DeWeese noted that the D'Amico study was the first to find an overall survival benefit in men with clinically localized disease. He pointed to the Bolla trial (RT vs RT + 3 year AS) which also had shown a cause specific and overall survival, but the Bolla study focused on locally advanced, high-risk, cancer (5 year overall survival: RT - 62%, RT+AS - 78%; cause specific survival, 79% vs 94%). DeWeese concluded that these two trials "strongly argue that patients with locally advanced and high risk prostate cancer are appropriately treated with a combination of AST and RT and the benefits of such combination therapy are real and quantifiable. However, he felt that some outstanding issues have to be addressed before calling these regimens "standard".

Bottom Line: A strong case is being made supporting a survival benefit from the addition of androgen suppression to radiotherapy in men with intermediate- and high-risk prostate cancer.