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PRIMARY TX OUTCOMES: Outcomes for intermediate risk prostate cancer: Are there advantages for surgery, external radiation, or brachytherapy?" ..

... is the title of the article by Drs. Klein, Ciezki, Kupelian and Madadevan in Urologic Oncology, January, 2009 in which a commendable effort is made to compare freedom from biochemical and clinical recurrence, and overall survival. The data base is 861 men with cT2b disease, ***or*** PSA > 10 to 20 ng/mL, ***or*** Gleason score 7 (D'Amico's definition of intermediate-risk disease) treated consecutively at the Cleveland Clinic between 1996 and 2004. Brachytherapy (144 Gy) was used in 204, external radiation therapy (81 Gy) in 336, and 321 underwent surgery. The median follow-up for BT was 39 months; for RT, 58 months; and for RP, 59 months. The overall percent of biopsies with Gleason score 7 was 67% - 66% for BT and RP, and 55% for RT. No adjuvant hormone or radiation therapy was given, but the frequency of "salvage"

radiation after a PSA rise to > 0.3 ng/mL in the RP group was not mentioned. For radiation therapy PSA "nadir + 2" was the threshold for recurrence.

The phrase "commendable effort" is appropriate in describing this study since achieving accurate comparisons of this sort is extremely challenging, and fraught with the classic "apple-to-oranges" trap. Even among "apples" there are Macintoshes and Granny Smiths, since outcomes for both surgery and radiation are quite dependent on the experience of the physician, and subcategory variations among compared cohorts can influence the accuracy of results.

There are recognized differences in treatment outcome between men with Gleason 3 + 4 versus 4 + 3. The D'Amico intermediate-risk status can be assigned to men with one, two, *or* all three of the elements in the definition. Nguyen and D'Amico et al. (Int. J Radiat. Oncol. Biol. Phys., March 2009) have shown that the risk of recurrence increases for a man as the number of his risk factors increases. Additionally, a pretreatment PSA velocity of > 2ng/mL/yr was found to constitute an independent fourth risk factor, conferring an especially high risk of recurrence. In their study of 1063 men with intermediate- to high-risk disease treated with RP or external radiation they reported that the hazard ratio for prostate cancer-specific mortality (PCSM) was 2.3% for the presence of two risk factors, 5.4% for three, and 13.6% for all four. The 5-year cumulative incidence of all-cause mortality at 5 years was 2.4% for one factor, 2.4% for any two factors, 7% for any three factors, and 14.7% for all four factors. "Prostate cancer is the leading cause of death in men with at least three risk factors."

An exacting critique of the Klein/Kupelian article might find it wanting since many of the sub-categorization mentioned above were not taken into consideration, but it is likely that with 861 men under study the nuances of risk cited in the previous paragraph would be randomly distributed among compared cohorts. However, even after these important caveats are recognized, a conscientiously offered comparison is to be welcomed and can provide an overall Gestalt that is rarely available.

So what is the overall Gestalt? Klein and Kupelian found "there were no significant differences in biochemical failure among the three treatment modalities." For BT, RP, and RT, PSA failure at a median of five years follow-up was 82%, 76%, and 80%; and at 8 years, 82%, 63% and 75%, respectively. There was a marginally significant difference in overall survival (OS) - (death from any cause) favoring RP ... (P=0.05). The OS for BT, RP, and RT at five years was 94%, 98%, 93%; and at 8 years was 94%, 88%, 82%, respectively. "Fewer than 2% of the 861 patients died of prostate cancer during the study" so prostate cancer-specific mortality could not be meaningfully estimated.

PRIMARY TX OUTCOMES: Outcomes of 125-Iodine Brachytherapy in Low and Intermediate Risk PCa Patients.

High quality outcomes from brachytherapy - as with surgery - are very much dependent on the skill and experience of the operator; both modalities, when performed well rise to the level of an art form. This article will review the E-published (January 23, 2009, UROLOGY) results presented in "Population-Based Study of Biochemical and Survival Outcomes After Permanent 125-I Brachytherapy for Low- and Intermediate-Risk Prostate Cancer." Morris, WJ, et al., representing a small group of radiation oncologists at the Vancouver Regional Cancer Center, BC, report the outcome of 1006 consecutive patients treated with 125-I brachytherapy (144 GY) between 1998 an 2003. Median patient age was 66 years (range 45 - 82); median pretreatment PSA, 6.4 ng/mL; and the median follow-up was 54 months for biochemical

outcomes and 66 months for survival. No external beam radiation was used, and 66% received 6 months of androgen deprivation therapy - three months prior to treatment and 3 months following seed implantation.

The low-risk group (Gleason score ≤6, PSA ≤10 ng/mL, and unilateral disease) comprised 586 men (58%). The remaining cohort of 419 (42%) was described as "low-tier" intermediate-risk patients "defined as organ-confined disease and either Gleason score 7 and initial PSA of ≤10 ng/mL or iPSA level of 10-15 ng/mL and Gleason score of ≤6." The clinical stage distribution was cT1, 45%; and cT2, 55%. Gleason score was ≤6 in 76%, and 7 in 24%.

Biochemical Outcome: The endpoint for biochemical failure was the Phoenix definition of post-treatment PSA nadir + ≥2 ng/mL. The overall 5-year rate for freedom from PSA failure was 95.6% ± 1.6%, and for 7 years, 94.0% ±2.2 ng/mL. The median PSA nadir was 0.05 ng/mL, approached at 48 months but further improved over the subsequent 1 and 2 years. A PSA bounce was observed in 22 patients.

Disease-Specific Survival: (actuarial): 99.8% at 5 and 7 years

Overall Survival: at 5 years, 95.2%, and at 7 years, 93.4% (markedly influenced by patient age, as expected).

Distant Metastases: The actuarial rate of freedom from distant metastases was 99.1% (five men developed distant spread).

The authors concluded that 125-I brachytherapy "provided excellent oncologic outcome for men with favorable-risk disease, with very low rates of biochemical or metastatic recurrence."

These Vancouver results compare favorably with brachytherapy outcomes for freedom from biochemical failure reported from other centers of excellence.

Memorial Sloan Kettering Cancer Center (Int.J.Rad.Oncl.Bio.Phys. 69;3;2007): low-risk, 98% (7-yr); intermediate-risk, 93% (7-yr);

Cleveland Clinic (IJROBP): intermediate-risk, 90% (5-yr);

W. Virginia & Seattle VA (seeds ± EBRT) (IJROBP 1;2005): low-risk, 98% (5-yr); intermediate-risk, 98% (5-yr);

Seattle Prostate Institute (new data from 1998-2000): intermediate-risk, 91.9% (9-yr).

HORMONE INTERVENTION: AVODART (Dutasteride): Its Effect Lingers On After It's Stopped

Avodart, the dual 5alpha-reductase inhibitor, has assumed a major clinical role for shrinking (by 25%) the prostate to reduce symptoms of BPH; and increasingly it is employed - sometimes with Casodex - to shrink the malignant gland prior to radiotherapy. Currently, Phase III studies are nearing completion for evaluating its usefulness in hormone-refractory disease; and its potential to prolong the duration of "treatment holidays" in regimens of intermittent hormone therapy is also under study. The full pharmacologic effect of dutasteride becomes evident in 1 to 2 months after initiation, and is achieved by reducing both serum and intraprostatic dihydrotestosterone (DHT) by greater than 90%. Much has been written describing the duration of testosterone suppression following the cessation of (say) Lupron.

Very little has been published about the recovery DHT levels after dutasteride is discontinued, nor about the associated slow recovery of PSA values to pretreatment levels rising from the 50% PSA reduction caused by the drug. Awareness of this duration of effect clearly is relevant to proper interpretation of subsequent PSA values after the drug has been stopped.

Clinical studies on this particular issue and other aspects of the metabolic effects of dutasteride were presented in two articles (courtesy of John Amory, who kindly corresponded with me). This subject was discussed by John Amory, University of Washington, and others in their article in J. Urol, June 2008, and also by Richard Clark et al., Journal of Clinical Endocrinology and Metabolism, May, 2004. Amory studied 99 cancer-free men, mean age 34; and Clark, 323 men with BPH, mean age of 62.6 - 65.5. By combining information from both articles the following points emerge.

Dutasteride, when dosed at 0.5 mg/day, reduces baseline serum DHT by >85% in 4 weeks, and by 24 weeks the majority men achieve a 95% steady state reduction (compared to finasteride's about 70% DHT reduction). Following drug discontinuance, 16 weeks are required for DHT to return to within 20% of baseline levels. This lingering effect is a consequence of the ~4 week serum half-life for dutasteride. Amory found that "The serum PSA took about 6 months to normalize, compared to six weeks for finasteride." During dutasteride therapy serum testosterone rises slightly but remains within normal range.

Both studies showed that dutasteride did not significantly affect bone mineral density or markers of bone metabolism, nor were there any significant changes in total or HDL cholesterol. Of note is that only 5% of serum testosterone undergoes 5alpha-reduction to DHT. In the young men studied by Amory, dutasteride led to a slight decrease in sex drive and overall satisfaction with sexual activity, but function in both domains returned to baseline at 21 weeks follow-up.

Clark expressed the useful overview that, "Whereas testosterone is largely responsible for muscle development, libido, and potency, DHT is essential for prostate growth and its effect on hair follicles."

The clinically important, but little recognized, finding from these studies is the delay of up to 6 months for PSA to return to baseline values.

The graph below (taken from the ONCOLOGY article by Morris, reviewed above) shows the effect on post-therapy PSA values resulting from androgen suppression from Lupron, 3-months prior to and 3-months following seed placement. The dashed line describes the PSA pattern for the Lupron treated cohort.

Since dutasteride only lowers PSA by 50%, pre-brachytherapy dutasteride might be expected to have a pattern of effect similar as Lupron, but less pronounced, on (say) the PSAs following a regimen of Casodex/Avodart.

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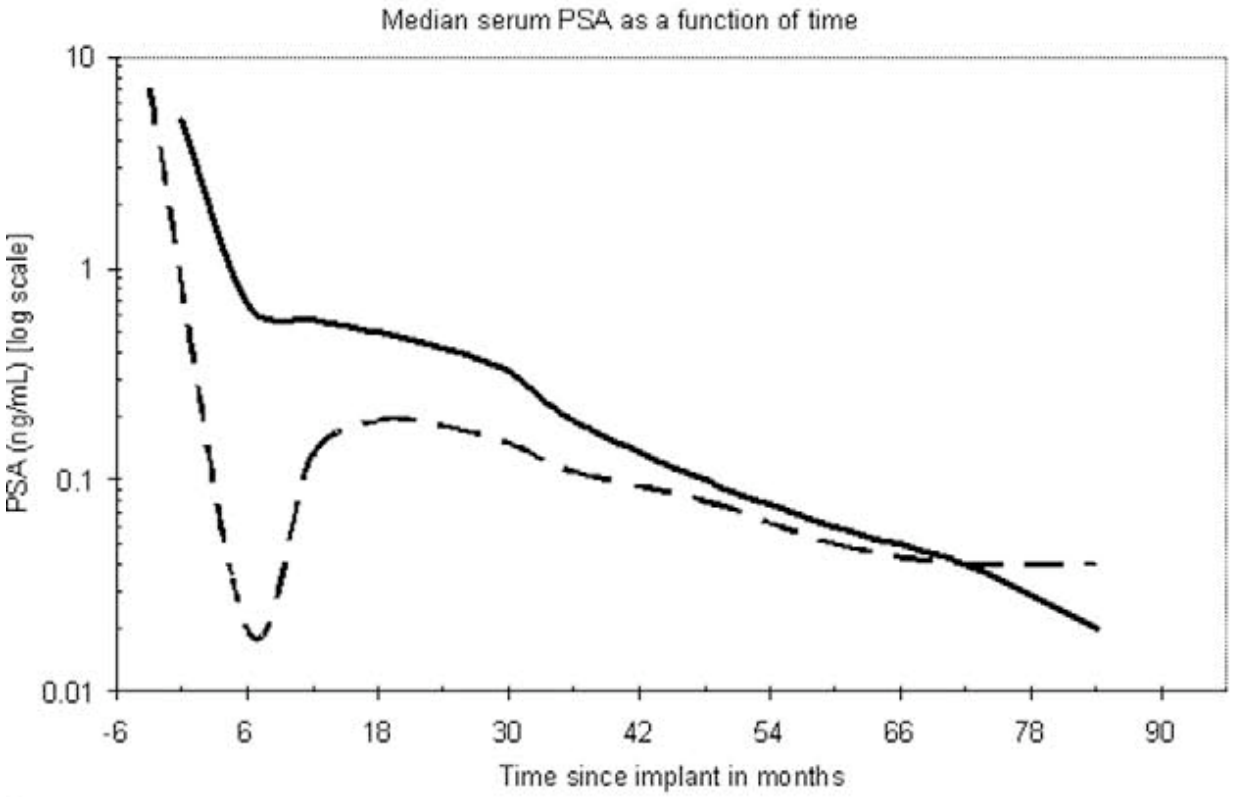

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USEFUL SOURCES OF INFORMATION

UroToday (http://www.urotoday.com) is an informative, high quality, and comprehensive "online news and education resource developed by world class leaders in Urology." On their Web site you can sign up for daily "UroAlerts" to be sent to your e-mail box and the service allows selecting personalized choices from 27 categories of urologic domains. I receive the alerts for prostate, bladder, and renal cancer, but many other offerings are available, such as erectile dysfunction, BPH & male LUTS, laparoscopic and robotic surgery, testicular cancer. The UroAlerts present brief summaries - more extensive than abstracts - of important new journal articles culled from the world's literature, sources that most of us do not follow. The summaries are often written by the article's author, and are complete with the primary reference and PubMed PMID number. For first time users

An excellent recent example is the excellent audio/visual presentation by Christopher Evans, a contributing editor with UroToday, on active surveillance for prostate cancer:

http://www.urotoday.com/61/browse_categories/prostate_cancer/wuf_2009__lecture_series__active_surveillance_for_prostate_cancer.html. For first time users a guide for getting a sign-in password is at this site.

This talk was presented at the Inter Urologic Forum - "State-of-the-Art in Urology" at Vail, CO, January, 2009. It is informative to clinicians and also would be useful to patients considering this management option.

Another lecture from the same conference is "The Urologist's Role in Treating Advanced Prostate Cancer" presented by Michael Benson M.D., Chair, Dept. of Urology, Columbia University College of P&S:

http://www.urotoday.com/index.php?option=com_content&task=view_ua&id=2220253.

The daily UroAlerts typically present about 6 to 8 well-selected, brief summary articles. A recent example of a reviewed journal article is "Gleason Score 7 Screen-Detected Prostate Cancers Initially Managed Expectantly: Outcomes in 50 Men" written by the author, Dr.Schroder, and e-published ahead of print for BJU Int., January 9, 2009.

The spot for signing up for this free service is in the upper right portion of the UroToday home page in the box marked "Member's Section," or you may sign up in directly at

http://www.urotoday.com/component/option,com_registration/Itemid,0/task,register/

UroAlerts are well worth the short time required to scan for articles of interest.

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