SEATTLE PROSTATE INSTITUTE

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Contents

		Page
PCA SCREENING	**Use of early PSA velocity [in PSA range < 4 ng/mL**	**1**
PREDICTING OUTCOME OF PRIMARY TX	**Predicting 10 Year Biochemical Recurrence-Free Survival Post Radical Prostatectomy.**	**2**
HORMONE INTERVENTION	**Just the Facts**	**2**
HORMONE INTERVENTION	**Latest Results for Adjuvant Androgen Deprivation**	3
PATHOLOGY	**Do Gleason Scores Erode Over Time?**	**3**
HORMONE INTERVENTION	Single Fraction Electron Significantly Suppresses Antiandrogen Induced Gynecomastia.	**4**
NEW AGENTS FOR TX	**Radiation Therapy Prevents Gynecomastia**	**4**

Your comments and requests for information on a specific topic are welcome at ecweber@nwlink.com

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PCA SCREENIING Use Of Early PSA Velocity [In PSA Range < 4 ng/mLl

"Use of early PSA velocity [in PSA range < 4 ng/mL] to predict eventual abnormal PSA values [> 4 ng/mL] in men at risk for prostate cancer", Riffenburgh, Prostate Cancer and Prostatic Diseases (2003)6, 39-44

A PSA velocity in excess of 0.75 ng/mL/year is generally regarded as the threshold for concern for underlying prostate cancer in the range when the PSA is greater than 4 ng/mL. Studies have shown that men whose values exceed this threshold have a 72% likelihood of having prostate cancer found on biopsy, while PC will be found in only 5% of men whose rate is slower. This study cited above focused retrospectively on the PSA velocity in 1551 men with PSA values less than 4 ng/mL and derived prognostic information from the increase in PSA between two sequential measurements, generally one year apart, in the PSA < 4 ng/mL range. They wished to know what increment of increase between these

two values would predict for a subsequent rise of PSA to above 4 ng/mL. In their retrospective study, as expected, a PSA value of > 4 ng/mL led to biopsy, and those biopsy results allowed them to retrospectively evaluate what rate of earlier PSA rise might likely be associated with the subsequent diagnosis of cancer. The PSA value is generally considered to be proportional to the volume of prostate cancer, and therefore in this range of PSA < 4 ng/mL the prostate cancer volume would generally be expected to be small. Therefore, it is not surprising that in the PSA range of < 4 ng/mL a much smaller (smaller than 0.75 ng) increment of increase in PSA could be an indication of underlying, developing cancer.

What resulted from this analysis? As expected, a rise of 0.75 ng between two values in the less than 4 ng/mL range carried with it the same prediction for cancer as it does in the PSA range above 4 ng/mL. The marker of .75 ng increase carries a high`specificity, 91%, but only a low sensitivity, 20%. The interesting findings from this study are in the less obvious details. The median increase between two values of the 1184 men who did not reach the cut-off point of 4 ng was very small, 0.02! However, the median increase was 0.13 ng in the men whose PSA ultimately rose to $\geq$ 4 ng/mL. The predictive difference between these two medians is significant at P = <0.001! The issue of variability in PSA measurement was addressed and found to be an insignificant factor.

Conclusion: small PSA increases carry consequences in the < 4 ng/mL range. Specifically, a rise of .25 ng between measurements had an accuracy of 60% in predicting a later rise to >4 ng/mL (specificity .75, sensitivity .39). Attention to these small increases gave an average "early warning" of 20 months for the subsequent PSA rise to >4 ng/mL. A practical conclusion from the study is that a man showing a < .02 ng rise between two readings may safely be retested at a two year interval. Other studies have reported approximately 20% positive prostate biopsy rate in men with a PSA in the 2.5 - 4.0 ng/mL range. In this study biopsies were performed in 251 men (out of 367) when the PSA became > 4 ng/mL and cancer was diagnosed in 37%.

Bottom Line: This study heightens the level of awareness regarding the significance of small increases in PSA occurring the PSA range of < 4 ng/mL.

PREDICTING OUTCOME OF PRIMARY TX Practical Guide For Predicting 10-Year Brfs Post Radical Prostatectomy.

The eminent threesome of Partin, Walsh, Epstein el. al. have collaborated in reporting follow-up data on 1955 patients operated upon by "one surgeon" between 1989 and 2001 and have constructed a practical guide useful for patient counseling and consideration of adjuvant therapy (Urol 62(5)2003). The basic elements for their prediction are pathologic stage, Gleason score, and margin status. The median follow-up was 5.3 years; no hormonal or radiation therapy; and progression defined as PSA $\geq$ .2 ng/mL. The group under study had favorable histologic characteristics: Gleason score of 2 - 4 in 1%, 5 to 6 in 63%, 7 in 30%, and 8 - 10 in 6%. They observed the already recognized upgrading and downgrading of Gleason scores that result from comparing an initial diagnostic biopsy Gleason score to the post-RRP score, i.e. Gleason 6 raised in 26.7% of cases, lowered in 6%; Gleason 7 raised in 12% of cases, and lowered in 20%. The characteristics of their final four groupings and the associated predicted likelihood of biochemical recurrence-free survival at 10 years are as follows: 1) Group 1: Gleason score $\leq$ 6, organ or specimen confined disease, with or without extracapsular extension, and negative surgical margins - 95% bRFS at 10 years. 2) Group 2: Gleason score 6 with positive surgical margins, or Gleason 7 with organ or specimen confined disease - 72%. Group 3: Gleason score 7 to 10 with extraprostatic extension and positive surgical margins, or Gleason score 8 to 10, or positive seminal vesicle(s) - 41%. Group 4: positive lymph nodes - 14%.

Bottom Line: There are more complicated predictive tools available, but the simplicity of this guide makes it user friendly.

HORMONE INTERVENTION Just The Facts, Please.

"Some LHRH agonists cause a transient worsening of signs and symptoms during the first week of therapy as a result of a surge in lutenizing hormone and testosterone, which peaks in 72 hours. An antiandrogen ... should be given with the first LHRH injection to prevent tumor flare. Medical castration occurs within 4 weeks." (Eric Small, quoted from a CME article.)

In contrast to the commonly employed partial LHRH agonists, the newer agent, Abarelix (100 mg/month), is a pure antagonist - a chemically modified gonadotropin-releasing hormone that blocks LH and folicle-stimulating production in the pituitary. As such, Abarelix does not cause an initial surge of testosterone, DHT, LH, or FSH, and Phase III studies found it led to a more rapid onset of medical castration than the available LHRH partial agonists.

The endocrine efficacy of Abarelix led to reduction in testosterone levels to $\leq$ 50 ng/dL at 8, 15, 29, 85, and 169 days of 79%, 88%, 96% (29 days), 97%, and 93% respectively. The percentages of patients with a testosterone fall to $\leq$ 20 ng/dL at the same time periods were 35%, 58%, 74% (29 days), 65%, and 78%. In this 70 man study the median baseline PSA was 92.4 ng/mL, and was lowered by an average of 75% by 15 days. (Koch, Urol, Nov. 2003, pp 877 - 882.)

A prior study of 269 men compared Abarelix and Lupron. No testosterone surge occurred with Abarelix compared to a surge in 82% of men in the Lupron group. Castrate testosterone levels were achieved with Abarelix in 24% by 1 day post treatment, and 78% at day 7 compared to 0% at both those time points for Lupron. By day 29 and 85 there was no difference between the two agents in extent of testosterone suppression. (McLeod D, Urol. 2001 Nov;58(5):756-61)

Bottom Line: Abarelix lowers testosterone levels faster than Lurpon and is not associated with testosterone surge.

HORMONE INTERVENTION Inning Box Scores for Adjuvant Androgen Deprivation Trials:

Pilepich in ASCO Proceedings 2003 (absr. 1530) presented an update on the Bolla trial (RTOG 85-31) of EBRT in men with either Stage cT3 disease or a >15% likelihood of nodal metastases. This study compared the application of immediate, long term application of AD post RT versus delayed AD administered on disease progression. The data reports estimated 5 and 10 year outcome. Results: for freedom from PSA > 1.5 ng/mL at 5 years for RT + immediate AD was 55% versus 21% for RT-delayed AD. The estimated outcome at 10 years: 30% (immediate) and 9% (delayed). Absolute survival data: at 5 years, RT + immediate AD, 76% v. 71% for RT-delayed AD; at 10 years: 53% v. 38%.

An excellent discussion of adjuvant AD in both RT and RP settings was presented by Messing (1), which included the results at a median follow-up of 7.1 years of the ECOG trial that bears his name. In this study men with cT1-2, N+, M0 cancer underwent RP followed by immediate AD or AD upon disease progression. Results: estimated 5 year overall survival - immediate AD 90% v. 78%; overall survival at median follow-up - immediate 85% v. 65% (P = 0.02). These data were further updated at a median follow-up of 11.2 years in abstract 1480 at the recent AUA meeting. The comparison was between hormone therapy versus observation: overall survival, 64% v. 47%; cancer-specific survival, 85% v. 53%; freedom from PSA failure, 55% v. 14%.

1. Messing E, The timing of hormone therapy for men with asymptomatic advanced prostate cancer, Urologic Oncology: Seminars and Original Investigations 21 (2003) 245-254.

PATHOLOGY Is a high grade Gleason ugly at birth, or does it only get ugly as it grows up?

Which is to raise the question as to whether any particular prostate cancer is "born"with a degree of differentiation (favorable or unfavorable) that then remains essentially stable; or does a cancer commence well-differentiated and then progressively dedifferentiate as a consequence of bursts of mutational selection? The answer, of course is currently not known, but hints arise from studies which incorporate surveillance protocols analyzing sequential prostate biopsies, usually done annually, prior to eventual prostatectomy, if indicated.

The most thoughtful discussion addressing both sides of this issue is by Epstein, Walch, and Carter, 2001, (1) in their article on dedifferentiation of prostate cancer. Their study was based on sequential histological data on men with T1c disease who were thought to have minimal tumor ($\leq$ 0.05 cc), defined by them as characterized by a biopsy with a Gleason score $\leq$ 6, < 3 positive cores none having > 50% cancer, and a PSA density <0.15 ng/mL. 70 such men were followed expectantly within a protocol of annual re-biopsy to evaluate for progression and observation as to whether dedifferentiation occurred in the short term. The mean baseline PSA for the group was 5.6 ng/mL and % free PSA averaged l7.3%. Nine of 70 (12.9%) changed from gleason $\leq$ 6 to $\geq$ 7 and 8 of 9 showed that grade change within 15 months. Only 1 of 24 biopsies done after 24 or more months had an upgrade. Epstein's years of personal observations led him to conclude, based on the short interval of 15 months, that the 12.9% early conversions were most likely due to sampling variations. The predominant type of change in the sequential biopsies was an increase in the extent of tumor with the Gleason score remaining stable. The same authors' follow-up article, 2002 (2), documented that the Gleason upgrades were in all instances to Gleason scores no greater than 7. The detailed data showed that progression was assigned mostly on the basis of changes toward more positive cores and greater extents of tumor per core, and not on increases in Gleason scores. An earlier study by Epstein and Partin (2) "documented that prostate cancer has the potential to be high grade early in the course and need not occur from low grade cancer that has evolved with time and volume."

Another approach to this issue arises from examining the histologic findings that are available from the studies that document the "stage migration" now being reported from early detection protocols wherein biopsies are performed at lower PSA values. In one study (3) of 875 men the mean PSA at the time of biopsy decreased from l3.11 ng/mL in 1996 to 7.33 ng/mL in 2001; organ confined disease found at prostatectomy increased from 64% to 81%; however, "mean Gleason scores *increased* [my emphasis] from 5.33 to 6.33 over the 6 years (P= < 0.05)".

1. Epstein J, Dedifferentiation of prostate cancer grade with time in men followed expectantly for stage T1c disease, J Urol, Vol 166, 1688-1691, November 2001
2. 2. Carter H, Expectant management of nonpalpable prostate cancer with curative intent: preliminary results, J Urol, Vol 167, 1231-1234, March 2002
3. 3. Berger AP, Early detection of prostate cancer with low PSA cut-off values leads to significant stage migration in radical prostatectomy specimens, Prostate, Vol 57(2): 93-8, 2003 Oct 1

Bottom Line: Short-term sequential observations suggest Gleason score stability; longer term data is needed. (I would encourage the readers to comment and add other references so that this discussion might be continued in later issues of PCa Commentary

HORMONE INTERVENTION Single Fraction (12 To 15 Gy) Electron Beam Radiotherapy Significantly Suppresses Antiandrogen Induced Gynecomastia And Breast Tenderness.

A randomized Scandinavian trial of pretreatment mammary irradiation in 253 men (174 treated, 79 no treatment) at one year follow-up found that physicians observed some form of gynecomastia in 71% (no-RT) v. 28% (RT). The assessment by the patients slightly differed: 78% (no-RT) v. 44% (RT). Breast tenderness was reported in 75% no-RT v. 43% treated. (Widmark, J Urol, January 2003)

NEW AGENTS FOR TREATMENT Treat Pca With 131-Iodine? A Really Novel Concept!

Metastatic thyroid cancer can be treated with radioactive iodine because thyroid cells uptake iodine via the "sodium iodide symporter". Kakinuma reported in the November 15, 2003 issue of Cancer Research a gene therapy technique in which a replication-deficient virus was employed to infect prostate cells with human cDNA for this symporter and a promoter of gene's expression thus enabling the cell to concentrate radioiodine. A "high-magnitude and tissue-specific" expression of the iodine intake gene was achieved and data confirmed the high degree of iodine uptake. Kalinuma thought that this technique, if satisfactorily developed, was a "promising candidate" for targeted radioiodine therapy for prostate cancer.