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The plethora of small scope reports on this subject makes it quite possible to loose sight of the forest for the trees. This excellent review from Belgium does a nice job of re-grounding clinicians by focusing on the big picture. It's worth a careful read, but I will present some "Cliff Notes."

Introduction: "There is a need for treatment strategies that improve outcome and preserve quality of life. However, currently no consensus exists on how patients with PSA recurrence
(PSAR) after RP should be treated." "To date the role of adjuvant hormone therapy (HT) after RP and the optimal timing and duration of HT remain controversial."

**Definition of PSA recurrence:** The AUA and European Association of Urology recommend declaring recurrence at a PSA of \( \geq 0.2 \) ng/ml confirmed by a second reading of \( \geq 0.2 \) ng/mL.

**Natural history of biochemical recurrence:** The original findings by Walsh regarding 1746 men who were followed without further intervention after RP for localized disease remains relevant: a median of 8 years to metastatic disease; and after treatment with androgen deprivation, 5 years to death. "Of these men, 17% had PSAR. The 5-, 10-, and 15 year PCa-specific mortality in these relapsing patients was 1, 5, and 11%, respectively.

**Diagnostic evaluation:** In the future the use of 18F-choline and 11C-acetate may become useful for staging men with PSA values of \(<2.5\) ng/mL, but currently they do not function well for PSA levels \(<0.5\) ng/mL. The value of the various methodologies for ProstaScint scanning remains controversial.

**Local and systemic failure:** "Local failure is predicted with an 80% probability by PSA relapse \(>3\) years after RP, a PSADT \(>11\) months, a Gleason score \(\leq 6\), and stage \(\leq pT3a, pNO\), or [a history of a] positive margin," in which cases salvage RT may be appropriate. "Systemic" failure following RP is predicted with \(>80\%\) accuracy by PSA relapse at \(<1\) year, a PSADT of 4-6 months, a Gleason score 8-10, and stage \(pT3b\) or \(pT3N1\)," in which situations HT may be of benefit in delaying progression.

**Side effects of LHRH agonists:** Hot flushes, loss of libido, erectile dysfunction, muscular atrophy and weakness, metabolic syndrome symptoms (weight gain, central obesity, and dyslipidemia), insulin resistance/diabetes, hair loss, mood disorders and depression, anemia, cardiovascular morbidity, and bone loss [and possibly mild cognitive dysfunction].

**Adjuvant HT after RP:** Immediate HT after diagnosis can delay disease progression - particularly in the men with a high risk of recurrence. However, Poppel cites a study by Struder et al. (JCO Oct 2004) which reached the conclusion that "For elderly, asymptomatic patients not undergoing curative treatment, we were unable to show any major advantage of immediate compared with deferred hormonal treatment regarding quality of life or overall survival in our limited number of patients [n=175; mean age 76 years]. Disabling complications were prevented in the deferred-treatment group by careful follow-up; 42% of these patients never required any tumor-specific treatment."

Survival advantage of immediate (adjuvant) androgen deprivation after RP has "only been proven in patients with positive lymph node PCa in a single randomized study," [i.e. Messing et al. Lancet Oncol 2006].

[A small study by Tenenholz (Urol Oncol 2007), suggested a survival benefit for relapsing patients following EBRT whose PSADT is "approaching 7 months" if hormone intervention was started early rather than delayed.]

A Mayo Clinic (Boorjian, J Urol 2007) study with 10.3 years follow-up found that adjuvant HT in node positive patients decreased biochemical and local recurrence but did not significantly impact systemic progression or CSS. Poppel states: "To date, no recommendations can be made regarding the optimal timing or duration of adjuvant HT after RP."

**Androgen deprivation:** "Although patients with post-operative PSAR frequently undergo ADT before evidence of metastatic disease, the benefit of this approach is uncertain (Poppel)." Moul
et al., stated in his article "Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy" (J Urol 2004), that early HT, given to 355 men at the time of PSA recurrence, was associated with delayed clinical metastasis [only] in patients with a pathological Gleason sum of greater than 7 or a PSA doubling time of 12 months or less." Delayed HT was given to 997 men at the time of clinical metastases. For their overall cohort of 1352 men, early HT had did not impact clinical metastases."

In a retrospective study, Markarov, Eisenberger, et al. of Johns Hopkins (J Urol 2008 - "The Natural History of Men Treated with Deferred Androgen Deprivation Therapy in Whom Metastatic Prostate Cancer Developed Following Radical Prostatectomy") reported on 91 men (for whom data was complete) treated with ADT at the time of metastases after RP. "The authors concluded that patients when closely followed after PSAR may have an excellent response to deferred ADT and a long survival with a median failure time of 168 months from RP to death."

Bottom Line: Multiple studies have shown - particularly in patients at high risk for recurrence - that ADT can delay PSA progression. However, Poppel and colleagues conclude: "Although studies have shown a modest survival advantage in high-risk patients who undergo early ADT after RP, there is no convincing evidence that it prolongs survival or reduces morbidity."

**HORMONE INTERVENTION: Hormonal Control of Prostate Cancer in PSA-Only Relapse with Combined Antiandrogen/5-alpha Reductase Regimens - An Alternative to Testosterone Deprivation with LHRH Agonists**

The motivation for a search for effective regimens for prostate cancer control that avoid the toxicity of testosterone deprivation, as stated by Dr. Moul, is to discover "methods of hormonal manipulation for treating biochemical failure, aimed at minimizing side-effects and reducing costs while maintaining adequate cancer control." (Moul, Crawford, McLeod et al., BJU Int 2009). Their study compared low-dose flutamide (125 mg twice daily) combined with finasteride (5 mg twice daily) to flutamide only in 56 men with PSA values ≥0.4 ng/mL (mean baseline PSA 7.43 ng/mL) after a variety of primary interventions. The combined regimen was found superior. At a median follow-up of 54 months (range 7-84) for the combined therapy group the mean nadir PSA level was 0.63 ng/mL; the complete response rate was 36% (complete response defined as <0.1 ng/mL for two consecutive tests); and by 54 months 42% had shown PSA progression. Side-effects included breast tenderness (70%), gynecomastia (40%), decline in libido (23%), and of men who were potent at baseline, 37.5% maintained potency. The moderate effectiveness of the combined therapy suggested to the authors the need for a Phase III trial against the standard LHRH regimen. Current considerations, however, might suggest that a better regimen would be a combination of bicalutamide and dutasteride.

Two small studies suggest a possible regimen for one arm in such a Phase III trial, i.e. the sequential use of a LHRH agonist following PSA failure after therapy with an antiandrogen/5-alpha reductase inhibitor combination.

Oh, Kantoff, et al. incorporated this type of sequential schema into a small study: "Finasteride and flutamide therapy in patients with advanced prostate cancer: response to subsequent castration and long-term follow-up," (Urology 2003). "A Phase II trial evaluated the combination
of finasteride (5 mg/day) and flutamide (250 mg three times daily) in patients with rising PSA levels after local treatment or with newly discovered metastatic disease." At a median of 7+ years of follow-up 25% of the men continued on the regimen. Twelve required salvage medical or surgical castration. Initial therapy yielded a median failure-free survival of 29.9 months. The overall median period of PSA control combining the duration of control for those men who underwent salvage castration and those continuing on initial treatment was 48.6 months. The 5-year overall survival was 65%. Oh concluded, "[Although] castration induced secondary responses that may be of shorter duration than if started initially, ... the overall period of hormonally responsive prostate cancer is more than 4 years."

The second small study, "Biochemical response of testicular androgen ablation among patients with prostate cancer for whom flutamide and/or finasteride therapy failed," (Urology 1998) was reported by Ornstein, Smith, and Andriole. Their most effective regimen in 18 study patients was finasteride (5 mg/day) combined with flutamide (250 mg three times daily). Upon eventual PSA failure all men underwent medical or surgical castration. At a range of follow-up of 22 +/- 14.5 months [after castration] 83% of men experienced an 80% decline in PSA and 67% have undetectable PSA levels.

The only published study to use the combination of bicalutamide (50 mg daily) and dutasteride (0.5 mg daily) is "Efficacy of Neoadjuvant Bicalutamide and Dutasteride as a Cytoreductive Regimen Before Prostate Brachytherapy," by Merrick, Wallner et al., (Urology 2006). At evaluation after 3 months of therapy, the combination regimen produced an average 34.6% reduction in the volume of the prostate which was "Comparable to previous reports of volume reduction using a LHRH agonist with or without an antiandrogen."

The authors capture the spirit of the quest in their comment "Bicalutamide and dutasteride confer significant androgen blockade without a decrease in serum testosterone, with a resultant lesser morbidity than associated with LHRH agonists"

Currently there is an ongoing phase 4 "proof of concept" study using a combination of Casodex 50mg plus placebo or Casodex 50mg plus dutasteride 3.5mg once daily for 42 months in men with asymptomatic (non-metastatic) prostate cancer who have failed first-line androgen deprivation therapy, as assessed by rising PSA. This study is active, but not recruiting. Information about this protocol is available at http://www.clinicaltrials.gov/ct2/results?term=NCT00470834. (The main purpose of a phase IV trial is to obtain additional safety information and develop new treatment uses for the drug - in this case dutasteride). The results of this protocol will be interesting as to whether the combination therapy can "rescue" men whose PSA rises on the LHRH agonist regimen; however, a more useful schema would have been to place the combination at the front - taking advantage of its Lupron toxicity sparing feature - and reserve the LHRH agonist for those who need rescue from PSA failure on the combination.

**Bottom Line:** Completed studies such as those cited above move the ball forward toward the goal of "minimizing side-effects while maintaining adequate cancer control."

**DIAGNOSTICS: Food For Thought:** Urine - The Next Frontier For Prostate Cancer Diagnosis?

Prostatic secretions flushed into urine following a gentle prostate massage are proving to be very informative about the internal state of affairs within the gland.
The increasing diagnostic utility of the PCA3 urine test has been already highlighted in the PCa Commentary (Indexed under "Diagnostics," Nov., 2008). Recently reported, although very early in development, is a new molecular biomarker methodology for the analysis of urine offering the potential of discerning genetic clues as to which genes are "turned on" in the prostate, thus facilitating cancer diagnosis and possibly indicating disease aggressiveness.

"Prostate cancer-derived urine exosomes: a novel approach to biomarkers for prostate cancer," describes the work of Nilsson et al., British Journal of Cancer, 2009. Exosomes are specialized nanovesicles secreted by a variety of normal and cancer cells. They contain unique transcripts of mRNA and microRNAs specific to the tumor cells of origin. These "RNA transcripts are enriched several 100-fold in the exosomes compared to donor cells in which these transcripts may be below the level of detection." The authors point out that because of tumor genetic heterogeneity prostate biopsies may fail to identify the inherent variety in tumor genetics among the multifocal malignant lesions within a single prostate gland. The secreted exosomes can be "informative as to the overall tumor malignancy."

The Nilsson study analyzed the exosomes for the presence of two established prostate cancer biomarkers: PCA-3 mRNA, and the chromosomal rearrangement, TMPRSS2:ERG fusion, which is found in 46% of prostate cancers and in 0% of benign prostate biopsies (Mosquera et al. Clin Can Res. 2009 July). These two transcripts studied by Nilsson were only two among the great variety of genetic material concentrated in exosomes. "Tumor exosomes are distinct from exosomes shed by normal cells, in particular, they are more abundant in cancer patients, and the exosomes shed from tumours seem to have an important role in the increased tumor growth, angiogenesis and the escape from immune-surveillance."

Skog et al., Nat Cell Biol. 2008 Dec. in a study of glioblastoma microvesicles (exosomes) contributed the provocative additional finding that genetic transcripts exported from tumor cells in exosomes are imported by neighboring normal cells by endocytosis, incorporated into the DNA, and are translated in protein, thus "delivering genetic information and proteins to recipient cells in the tumor microenvironment."

Nilsson concludes that the evaluation of tumor exosomes found in urine provides a "window into the tumour status, both with respect to tumor genotype/phenotype and metastatic potential."