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PCa Commentary

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THE PROSTATE HEALTH INDEX (*phi*) - The "New" PSA Test

No, this test currently is not a replacement for the venerable PSA, having been serviceable since the early 1990's, and still likely to be test of choice for following patients after primary therapy. However, this new test has been developed to improve the specificity for detecting clinically significant prostate cancer.

In June the FDA approved Beckman Coulter Diagnostics "*phi*" test to be available in the US later in 2012. The *phi* is a composite which incorporates into one number the results of three currently available tests: (1) the **standard PSA** (2) **free PSA**, and (3) the lesser known **[-2]pro-PSA**. The calculation involves a formula, $phi = ([-2]proPSA/fPSA) \times PSA^{1/2}$.

There is certainly room for improvement over the traditional performance of the PSA. In men with a normal DRE who have PSA values between 2-10 ng/ml, currently the predominant range of screening results, the specificity of PSA for finding cancer at biopsy is only ~25%. (In the general male population ≥ 50 years old that figure is 4%.) Studies to date have demonstrated a 2.5-fold increase in specificity for the *phi* compared to the PSA in the range of PSA 4-10 ng/ml. The expectation is that the *phi* will decrease the number of negative prostate biopsies. Data from the multi-center study reported below indicated a 31% reduction in biopsies which were found to be cancer free.

The major study presenting the research underlying the *phi* was reported by a large group of collaborators led by William Catalona in *J.Urol*, May 2011: "A Multi-Center Study of [-2]Pro-Prostate-Specific Antigen (PSA) in Combination with PSA and Free PSA for Prostate Cancer detection in the 2.0 to 10 ng/ml PSA Range".

Executive Summary: The "PCa risk increased directly with increasing *phi* values."

Using a *phi* value of <25 as the baseline with an assigned relative risk (RR) of 1.0, the probability of finding cancer on biopsy was:

- 11% for *phi* 0-24.9 (RR 1.0);
- 18.1% for *phi* 25.0-34.9 (RR 1.6);
- 32.7% for *phi* 35.0-54.9 (RR 3.0); and
- 52.1% for *phi* 55+ (RR 4.7).

The percentages of patients in these ranges were 24.9%, 32.8%, 29.5%, and 12.8%, respectively.

Study Details: The report was based on the biopsy results of 892 men ≥ 50 years with a normal DRE exam, ≥ 6 biopsy cores, and PSA ranging between 2 to 10 ng/ml. The study analyzed 430 men with cancer and 462 without.

The Prostate Health Index (phi) continued:

[-2]proPSA

Why include this isoform (also termed p2PSA) of PSA in the *phi*?

This precursor protein is much less recognized by clinicians, but Catalona indicates that:

- 1) "Preliminary evidence suggests that a higher percentage of p2PSA may be associated with more aggressive PCa", and
- 2) "At PSA of 2.0 - 10.0 ng/ml, p2PSA further improved specificity for PCa detection relative to %fPSA." [-2]proPSA is the primary isoform of PSA in prostate cancer tissue.

Association of *phi* with Gleason Score of 7 or greater: The study found a significant relationship of increasing *phi* values with greater cancer aggressiveness.

Results: Of the men found to have cancer on biopsy, Gleason score of ≥ 7 was found in 26.1% of those with *phi* values between 0-24.9; in 28.2%, *phi* 25.0-34.9; in 30.1% *phi* 35.0-54.9; and in 42.1% in men with *phi* values 55+

The authors speculate that the results of a *phi* test may guide in management decisions post-biopsy. For example, "A physician might recommend biopsy for a patient with a *phi* ≥ 55.0 (risk = 52.1%) and surveillance for some men with a *phi* < 25.0 (risk = 11.0%."

BOTTOM LINE: This study concludes that the "*phi* is highly effective when used in patients with moderately elevated PSA concentrations who may be most likely to benefit from early diagnosis and curative PCa treatment," and may serve to "reduce unnecessary biopsies".

ACTIVE SURVEILLANCE: A Work in Progress Aiming For Optimal Patient Selection

There is general agreement that a 12-core prostate biopsy - even the more informative extended biopsy, is fraught with misclassification of Gleason grading, i.e. "sampling error." There is sufficient inaccuracy so that in 20%-30+% of cases the prostates removed at surgery are diagnosed with a higher Gleason grade and stage than diagnosed at biopsy. This misclassification is especially relevant for patients initially judged to be at low risk for recurrence. The inaccuracy in large measure explains why the current criteria, useful as they are, for selecting candidate for active surveillance (AS) fall short of achieving the outcomes that are ultimately hoped for. The predictive imprecision at one level is histologic, resulting from biopsy sampling error, but at a higher level results from the current lack of validated molecular markers to optimize prediction of a tumor's future behavior even among those with apparent favorable histology. The validation of these tumor biomarkers is also a work in progress with numerous candidates under consideration.

The current most stringent criteria for optimal patient selection are: PSA < 10 ng/ml, stage T1c-T2a, ≤ 2 biopsy cores positive for cancer with than $\leq 50\%$ involvement in any one core, Gleason score 6 or less, and PSA density of ≤ 0.15 ng/mL per mL.

ACTIVE SURVEILLANCE: A Work in Progress continued:

Some studies have widened the criteria to allow Gleason scores of 3+4 and PSAs up to 15 ng/ml, PSAD \leq 0.2 ng/mL, and \leq 33% cores positive, especially for men older than 70 years. This Commentary article, however, will primarily focus on outcomes of AS studies of men meeting the strictest criteria, described (as above) by Johns Hopkins, as "very-low-risk."

CURRENT OUTCOMES FOR ACTIVE SURVEILLANCE TRIALS:

An excellent summary article offers a review of seven major AS trials: "Active Surveillance for Prostate Cancer: A Systematic Review," by Dall'Era and nine other prominent experts (*Eur Urol*, June, 2012). The largest studies enrolled 450 to 988 men mainly ranging in age between 60 and 70 years.

The key observations of these seven trials are:

- 1) short follow-up of about 2-4 years, except for the Toronto trial with F/U of 6.8 years
- 2) Gleason misclassification rates of 22% to 35%
- 3) discontinuation of AS and treatment initiated in about 1/3 of men at median of about 2 1/2 to 3 1/2 years into the study and
- 4) a prostate cancer specific mortality of 1% or less (not surprising considering the short follow-up period). Treatment was chosen as a matter of personal preference in 7-13% of the men.

In the Johns Hopkins trial intervention occurred at a median of 2.2 years with a range of 0.6 to 10.2 years, illustrating the benefit afforded to some men whose treatment was deferred to the longer end of the range. In a study by Shappley et al. (*JCO*, 2009) of 342 men on AS drawn from the Health Professional Follow-up Study, "174 (51%) remained untreated throughout follow-up (mean 7.7 years); the remainder were treated an average of 3.9 years after diagnosis."

A goal of improved patient selection for AS would be lengthening the period of delay before intervention.

Of special interest is the report by Klotz, *Curr Opin Urol*, May 2012. "Active Surveillance: the Canadian Experience." This trial was started in 1995 and is the first prospective and largest trial for this approach. In this trial only 71% were low-risk by D'Amico criteria. However, the cancer-specific survival at 5 and 10 years was 99.7% and 97.2%, respectively. An important observation was that of the 450 men (median age 70.3) during the 6.8 years of follow-up only 1% died of prostate cancer while "all cause" mortality was 21%, a ratio of 1/18.6 at 10 years!

The follow-up schedule in the Canadian trial was typical of standard policy with a confirmatory biopsy at 1 year to identify higher grade cancer missed at initial biopsy. "Surveillance" biopsies were performed every 3-4 years to evaluate for biologic progression. Serial PSA monitoring was done every 3 months for 2 years then and then every 6 months. Using a trigger for intervention of PSA doubling time of \leq 3 years or Gleason "up-grading," 20% of men underwent radical therapy. Regarding "up-grading" on surveillance biopsies Dell'Era comments: "It is unknown whether changes in histology over time represent tumor de-differentiation and growth or simply tissue undersampling; however, it is likely a combination of both."

SURGICAL PATHOLOGY: THE GOLD STANDARD

Many studies have checked the results of the biopsy Gleason score against the surgical pathology on the same prostate. The method is straightforward: choose a set of criteria for selection of candidates for AS, assemble a cohort of men who met those criteria who then underwent immediate prostatectomy, compare the biopsy diagnosis with the surgical pathology, and then evaluate how well the criteria were met. There is remarkable consensus in the findings of these studies.

The ongoing PRIAS study (Prostate Cancer Research International: Active Surveillance) is a representative example: "Analysis of outcomes after radical prostatectomy in patients eligible for active surveillance," El Hajj *et al.*, *BJU Int.* June 2012. The study focused on 626 men who met the PRIAS criteria for AS: T1c-T2, PSA level ≤ 10 ng/nL, Gleason score < 7 , PSA Density < 0.2 ng/mL per mL, and ≤ 2 positive biopsies. Stage T1c was reported in 82%, but the study also included 18% with the higher risk stages T2b and T2c, since the tripartite stage T2 had not been further segregated.

PRIAS results: upstaging to $> T2$ was seen in 20.6%; upgrading to Gleason 7 in 43.3% and to Gleason ≥ 8 in 1.6%. Unfavorable disease was defined as non-organ confined disease (pathological stage $> pT2$) and/or Gleason score > 6 in the surgical specimen, and this occurred in 51%.

Of interest, however, is that at the short 5-year follow-up the freedom from biochemical failure was similar ($P=0.06$) for those who met AS criteria and those were with unfavorable characteristics, i.e. about 95%.

NATIONAL COMPREHENSIVE CANCER NETWORK RECOMMENDATIONS:

THE NCCN practice guidelines, Version 1.2010 include AS as an option for men meeting the stringent criteria listed initially in this article. An important contribution for clinicians is presented in the section "Principles of Active Surveillance." Herein are listed discussion points that may be useful to an informed discussion with men contemplating AS. The points for benefits are intuitive - the gains can be substantial for the well-chosen and fortunate who delay (or completely avoid) treatment for many years. But the disadvantages discussed are worth noting: "1), chance of missed opportunity for cure; 2), risk for progression and/or metastases; 3), subsequent treatment may be more complex with increased side effects; 4) nerve sparing may be more difficult, which may reduce chance of potency preservation after surgery; 5), increased anxiety; 6), requires frequent medical exams and periodic biopsies; and, finally, 7), uncertain long-term natural history of prostate cancer."

BOTTOM LINE: Active surveillance is a recognized and serviceable option for selected men judged to be at low risk for recurrence, but further refinements are needed in selection criteria to achieve optimal outcomes.

IMPROVING ACTIVE SURVEILLANCE SELECTION CRITERIA: MRI Technology Can Lower Gleason Misclassification Rate

I am indebted to Dr. Jim Borrow, staff radiologist, First Hill Diagnostic Imaging, Seattle, WA, for his helpful suggestions for this article.

Misclassification is a histologic issue resulting from inadequate biopsy sampling of the primary tumor mass. Biopsies guided by transrectal ultrasound and otherwise random biopsies can miss the highest grade of tumor foci. Accurate sampling is confounded by prostate cancer's multifocality and the heterogeneous histology at different foci.

Multiparametric MRI (MPMRI) utilizing routine T2 weighted sequences, dynamic contrast enhanced (DCE) T1 and diffusion weighted (DW) sequences, can detect and localize clinically significant tumors. Tumor aggressiveness can be determined by DW-MRI based on detection of the rate of water diffusion through tissue, expressed as the Apparent Diffusion Coefficient (ADC). The lower the ADC value, the higher the Gleason grade. (See PCa Commentary, Vol. #75 for full discussion.)

In contrast to the random sampling at standardized locations in the prostate with transrectal ultrasound, tumors can be localized, volume calculated, and tumor targeted for biopsy with MPMRI. Additionally, targeting of the most aggressive component within a tumor by matching ADC values and DCE characteristics can avoid understaging prostate cancers.

The diffusion weighted sequence is also proving informative in estimating the Gleason grade of a tumor mass. The Gleason grade (a measure of cancer aggressiveness) is generally inversely proportional to the ADC value because tumor cells become more densely packed as the cancer becomes more aggressive. When cancer cells become more closely packed, the freedom of movement of water through cancer tissue is increasingly impeded, thus decreasing the ADC. A lower ADC value translates to a higher Gleason grade.

The dynamic gadolinium contrast enhanced (DCE) sequence - especially in the peripheral zone, takes advantage of the greater vascularity of cancer. Increased angiogenesis in tumors is characterized by a convoluted mass of small vessels with more permeable endothelium leading on DCE to early tumor contrast enhancement and rapid contrast "washout" - a signature of cancer compared to normal tissue. This phenomenon is less clearly seen in the central zone.

Peter Choyke, Director, Molecular Imaging Program, NCI, has made the imaging of prostate cancer a major focus of his work. He and colleagues published "MRI of localized prostate cancer: coming of age in the PSA era (*Diagn Inrv Radiology* 2012), an excellent review of the subject. Their assessment: "Multiparametric MRI including T2W-MRI, DW-MRI, MR spectroscopy, and DCE-MRI can potentially help to correctly stratify ... patients in the pretreatment phase because it may help predict patterns of tumor growth and thus identify prognosis."

In situations where the suspicion for prostate cancer is high, obtaining an MRI, with all its advantages, before the initial biopsy may be the preferred choice.

Improving Active Surveillance continued:

However, if an MRI study follows a biopsy, the MRI should be delayed 6-8 weeks to allow resolution of the tissue injury and bleeding secondary to the biopsy.

The relationship of the rate of water movement through tissue (ADC) with Gleason grade has been validated in many studies.

Two Examples: Hambrock *et al.* (*Radiology*. May 2011) compared the preoperative ADC in 62 tumors with their corresponding surgical specimens. Based on the ADC findings "A high discriminatory performance was achieved in the differentiation of low-, intermediate, and high-grade cancer."

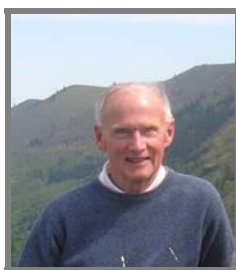
Naragajan *et al.* (*Advances in Urology* 2012) studied the prostates of 44 pts and sought to differentiate Gleason grades 3+3 vs. 3+4 vs. 4+3. "The ADC values were statistically significant between the three different scores with a trend of decreasing ADC values with increasing Gleason scores"

What would be achieved by gaining a more accurate estimate of the Gleason grade of cancer in men considering active surveillance?

As cited in this Commentary article, studies indicate that 20%-40% of prostate cancers assigned with biopsy Gleason scores of 3+3 on the basis of transrectal ultrasound guidance are in fact of higher grade and stage. Those studies also indicate that about 1/3 of men on AS undergo intervention in the course of surveillance at a median interval of 2 1/2 - 3 1/2 years after diagnosis. A more accurate initial estimate of a tumor's aggressiveness might influence those men with higher estimated Gleason grades to opt for intervention initially rather than active surveillance. Those men with the most solid estimates for Gleason 3+3 would likely enjoy a longer period before intervention might be indicated - and experience that longer interval with greater confidence.

BOTTOM LINE: Multiparametric MRI technology can improve the accuracy of the initial prostate biopsy in estimating a prostate tumor's Gleason grade and contribute to the optimal selection of men for active surveillance.

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



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