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PCa Commentary

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PSA AND TREATMENT DECISIONS:

"What If I Don't Treat My PSA-Detected Prostate Cancer? Answers From Three Natural History Models"…

... Really, can any man resist reading an article with this title?

The premise: "Making an informed decision about treating a prostate cancer detected after a routine prostate-specific antigen (PSA) test requires knowledge about disease natural history, such as the chances that it would have been clinically diagnosed in the absence of screening and that it would metastasize or lead to death in the absence of treatment."

Roman Gulati et al., Fred Hutchinson Cancer Research Center, in association with researchers at Michigan and Rotterdam, (*Cancer Epidemiol Biomarkers Prev; May 2011)* based their analyses on the extensive data bases of NCI's SEER registries, the control arm of the Prostate Cancer Prevention Trial, and on PSA-specific biopsy compliance rates data from the Prostate, Lung, Colon, and Ovarian cancer screening trial.

Consider the scene: A 50-year old man thought to be free of prostate cancer is sitting with his primary care provider discussing PSA screening. Data from the National Cancer Institute show that his risk of developing and being diagnosed with prostate cancer by age 60 is 2.39%; at 70, 8.58%, at 80, 14.67%; and 17.13% by age 90. What information might better inform his decision about testing? If tested and then diagnosed with cancer, what considerations are relevant about choosing to be treated? But first...

PROPER TERMINOLOGY IS IMPORTANT IN UNDERSTANDING RISK:
(since there easily can be some confusion on this subject).

A good primer is "The Role of Prevalence in the Diagnosis of Prostate Cancer," Delongchamps, *Cancer Control;* July 2006, which stresses that "Statistics for incidence and prevalence do not provide the same information."

1.) Prevalence refers to the total number of prostate cancers existing in a given population at a certain time. For prostate cancer the true prevalence is unknown. Prevalence is best estimated from incidental findings on autopsy studies or from whole-mount specimens from cystoprostatectomy. The best US data comes from Sakr (*In Vivo*. 1994 May/June) who reported finding invasive carcinoma at autopsy in 249 cases of men in their 20s, 30s, 40s, 50s, and 60s, at a rate of 2%, 29%, 32%, 55%, and 64% with another study reporting 83% between 71-80.

The time from cancer genesis to clinically diagnosable cancer ("sojourn time") is unknown but estimates suggest that this process may take more than 7-14 years. This interval differs from "lag time," which refers to the period between PSA detection of cancer and a clinical diagnosis, generally estimated at 4-9 years depending on the degree of aggressiveness.

2.) Incidence refers to the number of new cases of prostate cancer diagnosed in a certain period. Incidence figures vary according to the method and thoroughness of the effort to diagnose.

For example a prevalence/incidence hybrid figure was reported regarding the 2950 men in the control arm of the Prostate Cancer Prevention Trial (PSA <4 ng/ml; DRE, normal)."End-of-study" biopsies diagnosed cancer in 15.2% (15% of whom had Gleason sum $\geq$7).

The 15.2% figure from the PCPT is lower than the prevalence figures found in autopsy/cystoprostatectomy studies because of biopsy "sampling error" and the fact in the earlier period of a tumor's growth it not "biopsy-diagnosable."

PSA AND TREATMENT DECISIONS continued

The "What if I Don't Treat" article:

We are now ready to approach the findings in this article, which "projects risks of clinical progression events for PSA-detected localized prostate cancer for men who do not receive curative treatment." The modeling assumes that men whose PSA rises above a value of 4 ng/ml will be referred for biopsy - with all its diagnostic limitations. By employing natural history modeling, these studies project backward in time to estimate a hypothetical point of onset of a preclinical "*biopsy-diagnosable*" cancer. (This point is considerably later then the histological inception of the tumor; additionally, the model cannot provide a size for this "biopsy-diagnosable" tumor.)

The FHCRC model estimates the likelihood of three major clinical progression events: diagnosis as a consequence of clinical symptoms such as an abnormal DRE or obstructive voiding symptoms; diagnosis at clinical metastasis; and death for men 50-84 years old. Further subdivision is provided into groups by PSA values at detection of 4-7, 7-10, and >10 ng/ml; and Gleason scores of ≤7 and 8-10.

An inclusive tabulation of this data presents "Projected frequencies (%) of clinical progression events for PSA-detected locoregional stage cases who receive no primary treatment."

Examples:

1) **Men age 50-54,** Gleason ≤7, PSA 4-7 ng/ml are estimated to have a 91% likelihood of a later development of symptoms, a 12% chance of metastasis diagnosed by symptoms, and a 25% risk of cancer-specific death;

2) **For men age 60-64,** Gleason ≤7, PSA 7-10 ng/nl the corresponding figures are 80%, 11%, and 21%;

3) **For men age 70-74,** Gleason ≤7, PSA >10 ng/ml the figures are 73%, 10%, and 16%

The likelihood of death from cancer decreases as men age since death from other causes increases.

4) **For men age 60-64,** Gleason 8-10, PSA 7-10 ng/ml the figures are 81%, 28%, and 55%.

⇨

An instructive and useful figure can be derived from these estimates.

- In the first example by subtracting 91% from 100% the resulting 9% represents the chance of being "overdiagnosed," where immediate treatment confers no benefit.
- The corresponding figures for examples #2, #3, and #4 are 20%, 27%, and 19%.

In general the likelihood for overdiagnosis decreases at younger ages.

Summarized differently, "Among men age less than 60 years at PSA detection with Gleason score ≤7 disease, the three models project that *in the absence of treatment* 4%-9% and 15%-26% would die of their disease by 10 and 20 years after PSA detention. Corresponding projections at 10 and 20 years for men with Gleason score 8-10 disease are 29%-43% and 56%-68%."

To best correspond to management strategies in real life, the authors recalculated these mortality estimations assuming that men would undergo a prostatectomy at the time of projected clinical diagnosis. Intervention at this point reduced the risk of prostate cancer death for men <60 and Gleason score ≤7 from 23%-34% to 18%-27%, and for Gleason score 8-10 disease from 62%-80% to 51%-66%. For the authors these data "suggest that, for younger men, the risks of progressing to lethal disease remain nontrivial even if treatment is pursued at clinical diagnosis."

The authors are well aware of the limitations of their work, but point out that "This is the first study to project population-based natural history summaries in the absence of screening or primary treatment and the risk of clinical progression events following PSA detection in the absence of primary treatment."

BOTTOM LINE: After an abnormal PSA test, if a man is diagnosed with prostate cancer, now knowing his PSA level and Gleason sum, he can be informed from this natural history data about his personalized future risks if he forgoes initial treatment. Additionally, an estimation can be made to suggest the likelihood of his being "overdiagnosed". Of course, without testing there is no opportunity to be aware of these risks and make appropriate decisions ... and the adverse events will unfold on their own.

I would like to sincerely thank Roman Gulati for his many helpful suggestions for this article.

ACTIVE SURVEILLANCE: "Surgical management after active surveillance for low-risk prostate cancer: pathological outcome compared with men undergoing immediate treatment."
BJU Int. 2011 April

Once again Peter Carroll and colleagues have valuably contributed to the essential issue regarding active surveillance (AS), i.e. *Does selective delayed intervention sacrifice the opportunity to achieve optimal treatment outcome?*

This study analyzes changes in Gleason score between the initial diagnostic prostate biopsy and the pathologic Gleason score determined at immediate surgery compared to the score at delayed surgery. The authors acknowledged that their findings about Gleason score outcomes "are simply surrogates for the more clinically relevant outcome of disease-specific and overall survival," information that awaits larger trials with longer follow-up.

Adherence to stringent criteria for selection of low-risk patients for AS is essential for optimal outcome. There is consensus that favors the criteria of:

- PSA <10 ng/ml, Gleason sum ≤6, absence of Gleason grade 4 or 5.
- Cancer involvement of ≤33% of biopsy cores [of a total of 12], ≤50% of any single core, and clinical stage T1/2." (In the two groups on which the comparison in this article was based half of the men had ≤10% of any single core involved.)

Follow-up PSA measurements were made every 3 months, TRUS at 6-12 months, and repeat biopsies at 12-24 months. "Performing an immediate second biopsy within 3 months of diagnosis may serve to reduce the risk of clinical undergrading...." An earlier repeat biopsy might be chosen for those men edging toward the upper limits of these criteria.

The key analysis compared:
- 276 low-risk patients who underwent primary RP at a median time after diagnosis of 3 months and
- 33 men on AS (AS+RP) who eventually had surgery after a median interval on AS of 18 months (range 7-72).

The choice to depart from AS and undergo surgery was mainly "in response to Gleason upgrading on surveillance biopsies (23 men) or patient desire." For all men in the study the initial median PSA was 5.8 ng/ml; median age 59.

The Pathologic Findings for immediate RP compared to delayed surgery after a period of AS:

	Immediate RP	AS +RP
Gleason upgrading to ≥ 7	35%	30% (P=0.57)
Upstaging to pT3	10%	21% (P=0.06)
Positive Surgical Margins	12%	19% (P=0.30)

The question of whether a longer period of AS would yield poorer outcomes was also addressed.

Organ confined disease was the same (79%) in men on AS for longer than 18 months compared to a shorter duration. The majority of upgrades were to Gleason 3+4. "It is not known whether this change in Gleason score represents true grade progression or simply sampling error, although the current evidence suggests the latter."

The sample size of this analysis is small, but the findings are credible being consistent with other active surveillance studies in which patients met similar stringent criteria for defining low-risk. However, the authors acknowledge an important fact: *"These data also show how current methods for risk stratification still miss a substantial number of men with higher-risk features."*

BOTTOM LINE: After a diagnosis of prostate cancer, men with low-risk features may be safely offered management with active surveillance with selective delayed intervention without sacrificing optimal outcome.

ADJUVANT ANDROGEN DEPRIVATION WITH RADIOTHERAPY FOR INTERMEDIATE- AND HIGH-RISK PROSTATE CANCER

WHAT IS KNOWN?

(Nicely summarized in "Androgen deprivation therapy [ADT] for prostate cancer - review of indications in 2010 by Quon and Loblaw [University of Toronto]", *Current Oncology,* Vol.17, Supp.2, 2010.

When considering this issue it is essential that the studies under review employed current day radiotherapy (RT) dosing, i.e. 70 Gy or more, since optimal therapy in this range may obviate the apparent benefit that adjuvant ADT contributes to radiotherapy regimens using lesser doses.

Intermediate-risk: "For intermediate-risk patients, there is some evidence to support the short-duration use of ADT." (Quon)

The relevant study was reported by D'Amico (*JAMA* Aug 20O4) in which 206 men with localized cancer (T1c-T2b) were treated with 70 Gy RT randomized between 6 months of an LHRH agonist plus flutamide or no RT. Salvage was added when the PSA was >10ng/ml. Gleason score 8-10 occurred in 15% in both groups; 63% of the men in the study were Gleason 7, evenly balanced between the two groups; and PSAs ranged from 10-40 ng/ml.

Results: Overall survival at 5 years for RT/ADT v. RT was 88% v. 78%. At 5 years 82% of men receiving RT/ADT were free of salvage v. 57% RT alone.

Whether RT doses approaching 80 Gy would obviate the contribution from ADT is not known.

High-risk: "Multiple randomized clinical trials have established a role of combined ADT and RT in the treatment of high-risk PCA" (Quon)

The relevant issue for men at high-risk is not ***whether*** to use ADT but for ***how long***, i.e. short duration, ≤6 months, or up to 3 years. The length of exposure to ADT is critically important considering that the well known adverse effects of ADT compound as therapy lengthens.

A representative study (RTOG 92-02) addressing ADT duration was reported by Horwitz, *J Clin Oncol* 2008:26. The 1554 men in the trial had locally advanced cancer, T2c-4, and PSA values <150 ng/ml. RT was delivered to the pelvis with a prostate boost to 65-70 Gy. The ADT regimens compared 4 months of an LHRH agonist plus flutamide combined with RT v. the same initial therapy plus 24 additional months of ADT. Significant benefit from a total of 28 months of ADT was seen in all standard parameters of response except overall survival.

However, in patients with Gleason score 8-10 at 10 years follow-up an overall survival benefit was seen for long-term ADT, 45.1% v. 31.9%. The authors concluded that prolonged treatment should be standard for this group.

WHAT IS NEW?

Research on the optimal duration of ADT balancing benefit and toxicity in high-risk prostate cancer was reported by D'Amico and colleagues: "Surrogate endpoints for prostate cancer-specific mortality after radiotherapy and androgen suppression therapy in men with localized or locally advanced prostate cancer: an analysis of two randomized trials," *The Lancet,* Nov. 2011.

The authors acknowledge that "3 years of androgen suppression confers a small survival benefit [3.8% at 5 years] compared with 6 months of therapy in this setting of ***locally advanced disease***, but is associated with more toxic effects." Their goal was to discover metrics available ***early*** in the course of treatment to select men who may not require prolonged ADT.

Analysis was based on 734 men entered in studies by the Dana Farber Cancer Institute and the Trans-Tasman Radiotherapy Group. Each study assigned one group to receive RT plus ADT and another no ADT. Both studies "showed statistically and clinically significant reduction in prostate cancer specific mortality when 6 months of androgen suppression was added to radiotherapy versus radiotherapy alone."

ANDROGEN DEPRIVATION continued

The chosen early metrics were:

1) the PSA value at the end of the combination of 6 months of ADT and radiotherapy ("PSA end"); and
2) the PSA nadir achieved at the end of 6 months

Radiation dosages were 66 Gy for TTRG and 70 Gy for DFCI.

Their findings based on the two studies:

"Men treated with radiotherapy and 6 months of androgen suppression in both trials were significantly *less likely* to have "PSA end" and PSA nadir values of more than 0.5 ng/ml than those treated with radiotherapy alone (p<0.0001)."

The "PSA end" was assessed at a median of 1.8 months and the PSA nadir at 2.43 months after 6 months of treatment. After analysis the authors suggested that if either the "PSA end" or the PSA nadir is >0.5 ng/ml then those men will be recommended to continue ADT for 3 years or receive other regimens to reduce recurrence. Their conclusions reflect their analysis that these early metrics suitably predict prostate cancer specific mortality (PCSM).

Examples: 8-year PCSM data extracted from the article's graphs showing the difference in cumulative incidence of PCSM for men treated with 6 months of RT/ADT who achieved, or did not achieve, the desired metrics.

"PSA end"	<0.5 ng/ml - PCSM ~ 5%	"PSA end"	>0.5 ng/ml - PCSM ~15%
PSA nadir	<0.5 ng/ml - PCSM ~ 5%	PSA nadir	>0.5 ng/ml - PCSM ~28%

BOTTOM LINE: No prediction system will ever be perfect, but D'Amico's study provides a useful guideline for selecting the men with locally advanced prostate cancer for whom 6 months of ADT following RT provides the optimal balance between outcome and adverse effects.

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

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