PENINSULA PROSTATE INSTITUTE

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Issue 2 / July 2014

Greetings!

Welcome to another edition of the Peninsula Prostate Institute (PPI) Newsletter. In this installment we will cover a variety of prostate cancer topics ranging from the latest data on nutritional supplements to the latest diagnostic tests to the treatment of advanced cancer. Feel free to forward this information to whomever you like. Enjoy the rest of your summer and happy reading!

Sincerely,

R. Alex Hsi, MD

UPCOMING EVENTS

PPI Sponsored Golf Tourney, August 2nd. To register, go to Kitsap Cancer Services for more information.

PPI Nutrition Class Fall 2014
Wednesday September 10, 2014 from 11:00 AM to 1:00 PM PDT
Please join us for our nutrition class focusing on prostate health. Class will be held every other Wednesday from 11:00 am to 1:00 pm through November 19th. You may register yourself and a guest.
Peninsula Cancer Center Conference Room

SAVE THE DATE! Peninsula Cancer Center's 5-year anniversary open house is September 25th from 4-7PM. PCC is hosting a community event with champagne and nibbles. Join us in the celebration.

IN THE NEWS

Vitamin E and Selenium - It does a prostate no good!

A recently published report from a national multi-center study called the Selenium and Vitamin E Cancer Prevention Trial (SELECT) found that high dose supplementation with selenium and Vitamin E not only does not prevent prostate cancer, but in certain cases, actually increases a man's risk of developing high grade prostate cancer.

The Early Report:

The SELECT trial was a randomized and placebo-controlled trial that involved over 35,000 men whose purpose was to determine whether taking high dose Vitamin E (400 IU per day) and/or Selenium (200 mcg/day) could protect men from getting prostate cancer. Most multivitamins for adult men contain around 30 to 60 IU of vitamin E and 55 mcg of selenium. The trial began in 2001 and was designed to last for 12 years, but was stopped early in 2008 because it found no protective effect of selenium and there was a suggestion that those men who received vitamin E actually had an increased risk of developing prostate cancer. That suspicion was confirmed after following those men for a few more years at which time that increased risk of prostate cancer was quantified at 17% greater than those who did not receive vitamin E.

The Updated Report:

The most recent update of the trial published earlier this year showed more startling findings about vitamin E and selenium. Certain subgroups of patients had a dramatically increased risk of developing high grade (aggressive) prostate cancer. Prior to receiving the supplements, the study participants had their baseline selenium levels determined (by measuring levels in their toenails!). Among men with high baseline selenium levels, those who took the selenium supplements had a 91% increase in their risk of developing high grade prostate cancer. The study also found that men with low baseline levels of selenium who took vitamin E supplements had a 111% increased risk of developing high grade prostate cancer. The fact that only certain subgroups of men (high baseline selenium who took selenium supplements and low baseline selenium who took vitamin E supplements) illustrates the complex relationship between these substances in the body.

The Bottom Line:

Vitamin E and selenium supplements do not provide a protective effect against prostate cancer and in certain subgroups of men can dramatically increase the risk of developing an aggressive form prostate cancer. The Peninsula Prostate Institute recommends against taking any Vitamin E or selenium supplements.

Prolaris® - A Genetic Test for Prostate Cancer: Ready for Prime Time?

Many men diagnosed with low risk prostate cancer (Gleason score 6, PSA <10, clinical stage T1c or T2a) are offered watchful waiting or active surveillance as a way to manage their prostate cancer. Most of these cancers will take 10 years or more to become life threatening and some may never pose a threat at all. However, today's current classification system which uses Gleason score, PSA and clinical staging sometimes falls short of predicting whether or not and how long it may take for a man's prostate cancer to pose a threat to his life.

Recently, several new genetic tests have become available to try and better prognosticate whose low risk prostate cancer is really a "wolf in sheep's clothing". One commercially available test, known as Prolaris®, holds promise as test which may help in this regard. Prolaris® is a test that measures how fast a man's prostate cancer cells are dividing and thus, a measure of its aggressiveness. It provides a quantitative measure of RNA expression levels from a 46 gene panel which correlate with prostate cancer cell proliferation. Low expression levels are associated with a low risk of cancer progression while high expression levels are associated with tumor progression. Men with the same Gleason score, PSA and clinical stage could have very different Prolaris® test scores and thus a very different risk of dying of prostate cancer.

A recent study reported in May 2014 at the American Urological Association meeting in Orlando, FL revealed data on 761 men from the United Kingdom who had prostate cancer diagnosed with needle biopsy from 1990 to 2004 and who were "conservatively managed" with watchful waiting. Definitive treatment was provided at the onset of symptoms. With a median follow-up time of 9.5 years, 18% of men were found to have died of prostate cancer. Tumor tissue from the men's original prostate biopsy was then analyzed with the Prolaris® test. The results indicate that for each 1 unit increase in Prolaris score, patients had approximately twice the risk of dying from prostate cancer over 10 years.

Table - 10-Year Death Rate by Polaris® Score

Prolaris® Score	10-Year Death Rate, %
<0.0	7
0.0-1.0	15
1.1-2.0	36
>2.0	59

Further studies will need to be performed in order to verify these results. Another barrier to increased use of Prolaris® is the cost, about $3400, and limited coverage by insurance carriers. Hopefully, as other tests (such as the Oncotype Dx® assay from Genomic Health) become available and provide competition, these costs will come down. As further research is completed over the next few years, it is likely these tests will become a standard part of our prostate cancer management decision tree. Stay tuned folks....

To view the published abstract of the above mentioned clinical trial, please click: AUA abstract.

New Course CHAARTED for Metastatic Prostate Cancer

A recently reported clinical trial found that starting chemotherapy along with hormonal therapy in newly diagnosed hormone-sensitive metastatic prostate cancer improved overall survival compared to hormonal therapy alone.

The trial, known as CHAARTED (Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer ... yes that's a mouthful!) compared "upfront" chemotherapy (docetaxel) plus androgen deprivation therapy (ADT, usually a shot given every few months) to ADT alone in men with metastatic prostate cancer. Between 2006 and 2012, 790 men were enrolled and split into two groups, approximately half receiving chemotherapy and ADT while the other half received ADT alone. Those randomized to the chemotherapy arm of the study received docetaxel chemotherapy every three weeks for six cycles. Patients were also stratified by extent of metastatic disease into a high volume or low volume group; high volume was defined as visceral (internal organ) metastases and/or four or more bone metastases. The original design of the study called for enrollment of only patients with high volume metastases, but due to slow patient enrollment, the study investigators changed the design to include patients with low volume disease as well.

The median overall survival of the chemotherapy plus ADT group was 57.6 months versus 44.0 months ($p<0.001$) for the ADT alone group, a 13.6 month improvement in survival for the chemotherapy group. Analysis of the men with high volume disease only showed the addition of chemotherapy resulted in an even larger 17 month improvement in overall survival. The benefit of chemotherapy was not significant in men with low volume disease. The median time to progression (such as elevation in PSA level, new symptoms or worsening radiographic scans) was 20.7 months in the chemotherapy and ADT group versus 14.7 months in the ADT alone group ($p<0.001$), a 6 month improvement. Significant toxicity due to the chemotherapy was low with 6% of patients experiencing fever and low white blood cell count (febrile neutropenia), 1% experiencing significant neurologic side effects and 1 of 397 men receiving chemotherapy died as a result of the treatment.

Many leading oncologists have described the result of this study as a "game changer" for metastatic prostate cancer. "This is one of the biggest improvements in survival we have seen in a trial involving patients with an adult metastatic solid tumor," said lead investigator Christopher Sweeney, MD, from the Dana-Farber Cancer Institute in Boston. "The benefit is substantial and warrants this being a new standard treatment for men who have high-extent disease and are fit for chemotherapy." However, Dr. Michael Morris of the Memorial Sloan Kettering Cancer Center in New York also pointed out that those patients with metastatic prostate cancer at presentation "represent only about 4.2% of the overall prostate cancer population, and high-volume disease represents a fraction of that," implying that this finding may affect the treatment of only a very small number of patients. However, the recent federal government recommendation against PSA screening may lead to fewer patients diagnosed with early stage prostate cancer and more presenting with advanced cancers such as those men in the CHAARTED study.

The Bottom Line: The addition of chemotherapy to ADT in men presenting with hormone sensitive high volume metastatic prostate cancer increases survival by nearly 1.5 years, although currently the number of men in this group is relatively small.

To view the published abstract of the above mentioned clinical trial, click on this link.

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MP 79-17

VALIDATION OF A 46-GENE CELL CYCLE PROGRESSION (CCP) RNA SIGNATURE FOR PREDICTING PROSTATE CANCER DEATH IN A CONSERVATIVELY MANAGED WATCHFUL WAITING NEEDLE BIOPSY COHORT

Jack Cuzick, Steven Stone, Zi Hua Yang, Julia Reid, Gabrielle Fisher, Daniel Berney, Luis Beltran, Henrik Moller, David Greenberg, Michael Brawer, Alexander Gutin, Jerry Lanchbury, Peter Scardino

Center for Cancer Prevention, Wolfson Institute of Preventive Medicine, Myriad Genetics, Inc., Department of Molecular Oncology, Barts Cancer Institute, King's College London, Thames Cancer Registry, Eastern Cancer Registration and Information Centre (ECRIC) Unit C, Department of Urology, Memorial Sloan-Kettering Cancer Center

INTRODUCTION

- Since the natural history of newly diagnosed prostate cancer is variable and difficult to predict, validated prognostic biomarkers could have a major impact on patient care.
- Previously, a 46 gene cell cycle progression score (CCP score, based on measuring the expression levels of CCP genes) has proven to be a robust predictor of prostate cancer outcomes in various clinical settings, including in a conservatively managed cohort diagnosed by needle biopsy.[1-5]
- Here, we present a validation study of both the CCP score and a pre-specified linear combination of the score with standard clinical variables (clinical cell cycle risk (CCR) score) for predicting disease specific mortality (DSM) in a cohort of conservatively managed patients diagnosed by needle biopsy.

METHODS

- CCP score was generated from mRNA extracted from FFPE needle biopsies from 761 UK men diagnosed with clinically localized prostate cancer between 1990 and 2004 (Figure 1). The median year of diagnosis was 2002.
- Watchful waiting was the primary therapy.
- CCP score was calculated as previously described.
- Clinical variables were summarized by calculating a CAPRA score (a validated prediction score at disease diagnosis).
  - Two other previously published risk scores, the Kattan score[6] and the Cuzick score[7] were also calculated for each patient.
- The primary endpoint was DSM (17%), and the median clinical follow up was 9.52 years.
- The molecular data were generated blinded to disease outcome, and all analyses were pre-specified.

RESULTS

- In univariate analysis, the CCP score hazard ratio (HR) for DSM was 2.08 (95% CI 1.76, 2.46, $P = 6.0 \times 10^{-16}$) for a unit change in the score (Figure 2).
- In a multivariate analysis (n = 585) including CAPRA, the CCP score HR was only marginally decreased (1.76, 95% CI 1.44, 2.14), and remained highly significant ($P = 4.2 \times 10^{-9}$). The score performed similarly across clinical risk groups (Figure 3).

Figure 1 Cohort Assembly

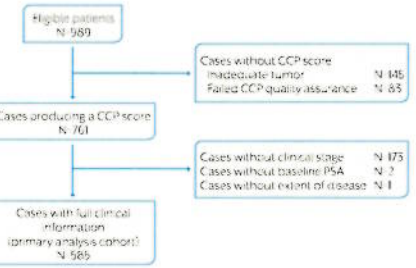
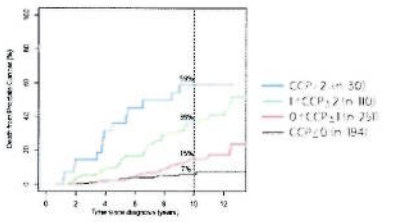


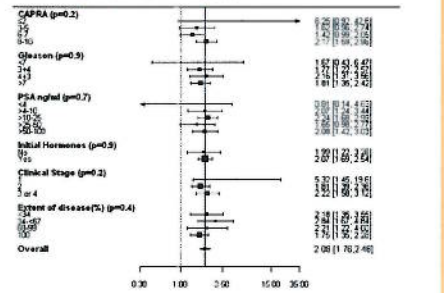
Figure 2 Kaplan Meier estimates of prostate cancer death according to CCP score (n=585)



Estimated 10 year risks and 95% confidence intervals are also shown.

- The Kattan nomogram and the Cuzick score were highly correlated with CAPRA (Kattan nomogram, $\rho = 0.8$, Cuzick score, $\rho = 0.85$) and the hazard ratio for adding the CCP score was similar regardless of which clinical score was used (CAPRA, HR = 1.76, Kattan, HR = 1.70, Cuzick, HR = 1.71).

Figure 3 Hazard ratio for prostate cancer death for a one unit change in CCP score for different clinical subgroups and CAPRA risk groups



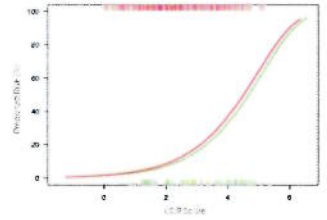
The area of the box is proportional to the amount of information available, and the horizontal bars represent 95% confidence intervals. P-values after each variable indicate significance of a test for homogeneity.

Figure 4 Likelihood ratio bar plots showing the relative contribution of information of CAPRA and the CCR score

Likelihood ratio bar plot shows the relative contribution of information by CAPRA and the CCR scores. Blue area on left bar is what CAPRA explains by itself, and the orange area is the additional information contributed by CCR. On the right bar, the orange area is what CCR explains by itself, and the blue area is additional information contributed by CAPRA. The p-value for the variable considered first is equivalent to the p-value for the univariate model, the p-values in the upper area of the graph are for additional information.

- The CCR score was also highly predictive of DSM ($P = 3.9 \times 10^{-16}$), and accounted for virtually all prognostic information (Figure 4).
- The 10 year risk of prostate cancer death as a function of CCR is shown in Figure 5, and is virtually identical to the 10-year risk curve derived from our previously published conservatively managed biopsy cohort.[7]

Figure 5 10-year predicted risk of prostate cancer death according to combined clinical cell-cycle-risk (CCR) score



Red line based on this cohort, green line on previous needle biopsy cohort. Ticks represent observed CCR scores.

CONCLUSIONS

- For patients managed by deferred treatment regimens (i.e. watchful waiting or active surveillance), the CCP score provides significant pre-treatment prognostic information that cannot be provided by clinical variables.
- As such, the CCP score is a valuable addition for the informed management of newly diagnosed prostate cancer patients.

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Presented at AUA - May 20, 2014

Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial.

Meeting:
2014 ASCO Annual Meeting

Category:
Genitourinary (Prostate) Cancer

Subcategory:
Prostate Cancer

Session Type and Session Title:
Plenary Session, Plenary Session Including the Science of Oncology Award and Lecture

Abstract Number:
LBA2

Citation:
J Clin Oncol 32:5s, 2014 (suppl; abstr LBA2)

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Background: Docetaxel (D) improves OS of men with mPrCa who have progressed on androgen deprivation therapy (ADT). We aimed to assess the benefit of upfront chemohormonal therapy for metastatic PrCa. **Methods:** 1:1 randomization to ADT alone or ADT + D dosed 75mg/m2 every 3 weeks for 6 cycles within 4 month (mos) of starting ADT. Stratification factors: high volume (HV) vs. low volume (LV) disease (HV: visceral metastases and/or 4 or more bone metastases); anti-androgen use beyond 30 days; Age ≥70 vs. < 70 years; ECOG PS 0-1 vs. 2; Prior adjuvant ADT > 12 vs. ≤ 12 mos; FDA approved drug for delaying skeletal related events. Key eligibility criteria: suitable organ

and neurological function for D; adjuvant ADT ≤ 24 mos and no progression within 12 mos of adjuvant ADT. OS was the primary endpoint and the study was powered to assess for a 33.3% improvement in median OS (80% power and 1-sided alpha=2.5%). Projected median OS for ADT alone: HV-33 mos; LV-67 mos. **Results:** 790 men were accrued from 7/28/06 to 11/21/2012: ADT N=393; ADT + D: N=397; balanced for demographic, stratification and disease factors. Median age: 63 years (range: 36 to 91); 98% ECOG PS 0 or 1; 89% Caucasian; 24% prior radiotherapy, 24% prior prostatectomy; HV 64% on ADT and 67% on ADT + D. Data released after 4th interim analysis in Sept 2013 when O'Brien Fleming upper boundary was crossed with 53.1% information. This report reflects 1/16/2014 data with median follow-up of 29 mos with 137 deaths on ADT alone vs. 104 deaths on ADT+D. ADT+D: Grade (G) 3/4 Neutropenic fever: 4%/2%; G3 neuropathy: 1% sensory, 1% motor; 1 death due to treatment (no deaths due to treatment on ADT). Efficacy data is in the table below. After disease progression, 123 pts on ADT alone and 45 pts on ADT + D received docetaxel. **Conclusions:** ADT + D improves OS over ADT alone in men with HV mPrCa. Longer follow-up is needed for men with LV mPrCa. Clinical trial information: NCT00309985.

Intent to treat analysis	ADT	ADT + D	P value	Hazard ratio (95%CI*)
PSA < 0.2 at 12 mos	9.4%	19.7%	<0.0001	
Median OS (mos)				
N=790	42.3	52.7	0.0006	0.63 (0.48, 0.82)
N=520-HV	32.2	49.2	0.0012	0.62 (0.46, 0.83)
N=270-LV	NR**	NR	0.0836	0.58 (0.31, 1.08)

* CI: confidence intervals; **NR: not reached.

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