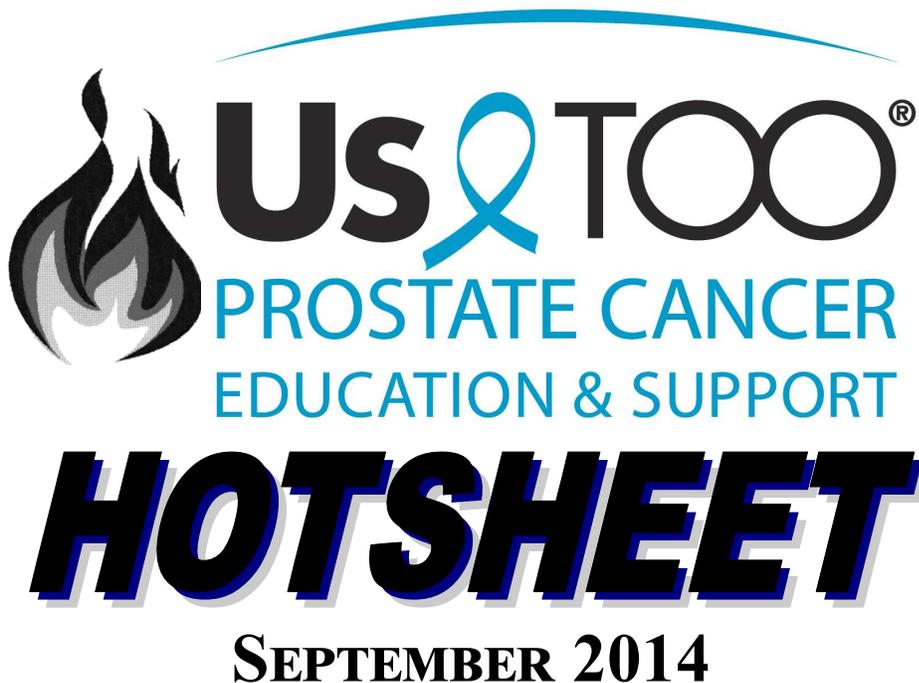


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SEPTEMBER IS PROSTATE CANCER AWARENESS MONTH!

DEPRESSION MAY KEEP SOME MEN FROM FIGHTING PROSTATE CANCER

Depression may be the source of disparities in the treatment men get for prostate cancer, according to a new study. In the analysis, older men who were depressed before they were diagnosed were more likely to have aggressive cancer, less likely to undergo the recommended treatment for their stage and type of disease, and more likely to die.

“We traditionally think of disparities in healthcare by race and socioeconomic status, but our research demonstrates that mental illness can also be a significant driver of treatment choice and outcomes in terms of prostate cancer,” stated study leader Dr. Jim Hu, director of robotic and minimally invasive surgery at the David Geffen School of Medicine at UCLA.

Past research has linked depression to a greater likelihood of getting less aggressive treatment and to poorer survival in other cancers, including breast and liver cancers. But little is known about how depression might affect men’s diagnoses and treatments for prostate cancer, Hu and his colleagues wrote online July 7th in the *Journal of Clinical Oncology*.

The researchers analyzed Medicare data on more than 40,000 men diagnosed with localized prostate cancer between 2004 and 2007 and observed through

(Continued on page 6)

ENZALUTAMIDE IN METASTATIC PROSTATE CANCER BEFORE CHEMOTHERAPY

Beer T, Armstrong A, Rathkopf D, et al on behalf of the PREVAIL Investigators

N Engl J Med 371:424–433, 2014

Background: Enzalutamide is an oral androgen-receptor inhibitor that prolongs survival in men with metastatic castration-resistant prostate cancer (CRPC) in whom the disease has progressed after chemotherapy. New treatment options are needed for patients with metastatic prostate cancer who have not received chemotherapy, in whom the disease has progressed despite androgen-deprivation therapy.

Methods: In this double-blind, phase 3 study, we randomly assigned 1,717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily. The coprimary end points were radiographic progression-free survival and overall survival.

Results: The study was stopped after a planned interim analysis (conducted when 540 deaths had been reported) showed a benefit of the active treatment. The rate of radiographic progression-free survival at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% confidence inter-

(Continued on page 8)

HEALTH CARE COSTS FOR PROSTATE CANCER PATIENTS RECEIVING ANDROGEN DEPRIVATION THERAPY: TREATMENT AND ADVERSE EVENTS

Krahn M, Bremner K, Luo J, Alibhai S

Curr Oncol 21:e457–e465, 2014

Background: Serious adverse events have been associated with androgen deprivation therapy (ADT) for prostate cancer (PCa), but few studies address the costs of those events.

Methods: All PCa patients (ICD-9-CM 185) in Ontario who started 90 days or more of ADT or had orchiectomy at the age of 66 or older during 1995-2005 (n = 26,809) were identified using the Ontario Cancer Registry and drug and hospital data. Diagnosis dates of adverse events-myocardial infarction, acute coronary syndrome, congestive heart failure, stroke, deep vein thrombosis or pulmonary embolism, any diabetes, and fracture or osteoporosis-before and after ADT initiation were determined from administrative data. We excluded patients with the same diagnosis before and after ADT, and we allocated each patient’s time from ADT initiation to death or December 31, 2007, into health states: ADT (no adverse event), ADT-ae (specified single adverse event), Multiple (>1 event), and Final (≤180 days before death). We used methods for Canadian health administrative data to

(Continued on page 8)

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OPTIMIZATION OF PROSTATE BIOPSY IN PATIENTS CONSIDERED FOR ACTIVE SURVEILLANCE: THE ROLE OF THE CONFIRMATORY BIOPSY AND TRANSPERINEAL TECHNIQUES

Fernandez Gomez JM,
Garcia Rodriguez J

Arch Esp Urol 67(5): 409-418, 2014

Objectives: To review the pathological criteria used to select patients for active surveillance, the optimization of biopsies and the role of confirmatory biopsy and of the transperineal approach.

Methods: A bibliographic revision of the last years about active surveillance in prostate cancer as well as prostate biopsy, optimal rebiopsy protocols and transperineal approach has been carried out.

Results: Misclassification of insignificant disease based on pathological criteria of the first standard biopsy range from 20 to 30 percent of men. It is likely that many patients who ultimately progress on active surveillance had at the time of diagnosis more advanced disease that was missed by transrectal ultrasound (TRUS) biopsy. This is the main cause of progression on initial follow-up biopsy within one year of starting active surveillance. Although the role of immediate prostate rebiopsy after the diagnosis of low-risk prostate cancer and has not been well described, repeat biopsy before the initiation of active surveillance performed shortly after diagnosis (six months) identifies most patients who harbor high-grade or more extensive cancers that may not be appropriate for a surveillance strategy.

Conclusions: PSA, PSAD, and number of cores at initial diagnosis are not helpful in predicting misclassification of active surveillance eligibility. The role of MRI for active surveillance remains unclear and the technique of MRI/US fusion biopsy still lacks consensus on a standardized procedure. Patients considering active surveillance should undergo immediate confirmatory biopsy within six months to decrease the risk of substantially underestimating cancer size and grade, even in patients with strict criteria in the initial biopsy and subsequently, to better assess the risk of progression. In this way, most protocols of AS recommend performing volume-based biopsies in the confirmatory procedure. Perhaps, an extensive transperineal template-guided mapping

(Continued on next column —>)

CHARACTERISTICS AND EXPERIENCES OF PATIENTS WITH LOCALIZED PROSTATE CANCER WHO LEFT AN ACTIVE SURVEILLANCE PROGRAM

Berger Z, Yeh J, Carter H, Pollack C
Patient 12 June 2014; Epub

Background: Understanding the experiences of men leaving active surveillance programs is critical to making such programs viable for men with localized prostate cancer.

Objective: To generate hypotheses about the factors that influence patients' decisions to leave an active surveillance program.

Methods: Using data from the Johns Hopkins active surveillance cohort, bivariate analyses and multinomial regression models examined characteristics of men who self-elected to leave, those who stayed in the program, and those who left because of disease reclassification. We interviewed patients who self-elected to leave.

Results: Of 1,159 men in active surveillance, nine percent self-elected to leave. In interviews with a sample of 14 men who self-elected to leave, uncertainty involved in active surveillance participation, existence of personal criteria distinct from providers' clinical criteria and fear of cancer were important factors in decisions to leave.

Conclusion: Men leaving active surveillance were motivated by a number of factors, including patient-defined criteria, which might differ from clinical recommendations. To ensure active surveillance participation, it may be important to address cancer-related anxiety and personal criteria underlying patient decisions.

biopsy (TTMB) procedure could more accurately identify those men with occult significant disease. With confirmatory biopsies to identify a patient group that is unlikely to progress during the first five to 10 years of active surveillance, the need for an intensive biopsy schedule during follow-up of patients undergoing active surveillance might be reduced.

ELEVATED ALKALINE PHOSPHATASE VELOCITY STRONGLY PREDICTS OVERALL SURVIVAL AND THE RISK OF BONE METASTASES IN CASTRATE-RESISTANT PROSTATE CANCER

Metwalli AR, Rosner IL, Cullen J, et al
Urol Oncol 11 June 2014; Epub

Objectives: In patients with a rising prostate-specific antigen (PSA) level during treatment with androgen deprivation therapy, identification of men who progress to bone metastasis and death remains problematic. Accurate risk stratification models are needed to better predict risk for bone metastasis and death among patients with castration-resistant prostate cancer (CRPC). This study evaluates whether alkaline phosphatase (AP) kinetics predicts bone metastasis and death in patients with CRPC.

Methods and Materials: A retrospective cohort study of 9,547 patients who underwent treatment for prostate cancer was conducted using the Center for Prostate Disease Research Multi-center National Database. From the entire cohort, 347 were found to have CRPC and, of those, 165 had two or more AP measurements during follow-up. To determine the AP velocity (APV), the slope of the linear regression line of all AP values was plotted over time. Rapid APV was defined as the uppermost quartile of APV values, which was found to be ≥ 6.3 IU/L/y. CRPC was defined as two consecutive rising PSA values after achieving a PSA nadir < 4 ng/mL and documented testosterone values less than 50 ng/dL. The primary study outcomes included bone metastasis-free survival (BMFS) and overall survival (OS).

Results: Rapid APV and PSA doubling time (PSADT) less than 10 months were strong predictors of both BMFS and OS in a multivariable analysis. Faster PSADT was a stronger predictor for BMFS (odds ratio [OR] = 12.1, $P < 0.0001$ vs. OR = 2.7, $P = 0.011$), whereas rapid APV was a stronger predictor of poorer OS (OR = 5.11, $P = 0.0001$ vs. OR = 3.98, $P = 0.0034$). In those with both a rapid APV and a faster PSADT, the odds of developing bone metastasis and death exceeded 50%.

Conclusion: APV is an independent predictor of OS and BMFS in patients with CRPC. APV, in conjunction with PSA-based clinical parameters, may be used to better identify patients with CRPC who are at the highest risk of metastasis and death. These findings need validation in prospective studies.

PITFALLS OF ROBOT-ASSISTED RADICAL PROSTATECTOMY: A COMPARISON OF POSITIVE SURGICAL MARGINS BETWEEN ROBOTIC AND LAPAROSCOPIC SURGERY

Tozawa K, Yasui T, Umemoto Y, et al
Int J Urol 10 June 2014; Epub

Objectives: To compare the surgical outcomes of laparoscopic radical prostatectomy (RP) and robot-assisted RP, including the frequency and location of positive surgical margins.

Methods: The study cohort comprised 708 consecutive male patients with clinically localized prostate cancer who underwent laparoscopic RP ($n = 551$) or robot-assisted RP ($n = 157$) between January 1999 and September 2012. Operative time, estimated blood loss, complications, and positive surgical margins frequency were compared between laparoscopic RP and robot-assisted RP.

Results: There were no significant differences in age or body mass index between the laparoscopic RP and robot-assisted RP patients. Prostate-specific antigen levels, Gleason sum and clinical stage of the robot-assisted RP patients were significantly higher than those of the laparoscopic RP patients. Robot-assisted RP patients suffered significantly less bleeding ($P < 0.05$). The overall frequency of positive surgical margins was 30.6 percent ($n = 167$; 225 sites) in the laparoscopic RP group and 27.5 percent ($n = 42$; 58 sites) in the robot-assisted RP group. In the laparoscopic RP group, positive surgical margins were detected in the apex (52.0%), anterior (5.3%), posterior (5.3%) and lateral regions (22.7%) of the prostate, as well as in the bladder neck (14.7%). In the robot-assisted RP patients, they were observed in the apex, anterior, posterior, and lateral regions of the prostate in 43.0, 6.9, 25.9 and 15.5 percent of patients, respectively, as well as in the bladder neck in 8.6 percent of patients.

Conclusions: Positive surgical margin distributions after robot-assisted RP and laparoscopic RP are significantly different. The only disadvantage of robot-assisted RP is the lack of tactile feedback. Thus, the robotic surgeon needs to take this into account to minimize the risk of positive surgical margins.

SURVIVAL ANALYSIS OF PATIENTS WITH BIOCHEMICAL RELAPSE AFTER RADICAL PROSTATECTOMY TREATED WITH ANDROGEN DEPRIVATION: CASTRATION-RESISTANCE INFLUENTIAL FACTORS

Algarra R, Hevia M, Tienza A, et al
Can Urol Assoc J 8:E333–E341, 2014

Introduction: We evaluate the prognosis of patients with biochemical recurrence (BCR) treated with androgen deprivation therapy (ADT) and to determine the influential factors to castration resistance (CR) and death.

Methods: From a series of 1,310 patients with T1-T2 prostate cancer treated with radical prostatectomy between 1989 and 2012, 371 had BCR. Patients with lymph node involvement were excluded. We analyzed only the 159 treated with salvage ADT. At the end of the study, 77 (48%) had developed CR.

Results: The median follow-up to CR was 9.2 years. The CR-resistant free survival (RFS) was $76 \pm 3\%$, $62 \pm 3\%$ and $43 \pm 9\%$ in 5, 10 and 15 years, respectively. The RFS median time was 14 years. In the multivariate study, the prostate-specific antigen (PSA) doubling time (PSA-DT) was < 6 months ($p = 0.01$) (hazard ratio [HR] 3; 95% confidence interval [CI] 1.4-6.8, $p = 0.007$); seminal vesicle involvement (HR 3.1; 95% CI 1.5-6.2, $p = 0.01$) and PSA velocity in ng/mL/year (HR 1.3; 95% CI 1.1-1.5, $p = 0.002$) with better cut-off points of 0.84 ng/mL/year ($p = 0.04$) (HR 4; 95% CI 1.7-9.4, $p = 0.001$) were influential variables. Specific survival (SS) at five, 10 and 15 years since surgery was 96 ± 1 , 85 ± 2 and 76 ± 4 , respectively. The time of CR to death was $30 \pm 6\%$ at five years, with the median at 3.2 years. In the multivariate only, Ki-67 (HR 1.04; 95% CI 1.005-1.08, $p = 0.02$) had an independent influence.

Conclusions: In BCR patients treated with ADT, the median to CR was 14 years. PSA-DT < 6 months, PSA velocity (ng/mL/year) and seminal vesicle involvement were influential variables. From the CR, the median time to death was 3.2 years. Ki-67 marker was an independent influence.

FDA ADVISORY PANEL RECOMMENDS AGAINST APPROVAL OF ULTRASOUND THERAPY FOR EARLY PROSTATE CANCER

A Food and Drug Administration advisory panel agreed that a device that thermally ablates the prostate gland using high-intensity focused ultrasound should not be approved for treating men with localized prostate cancer now, because of issues that included no proof of efficacy and a high rate of adverse events for a noninvasive treatment.

At a meeting on July 30, the FDA's Gastroenterology and Urology Devices Panel voted 8-0, with one abstention, that the benefits of the high-intensity focused ultrasound (HIFU) therapy did not outweigh the risks for the proposed indication, the primary treatment of prostate cancer in subjects with low-risk, localized prostate cancer.

Available in Europe for 15 years, the Ablatherm® integrated imaging device is manufactured by EDAP TMS, a French company. The components of the computer-controlled device include a treatment module, a control console, and an endorectal probe that is inserted rectally, heating the target tissue to therapeutic levels, while the patient is under general or spinal anesthesia.

The company describes HIFU therapy as a "minimally invasive treatment during which the Ablatherm device precisely focuses ablative energy on the prostate gland while avoiding damage to sensitive adjacent anatomy."

But in separate questions, the panel unanimously voted that there was not reasonable assurance that the device was effective for the proposed indication. The vote on the safety issue alone was mixed, with panelists voting 5-3, with one abstention, that there was not reasonable assurance that the device was safe for the indication.

The company had problems completing enrollment in the U.S. pivotal trial, which compared HIFU treatment to cryotherapy, and provided several other analyses, including comparisons of the results with data from a registry and other clinical trials. The FDA reviewers raised multiple issues with the data, and panelists agreed, citing issues with safety and efficacy, including the efficacy endpoint used in the pivotal trial.

"I don't think the potential benefits outweigh the risk," said Dr. Eric Klein, chairman of the Glickman Urological and Kidney Institute, at the Cleveland

Clinic. His negative vote on the efficacy question, he noted, "relates mostly to the fact that patients with low-risk prostate cancer are at low risk for progression and being harmed by their disease and there are other management strategies that have lower risk than this proposed therapy."

Dr. Patrick Walsh, professor of urology, Johns Hopkins University, Baltimore, said that "at the present time, I do not believe there's any evidence that efficacy, which has not been proven, outweighs what I look at as significant side effects." Describing a noninvasive treatment that has a 41 percent rate of serious adverse events (which was reported in the U.S. pivotal study) as safe was "excessive," he added.

Another panelist, Dr. Marc Garnick, professor of medicine, Harvard Medical School, Boston, said that he appreciated the technologic advance that HIFU represents and acknowledged the difficulties involved in studying the treatment in the low-risk population. However, as a practicing physician who counsels many patients with early-stage, low-risk cancer trying to make a decision about primary therapy versus active surveillance, he said it "would be very, very difficult for me to make a recommendation for HIFU therapy if one takes a look at the metastasis-free survival and the cancer-specific survival in patients with low-risk features that basically don't get any therapy and compared that to some of the vagaries of the safety considerations that they would be subjected to with HIFU."

The U.S. pivotal study was a nonrandomized, multicenter prospective study comparing HIFU to cryotherapy in patients with low-risk, localized prostate cancer (a prostate-specific antigen level of 10 ng/mL or less, clinical stage T1 to T2a cancer, and a Gleason score of 6 or less). But the study was not completed because of problems enrolling patients, and only 135 patients were enrolled in the HIFU arm and five in the cryotherapy arm, instead of 205 patients in each arm, as planned.

Among the 135 HIFU-treated patients, the primary endpoint, biochemical relapse-free survival (based on the Phoenix criteria for biochemical recurrence, the nadir PSA level plus 2.0 ng/mL) at two years was 90.5%, and the cumula-

tive positive biopsy rate was 28 percent.

Other analyses provided by the manufacturer included a comparison of long-term follow-up data on a subgroup of 227 patients from a European registry of patients treated with Ablatherm HIFU, who met the criteria of those on the pivotal study, with outcomes among 148 patients with low-risk prostate cancer in the radical prostatectomy arm of the U.S. Veterans Affairs PIVOT (Prostate Cancer Intervention Versus Observation Trial). PIVOT investigators compared radical prostatectomy with observation among men with clinically localized prostate cancer; the trial was conducted between 1996 and 2002. Metastases were reported in three of the 227 HIFU-treated patients (1.3%) and in six of 148 (4.1%) of those in PIVOT. The cumulative risk at eight years was similar in both groups, 1.1 percent among those treated with HIFU and 1.4 percent among the low-risk PIVOT patients.

In the pivotal study, almost all of the patients (97%) treated with HIFU had an adverse event; 82 percent had a moderate or severe adverse event. Adverse events included erectile dysfunction in 67 percent, urinary retention in 49 percent, urinary incontinence in 39 percent, urinary stricture in 35 percent, urethral injury in 15 percent, and bowel dysfunction in 21 percent. Most of these adverse events resolved in most patients over time, but at 24 months, 44 percent of treated patients still had erectile dysfunction.

The FDA reviewers said that it was unclear whether HIFU therapy provides a benefit for patients with low-risk prostate cancer, and said that they were concerned about the 28 percent positive biopsy rate in the pivotal trial.

Based on the evidence provided, "we can conclude that a single whole-gland HIFU treatment session does not get rid of all the cancer within the prostate gland in a significant percentage of patients," said one of the FDA reviewers, Dr. Jonathan Jarow of the FDA's office of hematology and oncology products in the FDA's Center for Drug Evaluation and Research. "The FDA has never approved a treatment for prostate cancer based on PSA results," he pointed out.

Panelists generally agreed that the biochemical survival rate at two years using the Phoenix criteria could not be used to

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THE BEST COURSE OF ACTION AFTER PROSTATE CANCER SURGERY INDICATED BY GENOMIC ANALYSIS

There is controversy over how best to treat men after they've undergone radical prostatectomy (RP) for prostate cancer. Does one wait until the cancer comes back or provide men with additional radiation therapy (RT) to prevent cancer recurrence? Now, a new study from Thomas Jefferson University shows that a genomic tool can help doctors and patients make a more informed decision.

"We are moving away from treating everyone the same," says first author Robert Den, MD, Assistant Professor of Radiation Oncology and Cancer Biology at Thomas Jefferson University. "Genomic tools are letting us gauge which cancers are more aggressive and should be treated earlier with RT, and which ones are unlikely to benefit from additional therapy."

Although RP for prostate cancer is meant to be curative, in some men, the cancer can regrow. Doctors have developed high risk criteria based on clinical factors, but these criteria are imperfect predictors of cancer returning, or recur-

(Continued on page 6)

HIFU®

(Continued from page 4)

show the treatment was effective for a non-radiation treatment in patients with low-risk prostate cancer, pointing out that the criteria had not been validated with this technology. Several panelists said that the device might be effective but that it was not possible to determine that with the available data.

In a statement issued by EDAP after the meeting concluded, Marc Oczachowski, the company's chief executive officer, said that the company "will continue to work diligently with the FDA as it carefully completes its final review" of the Ablatherm HIFU application. The device has been used to treat about 40,000 patients with low-risk disease worldwide, according to EDAP.

The FDA usually follows the recommendations of its advisory panels.

Panel members have been cleared of potential conflicts.

Family Practice News, 31 July 2014

DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN

"Get your flu shot now to reduce your risk of dying from cardiovascular disease? Yes! How about the Shingles vaccine? Yes! Moyad has lost it!"

Mark A. Moyad, MD, MPH, Univ. of Michigan Medical Center, Dept. of Urology

Editor's note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Bottom Line:

Please get you annual flu shot now (not later in the year because it takes one-two months to be fully effective) to reduce your risk of dying from cardiovascular disease, which is the leading cause of death in U.S. for only (sarcasm city and I am the mayor) 114 of the last 115 years and the number one or two cause of death in prostate cancer patients. Oh, and you should also get a flu shot because it can reduce your risk of the flu and complications from the flu which causes tens of thousands of deaths a year from pneumonia. Oh, and you should also get a flu shot because most pharmacies and doctor's offices give kids candy after the shot and you can steal some for yourself when the health care professional is not looking! I love those mini-tootsie rolls more than life itself! When will they sell them as an IV treatment option to improve overall mood?

In one of the largest reviews of the influenza vaccines and cardiovascular outcomes, two investigators looked at six randomized trials and found strong reduction in future cardiovascular events in those that were vaccinated.

It has been known for some time that influenza infections could be an independent risk factor for fatal and non-fatal cardiovascular events, but no one is sure why. It is possible that an infection could be the stimulus to rupturing of a vulnerable blood vessel plaque, and/or change the way the heart beats, and/or increase fluid overload in those with heart failure, and/or increase inflammation of the heart blah blah blah... There are many ways the "flu" can do this but still only 33-50% of eligible folks, including those with cardiac disease, get the flu shot.

Let me quote the researchers after looking at all these studies.¹ "Still, despite differences in trial designs, risk of bias, sample size, cardiovascular risk of participants, circulating influenza activity, vaccination strategy, duration of follow-up, and number of observed events, our meta-analysis demonstrated a consistent association between influenza vaccina-

tion and a lower risk of cardiovascular events." WOW! In fact, the higher the risk of a future cardiovascular event the more likely the benefit! By the way, another recent review of a small number of studies of cancer patients receiving a flu shot despite being immune suppressed also found a reduction in the risk of mortality with the vaccine!² WOW AGAIN! If that isn't enough I even believe the shingles vaccine may even reduce the risk of stroke from new research!³

It is September, which means you should be getting your flu shot now, and if you qualify for the shingles vaccine (50+ even if you have had shingles before) then also go in and get that one—pretty please with tootsie rolls on top!

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3. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. *Clin Infect Dis* 2014;58:1497–1503.



DEPRESSION MAY KEEP SOME MEN FROM FIGHTING PROSTATE CANCER

(Continued from page 1)

2009, including 1,894 who were also diagnosed with depression during the two years before their cancer was detected.

“First, we found that men with prostate cancer who were older, lower income, with more medical (conditions), white or Hispanic (versus Black and Asian), unmarried, residing in nonmetropolitan areas were more likely to be depressed,” Hu said. “In addition, depressed men were less likely to seek out definitive therapy (surgery or radiation) in contrast to non-depressed men,” he said. After adjustment for differences in tumor characteristics and chosen treatments, depressed men had worse overall survival compared to men who were not depressed, Hu noted.

Hu was surprised by the results because depressed men were more likely to see physicians in the two years before their prostate cancer diagnosis compared to non-depressed men (an average of 43 times versus 27 times, respectively). The team also found that depressed men were more likely to opt for expectant management.

It’s possible, Hu and his colleagues write, that depression makes men less interested in screening, leading to their cancers being diagnosed at a later stage, and makes them choose less aggressive treatment. The greater number of doctor visits might be focused on mental illness, leading to less attention toward cancer screening.

These findings cannot prove there’s a cause and effect at work, the authors caution. However, they suggest that physicians should take care to ensure prostate cancer patients are getting the

mental health treatment they need so depression doesn’t bias a patient’s treatment choices and chances for survival.

“Mental health is an important aspect of prostate cancer care,” said Dr. Behfar Ehdai, a surgeon at Memorial-Sloan Kettering Cancer Center in New York, who was not involved in the study. “Given the prevalence of depression in these men, survivorship in that light has been underreported in the literature.”

“We know that men who are diagnosed with prostate cancer have an increased risk of suicide - this was shown in a Swedish study looking at men from Sweden,” he told Reuters Health. “This adds more data from the United States, specifically looking at men age 67 and older, that also demonstrates that mental health should be assessed and be part of our prostate cancer care,” he said.

But Ehdai emphasized that this study does not suggest the less aggressive approach of expectant management is associated with poor outcomes, or that depression increases the risk of dying from prostate cancer. “The endpoint evaluated is overall survival, and we do know that from previous studies, depression is associated with cardiovascular events, for example, which are also associated with increased risk of mortality,” Ehdai said. “That distinction between deaths from prostate cancer or progression of the disease, and overall deaths from any cause is important,” he added.

Ehdai said that future studies are needed to determine the impact of mental health issues on treatment decision making, especially in men with intermediate - or high-risk disease who appear not to be receiving the appropriate treatment.

“As healthcare providers, we need to be aware of the greater risk for aggressive prostate cancer in depressed men,” Hu said. “Additionally, depressed men may require special attention in light of the lower initiative to follow through with physician recommendations.”

Hu added that encouraging depressed men with prostate cancer to join prostate cancer support groups may help spur them to pursue recommended treatments.

Reuters Health, 22 July 2014

GENOMIC TESTS POST-SURGERY

(Continued from page 5)

rence. Only about 50 percent of high risk men ever go on to develop metastases, raising the question of whether those who receive additional therapy are being overtreated.

In an attempt to better understand how to treat their patient population, researchers led by Drs. Den and Adam Dicker, MD, PhD, Chairman of the Department of Radiation Oncology at Jefferson, together with other members of the Kimmel Cancer Center Genitourinary team including Dr. Leonard Gomella, Chairman of the Department of Urology, assessed whether a genomic test designed to predict prostate cancer metastasis could also predict which men would most benefit from RT after RP.

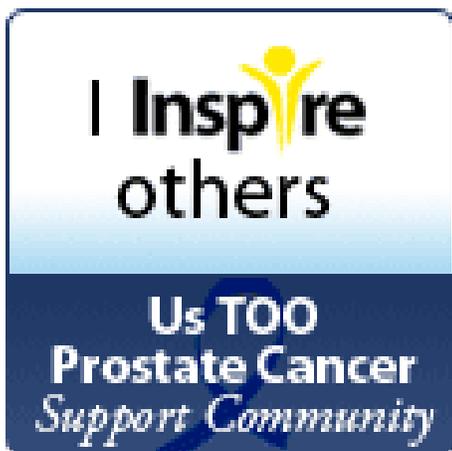
The test, called Decipher, from the genome diagnostics company GenomeDx, generates a gene signature from a patient’s cancer tissue sample. Based on this signature, the test stratifies men into high-, intermediate- and low-risk for cancer recurrence and metastases.

The researchers tested the genomes from tumor samples of 139 men who had received RT following RP at Jefferson. Using medical records, the researchers grouped the men by the treatments they received after surgery, and matched their records to the results of the genomic analysis.

The genomic analysis correctly predicted outcomes. Men with a high Decipher score were more likely to develop metastases than those with a low score. In addition, those with a high Decipher score who received RT earlier had longer survival than those who did not receive RT immediately after surgery. The results showed that men treated with RT after RP maintained low PSA levels for twice as long as those who were not treated with RT.

“Our analysis suggests that genomic analysis scores could be used, in concert with other diagnostic measures such as PSA testing, to help determine which patients would benefit from additional radiation therapy and more aggressive measures, and which are less likely to benefit,” says Dr. Den.

Medical News Today, 1 August 2014



DOCTOR CHODAK’S BOTTOM LINE (Ref Key: article #, page #, column #)

Gerald Chodak, MD Author, *Winning the Battle Against Prostate Cancer*, Second Edition <http://www.prostatevideos.com>

Editor’s note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

a1p1c1 Little is known about the impact of depression in men with prostate cancer. Hu and co-workers conducted a retrospective analysis of men in the SEER database to assess if a diagnosis of depression had any impact on overall mortality. They did find some correlation; depressed men with intermediate risk or high-risk cancer had a worse survival than men without a recent diagnosis of depression. The authors acknowledge that their findings do not prove there is a cause and effect relationship and the higher mortality in depressed men may have nothing to do with their prostate cancer. Also, the authors did not find that prostate cancer mortality was higher in the depressed men. Nevertheless, doctors treating prostate cancer should be on the lookout for men with depression to ensure they are adequately treated following a diagnosis of prostate cancer.

The Bottom Line: A history of depression in a man diagnosed with prostate cancer may be a warning sign that needs careful attention as part of the overall disease management program.

a2p1c2 This month’s *HotSheet* contains information about the very important PREVAIL study comparing enzalutamide to placebo in men with metastatic disease who had not yet received chemotherapy. The important finding was that enzalutamide improved overall survival in addition to showing improvement in time to a skeletal related event such as bone pain or fracture. It also delayed the time until cytotoxic chemotherapy. The treatment was well tolerated with an acceptable level of side effects. We can expect that the FDA likely will grant approval for this drug in this setting, which will further complicate the choice of treatment for men with CRPC. Approved therapies include Provenge® and abiraterone acetate plus prednisone. The addition of enzalutamide will lead doctors to question which one should be used first, second or third. Studies are definitely needed to determine if one sequence offers any advantage.

The Bottom Line: We can expect the FDA will approve enzalutamide for CRPC pre-chemotherapy in the near future resulting in an even greater need to determine the optimal sequence of approved therapies for these men.

a3p1c3 For years, men with non-metastatic prostate cancer have been treated with androgen deprivation therapy (ADT) despite any proof that it may be beneficial. Recently, however, a randomized study was reported showing no benefit and a significant incidence of side effects. Now the impact of ADT on overall health care costs provides an additional reason to withhold this treatment in men with non-metastatic disease. Krahn and co-workers recently analyzed data from men in Canada who received ADT and quantified the cost consequences of treating the various side effects. They found it increased the overall cost of management by 100-265 percent.

The Bottom Line: Lack of efficacy and the added cost of treating side effects are two strong reasons to avoid ADT in men with non-metastatic prostate cancer.

a4p2c2 Improving the selection criteria is another opportunity to keep more men on active surveillance (AS). One option discussed by Fernandez, et al is to employ confirmatory biopsies when random biopsies were used to make the diagnosis. Alternatives include saturation biopsies or MRI directed biopsies. Genetic testing may be a better solution and studies are now testing a variety of genes.

The Bottom Line: New methods are needed to select optimal patients for AS.

a5p2c3 As more men select AS over immediate treatment for localized prostate cancer, a growing problem is that a number of men choose to stop this approach and undergo definitive therapy for reasons other than worsening of their cancer. Understanding those reasons is a first step toward trying to help men remain on AS unless their cancer changes. That is the subject of a small group of men on this therapy from Johns Hopkins. Berger and co-workers identified at least two items cited by a small group of men; their own criteria for worsening of their disease, which differed from that of the doctor, and anxiety. Although the study sample is small, it begins to identify opportunities that might be addressed by clinical staff when a man selects this therapy. Clearly more work is needed in this area.

The Bottom Line: Anxiety and patient’s own criteria are two areas that can be addressed by the clinician if a man selects AS to help him remain on that treatment approach.

a6p3c1 One test that has lost favor among doctors treating progressive prostate cancer is alkaline phosphatase (AP). A study by Metwalli et al retrospectively reviewed relationships between AP and found that the rate of rise of AP and PSA velocity both predicted a poor outcome. However, another study looking at AP also measured N-telopeptide and found that the latter marker was an even better predictor of overall survival.

The Bottom Line: Although changes in AP may be helpful in managing men with progressive disease, it is unclear how well it would perform when compared to N-telopeptide. More prospective studies are needed to further understand any potential role of these markers in managing men with advanced disease.

a7p3c2 Laparoscopic vs. robotic radical prostatectomy (RP) – is one better than the other? Tozawa, et al addressed that question in a non-randomized comparative study. The authors found differences in the rate of positive surgical margins. Unfortunately, several confounding factors could explain these results such as different experience of the surgeons and variations in the size of the tumor given the time differential of when cases were accumulated.

The Bottom Line: Laparoscopic and robot-assisted radical prostatectomies both have merits but without a randomized study, the relative merits cannot be determined.

Advanced Prostate Cancer Resource Kit

Us TOO International Prostate Cancer Education & Support Network is Here for You

If you're looking for valuable knowledge and perspective to help you manage your advancing prostate cancer, the information in this kit will be of great interest to you. Available online or in print, it's one of the many resources from Us TOO that will help you ask the right questions, evaluate your options, and make choices that are best for you and your family. You can also attend a local support group meeting, access our website and online discussion communities, read our monthly newsletters, or call us to request whatever assistance you need.

The mission of Us TOO International is to help men and their families make informed decisions about prostate cancer detection and treatment through support, education and advocacy. Us TOO was started as a 501(c)3 not-for-profit organization in 1992 by prostate cancer survivors to serve prostate cancer patients and their families. Inspired by the progress made in the fight against breast cancer, they recognized that "Cancer affects us, too."

Us TOO is the leading non-profit organization focused solely on prostate cancer, pre-to-post support, education and advocacy. Through a network of 325 support group chapters throughout the United States and in numerous cities around the world, Us TOO provides free resources for every phase and aspect of the disease. For more than 20 years the collective effort of the organization's leadership and tireless energy from volunteers around the world have helped exceed the lives and improve the quality of life for thousands of men battling prostate cancer.

Advancing Disease: This kit was created to address the increasing number of requests for information specific to advancing disease. Most men with advancing disease have been managing their prostate cancer for some time and are familiar with the basic information surrounding the disease including anatomy, initial treatment options, and side effects from those treatments. Therefore, the material in this kit is focused on providing you with accurate, unbiased information that's most relevant and most useful to help you make the best decisions for effectively managing your advancing prostate cancer.

ENZALUTAMIDE

(Continued from page 1)

val [CI], 0.15 to 0.23; P <0.001). A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data-cutoff date (29% reduction in the risk of death; hazard ratio, 0.71; 95% CI, 0.60 to 0.84; P <0.001). The benefit of enzalutamide was shown with respect to all secondary end points, including the time until the initiation of cytotoxic chemotherapy (hazard ratio, 0.35), the time until the first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs. 5%), the time until prostate-specific antigen (PSA) progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) (P <0.001 for all comparisons). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment.

Conclusions: Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer.

HEALTHCARE COSTS OF ADT

(Continued from page 1)

estimate annual total health care costs during each state, and we examined monthly trends.

Results: Approximately 50% of 21,811 patients with no pre-ADT adverse event developed one or more events after ADT. The costliest adverse event state was stroke (\$26,432/year). Multiple was the most frequent (n = 2,336) and the second most costly health state (\$24,374/year). Costs were highest in the first month after diagnosis (from \$1,714 for diabetes to \$14,068 for myocardial infarction). Costs declined within 18 months, ranging from \$784 per 30 days (diabetes) to \$1,852 per 30 days (stroke). Adverse events increased the costs of ADT by 100% to 265%.

Conclusions: The economic burden of adverse events is relevant to programs and policies from clinic to government, and that burden merits consideration in the risks and benefits of ADT.



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