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Affected by Prostate Cancer?



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Hot SHEET

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Multiparametric MRI Avoids Many Biopsies but Misses a Few Cancers Compared with TRUS-Guided Biopsied

Use of multiparametric MRI (MP-MRI) as follow-up to a suggestive PSA test or digital rectal exam (DRE) reduced prostate biopsies by 73% but identified fewer prostate cancers compared with upfront transrectal ultrasound (TRUS)-guided biopsy, a decision-tree analysis showed. For every 100 men evaluated, MP-MRI led to 73 fewer biopsies and identified 16 prostate cancers. TRUS-guided biopsy, by definition, required biopsy of all 100 men and led to the

diagnosis of 20.4 prostate cancers. Assuming a background cancer prevalence of 24%, reliance on MP-MRI would have missed twice as many cancers.

The estimated cost per 100 men was \$90,400 for TRUS-guided biopsy versus \$87,700 for MP-MRI, as reported at the 2015 American Urological Association (AUA) annual meeting.

"Multiparametric MRI substantially reduced the number of biopsies and was cost equivalent to the TRUS biopsy arm for the base case," said lead author Ahmed Haddad, MD, a fellow at the University of Texas Southwest-

ern Medical Center in Dallas. "Multiparametric MRI missed a small number of cancers as compared with TRUS biopsy, and further studies are needed to determine the clinical significance of the missed cancers."

More than one million TRUS-guided biopsies are performed annually in the United States in follow-up to an abnormal PSA test or DRE. TRUS-biopsies are associated with discomfort and carry a risk of potentially serious complications, such as sepsis. Improvements in MRI technology, such as the development of multiparametric al-

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Urine Assay Shows Promise as Test for High-Grade Prostate Cancer

A urine assay that targets expression of exosomal messenger RNA (mRNA) demonstrated high negative predictive value for high-grade prostate cancer in a study that validates the emerging test as a tool to help determine whether patients need initial biopsies, according to a report at the 2015 American Urological Association (AUA) annual meeting in New Orleans.

Use of the EXO106 test should reduce prostate needle biopsies by 27% while missing fewer than 5% of higher-grade Gleason score (GS) $\geq 4+3$ cancers, researchers indicated.

"Exosomal mRNA can be isolated and analyzed, using a first-catch, random urine," said principal investigator James M. McKiernan, MD, a professor of Urology and director of urologic oncology at New York-Presbyterian Hospital/Columbia University Medical Center in New York. "The EXO106 provides a high negative predictive value for high-grade cancer."

"The assay demonstrated significantly better diagnostic performance compared with prostate-specific antigen (PSA) testing alone or PSA plus standard clinical characteristics," he added.

"Exosomes are secreted by virtually all cells into biological fluids, as a means of cellular communication. They are lipid bilayer-protected vesicles that remain stable under varying conditions and afford protection for their contents against degradation. Exosomes contain multiple forms of RNA, as well as DNA and protein," said McKiernan.

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Chemo + ADT Still Winning in Prostate Cancer

Men with advanced prostate cancer lived significantly longer if they received upfront docetaxel chemotherapy in addition to androgen deprivation, results of a randomized trial showed.

As compared with men who received only androgen deprivation therapy (ADT), those who also got docetaxel had a 10-month improvement in median overall survival (OS). The difference translated into a 24% reduction in the mortality hazard. Subgroup analysis showed that patients with metastatic disease at the start of treatment derived even greater benefit from docetaxel, a 22-month improvement in median OS.

The study is at least the third reported within the past year showing a significant survival benefit with upfront docetaxel, making a strong case for standard of care, as reported during a press briefing prior to the American Society of Clinical Oncology (ASCO) meeting, which began on 29 May 2015.

"Our headline conclusion would be that docetaxel would be considered routine therapy for men with newly diagnosed metastatic disease," said Nicholas James, MD, of the University of Warwick and Queen Elizabeth Hospital in Birmingham, UK. The addition of zoledronic

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Statins May Slow Prostate Cancer Progression

Statins, widely used to lower cholesterol levels, may also slow the progression of prostate cancer in patients receiving androgen deprivation therapy (ADT), a new study suggests.

Among 926 men undergoing ADT for advanced prostate therapy, those taking statins saw significant benefits, researchers said. Their cancers remained stable for an average of 27.5 months before disease progression, compared with an average of 17.4 months among men not taking statins.

"These findings are preliminary, so I would not recommend that everybody start on statins to slow prostate cancer," said study senior author Dr. Philip Kantoff, chief of solid tumor oncology at the Dana-Farber Cancer Institute in Boston. He also cautioned that these findings apply only to men who have advanced prostate cancer that has relapsed after hormone therapy. "This does not speak to early-stage prostate cancer or whether statins are beneficial in preventing prostate cancer," he said.

Men in the study, conducted from 1996 to 2013, were followed for nearly six years on average. The report was published May 7 online in *JAMA Oncology*.

ADT is the usual treatment for men suffering from prostate cancer that has spread beyond the prostate gland. ADT deprives the body of testosterone, the male hormone that helps cancer cells grow. However, over time, the therapy becomes less effective and the cancer begins to grow again.

Essentially, Kantoff explained, statins keep testosterone from entering cancer cells. "They block dehydroepiandrosterone sulfate (DHEA-

S), a precursor of testosterone, thus preventing cancer cell growth," he said. More specifically, lab experiments indicated that statins use up the available supply of a protein called SLCO2B1, that allows drugs and hormones to enter cells. This appears to keep DHEA-S from the cancer cells, making ADT more effective.

"This is a plausible mechanism by which a statin may have a benefit to prostate cancer patients," Kantoff said. "Adding a statin to hormone therapy may be a way to make hormone therapy last longer and prevent cancer from progressing," he added. Kantoff added the disclaimer that more studies are needed to verify their findings. "We have a strong hypothesis, but it is by no means proof that statins prolong the time to relapse. But the data is

Best Evidence Yet: Ejaculation Reduces Prostate Cancer Risk!

Good news, men: you may be able to decrease your risk for prostate cancer by ejaculating — frequently, according to research presented here at American Urological Association (AUA) 2015 Annual Meeting.

The frothy advice is not new but is now backed up by the "strongest evidence to date" on the subject, according to lead author Jennifer Rider, ScD, MPH, an epidemiologist at the Harvard T.H. Chan School of Public Health in Boston. "There is no modifiable risk factor for developing prostate cancer," Dr. Rider told Medscape Medical News. "It would be exciting to tell men that there was a way to modify their risk."

However, she noted that these are observational data and urged caution when "interpreting them."

strongly suggestive that that's the fact," he said.

Dr. Jorge Ramos, a hematology and oncology fellow at the University of Washington/Fred Hutchinson Cancer Research Center, and co-author of an editorial accompanying the study, discussed the study's relevance. "Other studies have suggested that statins might have a role in preventing cancer or reducing the risk of dying from cancer," he said.

"Statins by themselves probably won't prevent cancer from growing, but in combinations with other treatments could improve outcomes for patients," he stated. However, Ramos agreed clinical trials are needed before people start taking statins to prevent or slow cancer.

HealthDay News

The results are "fascinating," said Jesse Sammon, MD, a urologist at the Henry Ford Hospital in Detroit, who attended Dr. Rider's presentation. "It was the highlight of the session on cancer epidemiology; the moderator called it the 'study most likely to be tweeted'." These are "incredibly high-quality data," added Sammon, who was not involved with the study.

The data come from nearly 32,000 men in the prospective Health Professionals Follow-up Study, who now have been followed for 18 years. During the study period, 3,839 men have been diagnosed with incident prostate cancer, 384 cases of which were lethal.

At recruitment in 1992, all participating men were asked to report their average

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Doc Moyad's What Works & What is Worthless Column, Also Known as "No Bogus Science" Column –

"Ginseng Shoots and Scores Again Against Cancer-Related Fatigue (CRF)!!!"

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

Editor's Note: Us TOO invites certain physicians and others to provide information and commentary for the *Hot SHEET* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

Bottom Line:

A Mayo Clinic initiated major clinical trial previously demonstrated that American Ginseng at a dosage of 2000 mg per day (3-5% ginsenosides = active ingredients) significantly reduced cancer-related fatigue (CRF) in eight weeks, and now a smaller study from MD Anderson Cancer Center just demonstrated a significant reduction in CRF and improved quality of life and appetite and sleep in just one month with Panax ginseng (similar to American but with slight differences)! How awesome is this!!!^{1,2}

What is more awesome than Coach Jim Harbaugh at Michigan? Almost Nothing! However, what is definitely awesomerrr (I just made up that word and I love it) is the ongoing research with ginseng to reduce cancer-related fatigue (CRF)!!! This is a fabulous story my friends and enemies! So, the next time someone tells you that a dietary supplement cannot help cancer patients then you should tell that person that they are grossly misinformed and should be punished (aka should buy a round of expensive beers for Dr. Moyad). A few years ago 2,000 mg of American Ginseng (3% ginsenosides and another CRF trial by this group used a 5% ginsenoside 1,000 mg per day product³) demonstrated an ability to significantly reduce CRF in patients being treated for a variety of cancers including breast, prostate... and side effects were similar to the

placebo. They utilized a "pure ground root" ginseng product from the Ginseng Board of Wisconsin (just go to their website ginseng-board.com and you will see an article on the trial and how to purchase the product), which is the one I recommend and I have ZERO affiliation or relationship with this company, but just believe that we need to copy what worked from the research. Hey-just like with prescription drugs folks! Now, a small trial from MD Anderson Cancer Center (seems like a reputable place like the Mayo Clinic...sarcasm alert) using 800 mg per day of Panax or Asian ginseng (similar but not exactly the same as American ginseng with a 7% or more ginsenoside concentration from Indena S.p.A. Milan, Italy... Gratz!) in 30 patients significantly reduced fatigue and improved quality of life and

this also appeared to then improve sleep and appetite and other issues related to CRF in 30 days! What is the catch? There was no placebo arm in this study but these findings are consistent with what has been demonstrated against placebo from other studies (such as the Mayo clinic trials). In other words, CRF can be tough to deal with from androgen deprivation treatment (ADT) to Xtandi to Zytiga to chemotherapy... and now ginseng appears to be one of the only safe and low-cost options that cancer doctors are just now beginning to endorse! How awesomerrr is that!!! Man, I love this stuff!

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2. Yennurajalingam S, et al. Integrative Cancer Therapies 2015, Epub ahead of print.
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Prostate Tumors with Genetic Abnormalities Respond to Olaparib

Olaparib (Lynparza) achieved encouraging response rates in men with metastatic prostate cancer, particularly those with mutations in genes involved in DNA repair (BRCA2 and ATM, most commonly). If validated, these results of the TOPARP-A trial will usher in the first drug targeted to somatic or germline mutations for prostate cancer.

Olaparib is approved for the treatment of ovarian cancer and inherited BRCA mutations. This is the first trial to suggest this drug can benefit men with similar genomic abnormalities and prostate cancer.

"TOPARP-A was initiated to show the anticancer effect of the PARP (poly ADP-ribose polymerase) inhibitor olaparib in men with metastatic castration-resistant prostate cancer (mCRPC) and identify a molecularly distinct subgroup of patients that responds to the drug. These are potentially the first clinical data supporting molecular stratification of treatment for prostate cancer, and we are testing this idea in the second stage of

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Androgen Deprivation Therapy May Lead to Cognitive Impairment in Prostate Cancer Patients

Cognitive impairment can occur in cancer patients who are treated with a variety of therapies, including radiation therapy, hormone therapy, and chemotherapy. This side effect, when occurring with chemotherapy, is commonly referred to as "chemobrain." Signs of cognitive impairment include forgetfulness, inability to concentrate, trouble multitasking, and issues with information processing. It is estimated that 15% to 70% of cancer patients experience some kind of cognitive impairment as a result of treatment.

There have been several studies analyzing this side effect in breast cancer patients, but few have investigated cognitive impairment following androgen-deprivation therapy (ADT) for men being treated for prostate cancer. A new Moffitt Cancer Center study indicates that men who are on ADT have greater odds of experiencing impaired cognitive function. These results were published by Gonzalez et al in the Journal of Clinical Oncology, published online before print 11 May 2015.

About 44% of prostate cancer patients undergo ADT at some point in their treatment, and it is often used on an open-ended basis for advanced prostate cancer.

In this study, researchers compared the cognitive ability of 58 prostate cancer patients receiving ADT with 84 prostate cancer patients who did not receive ADT and 88 men without cancer. The research showed that the men treated with ADT were 70% more likely to experience cognitive impairment at 6 months and more than

Olaparib

(Continued from page 3)

this trial, TOPARP-B. For TOPARP-B, we are enrolling only patients who screen positive for the DNA repair mutations linked to response in TOPARP-A," said presenting author Joaquin Mateo, MD, Clinical Research Fellow at the Institute of Cancer Research and The Royal Marsden NHS Foundation Trust in London, speaking at the annual meeting of the American Association for Cancer Research (AACR). TOPARP-A enrolled 50 men with mCRPC, all of whom progressed after prior treatment, including taxanes. No man was previously exposed to platinum chemotherapy or a PARP inhibitor. These men were unselected for genetic abnormalities. Men were biopsied and underwent repeat biopsy after treatment. Whole-exome sequencing was performed after the response rate was determined. Among 49 men with evaluable data, 16 had a response to olaparib, for an overall response rate of 32.7%. Six men had confirmed radiologic responses, according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria, and 11 men had a PSA decline >50%. "The majority of men had responses for more than six months; four men responded for more than a year; and five men are still on therapy," Dr. Mateo said. Next-generation sequencing identified mutations in genes associated with DNA repair in biopsies from bone marrow and metastases, including BRCA2 and ATM genes, in tumor tissue from 16/49 evaluable men. Of these 16 mutation-positive patients, 14 (88%) responded to olaparib. Most of the mutations were somatic, developing in the

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Chemo-ADT Combo Still Winning in Prostate Cancer (Continued from page 1)

acid (ZA) to ADT and docetaxel improved survival but not significantly so compared with docetaxel alone, he added. The addition of ZA alone did not improve OS or failure-free survival (FFS).

"For nonmetastatic disease, there remains uncertainty as to whether there is a survival benefit or not, but it certainly increased FFS by a substantial amount," James continued. "So we would argue that docetaxel should be considered for selected men with high-risk nonmetastatic disease in view of the substantial prolongation of FFS."

For years, ADT has represented front-line therapy for men with advanced prostate cancer. The demonstrated survival benefit of docetaxel (Taxotere®) in castration-resistant prostate cancer led to speculation that upfront use of the taxane might offer benefits to men with advanced disease and no prior exposure to ADT.

To examine the impact of upfront docetaxel in hormone-naïve advanced prostate cancer, investigators throughout the UK randomized 3,000 men 2:1:1:1 to four treatment groups: ADT alone, ADT plus docetaxel, ADT plus ZA, or ADT plus docetaxel and ZA.

Eligibility criteria allowed for enrollment of men who had high-risk, locally advanced disease; lymph node-positive disease; metastatic disease; and men with aggressive post-treatment relapse, defined as rapid rise in PSA level or baseline PSA >20 ng/mL. Men had a median age of 65 and a median PSA of 65 ng/mL. James said 61% of the patients had metastatic disease, 14% had nodal involvement but no distant metastases, and 22% had neither nodal involvement nor metastasis.

The primary endpoint was OS. The data showed no beneficial effect of zoledronic acid on the primary endpoint, so James focused on the comparison of ADT alone vs. ADT plus docetaxel. After a median follow-up of 42 months, the docetaxel-ADT group had a median OS of 77 months versus 67 months for the men who received only ADT (HR 0.76, 95% CI 0.63-0.91, P=0.003). Analysis of failure-free survival (a secondary endpoint) showed a 38% reduction in the hazard for progression or death (HR 0.62, 95% CI .54-0.70).

A subgroup analysis showed that men who were free of distant metastasis at enrollment (M0) did not derive a significant survival benefit from the addition of docetaxel (HR 1.01, 95% CI 0.65-1.56). Men who had metastatic disease (M1) had a 27% improvement in survival (HR 0.73, 95% CI 0.59-0.89) and drove the survival benefit (43 versus 65 months).

James pointed out that 93 patients in the M0 subgroup had died during follow-up, too few deaths to reach definitive conclusions about the potential survival benefits of docetaxel in that subgroup of patients. "About 40 percent of the patients are M0. The M0 analysis is not fully powered up," he said. "There's a high degree of uncertainty as to where the real study of the hazard ratio of the M0 patients will turn out to lie."

The analysis of FFS showed a significant advantage for the docetaxel group overall and in men who had no distant metastases (HR 0.57, 95% 0.42-0.76) or who had metastatic disease at enrollment (HR 0.62, 95% 0.54-0.73).

"The growing data supporting upfront chemotherapy reflects a major shift in

the historical view of clinical management of advanced prostate cancer, as it primarily affects a population of older men," said moderator Gregory Masters, MD, of the Helen F. Graham Cancer Center in Wilmington, DE.

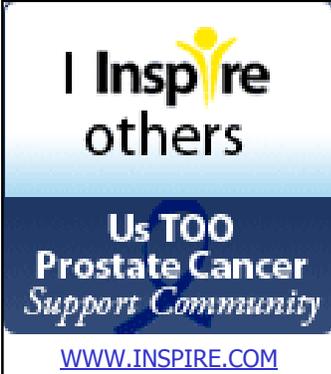
"The paradigm for years or even decades has been to treat this with hormone therapy because it is relatively less toxic ...," he said. "The bias has been to hormone therapy until it's exhausted, until there's no response left, and then, at the last moment, use chemotherapy."

"Starting last year, we began to see that might be the wrong strategy, at least in some men. Giving chemotherapy early on, upfront, with hormone therapy, might be better than the sequence of hormone therapy and then chemotherapy only at the last stages."

Acknowledging that docetaxel currently does not have approval for upfront treatment of advanced prostate cancer, James said the mounting evidence could lead to regulatory approval and support in clinical guidelines.

Presented at the 2015 AUA Annual meeting, abstract 5001.

MedPageToday
15 May 2015



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Urine Assay for High-Grade Prostate Cancer *(Continued from page 1)*

EXO106 is a urine-based liquid biopsy test that assesses expression of three genes on exosomal RNA: ERG, PCA3, and SPDEF.

Expression patterns are evaluated by a multivariate algorithm to predict the presence of high-grade prostate cancer (GS ≥ 7). Test results are expressed as an EXO106 risk score.

Overall, the EXO106 test missed 12/148 (8.1%) cases of high-grade (GS ≥ 7). However, GS 4-predominant pattern (4+3) accounted for three of the false-negatives, and the lower-risk 3+4=7 pattern associated with three or fewer positive biopsy cores accounted for the remaining false-negatives.

When the definition of high-grade disease was limited to GS $\geq 4+3$, the assay had a false-negative rate of <5%. The EXO106 assay also detected biopsy-confirmed high-grade prostate cancer in more than 90% of cases.

McKiernan reported findings from a multicenter evaluation of EXO106. Investigators at 22 centers in the US enrolled 1,560 men with GS >7 prostate cancer. After ex-

cluding 9% of urine samples, the study population comprised a training set of 499 men and a 519-man intended-use population.

The study included men 50 or older with no previous prostate biopsy, PSA of 2 to 10 ng/mL, and a scheduled biopsy for suspected prostate cancer. Men receiving therapy known to influence PSA levels were excluded. Assay results were based on a first-catch, random urine not associated with digital rectal exam (DRE), and were shipped to a central laboratory for analysis.

The primary objective was to determine if the EXO106 assay added to standard of care (PSA, age, race, and family history for prostate cancer) would result in an area under the curve (AUC) greater than that of standard of care. The secondary objective was the performance of the EXO106 at a predefined cutpoint (sensitivity, specificity, negative predictive value [NPV], and positive predictive value [PPV]).

The 519-man primary study population had a median age of 63 and a median prebiopsy PSA level of 5.12 ng/mL.

DRE was suspicious in 18% of cases, and 23% of the men had a positive family history.

Biopsies involved a median of 12 cores. The biopsy result was positive in 48% of cases. Biopsies showed GS 6 prostate cancer in 20% of cases, GS 3+4 in 16%, GS 4+3 in 7%, GS 8 in 2%, and GS 9 in 3%. Overall, 28% of the biopsies showed GS $\geq 3+4$.

Comparing AUCs, PSA alone, standard of care, EXO106 alone and EXO106 plus standard of care were 0.545, 0.631, 0.711 and 0.725, respectively. The primary endpoint was reached as EXO106 added to standard of care showed significantly better diagnostic performance vs. standard of care ($P < 0.00004$).

Analysis of EXO106 performance by the prespecified risk score cutpoint showed a sensitivity of 91.9%, specificity of 34.0%, PPV of 35.7%, and NPV of 91.3%.

Exosome Diagnostics, Inc., plans to launch the test commercially in 2016 and also intends to seek FDA approval.

Presented at the 2015 AUA Annual meeting, abstract PII-LBA2.

OncLive, 16 May 2015

Olaparib

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tumor. BRCA2 was the most common gene, found in seven men, all of whom responded to olaparib. ATM was the second most common abnormal gene, found in five men, four of whom responded to olaparib. One man had progressive disease.

Losses in other genes that sensitize patients to olaparib were identified, including PALB2 and HDAC2.

The specificity of the DNA gene repair panel was 94%, meaning that 94% of men not responding to olaparib did not have mutations in these genes. This will help clinicians select the right treatment, because they can be reasonably certain that olaparib will not benefit a man who tests negative for these mutations.

"There were no surprises regarding safety," Dr. Mateo said. "Compared with tolerability in ovarian cancer, olaparib was better tolerated. We did not see major gastrointestinal toxicities" added Mateo.

Presented at the 2015 AACR Annual meeting, abstract CT322.

The ASCO Post, 25 May 2015

The "Timing of Androgen Deprivation Therapy in Prostate Cancer Patients with a Rising PSA (TOAD)" Collaborative Randomised Phase III Trial

Dr. Gillian Duchesne, a radiation oncologist from the Peter MacCallum Cancer Center in Melbourne, Australia, presented the initial results of the TOAD study at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO). TOAD was a phase III randomized clinical trial assessing the timing of androgen deprivation therapy (ADT) among asymptomatic men with biochemical recurrence (BCR) of prostate cancer. The investigators sought to determine whether early initiation of ADT among men

with BCR who lack further curative treatment options is associated with better outcomes than delayed ADT.

They hypothesized that immediate treatment with ADT at the time of BCR would improve overall survival (OS) and have acceptable profiles of toxicity and quality of life compared to delayed ADT.

There were two patient groups in the study. Group 1 included men who had undergone one or more treatments with curative intent with subsequent BCR, and

Group 2 included men with asymptomatic, newly diagnosed advanced stage prostate cancer who were not candidates for curative treatment. Men in Groups 1 and 2 were randomized to receive immediate ADT vs. delayed ADT, and the combined data from the BCR and advanced groups was analyzed. Men were stratified for prior treatment (surgery and/or radiation), onset of BCR (< 2 vs. ≥ 2 years), type of ADT planned (continuous [CADT] vs. intermittent [IADT]), treatment center, and PSA

doubling time (< 10 or ≥ 10 months). Delayed treatment was defined as initiation of ADT ≥ 2 years after BCR (Group 1), if clinically appropriate, unless PSA doubling time was < 12 months and PSA > 10 ng/mL, or if men with metastatic disease had a PSA > 60 ng/mL, or PSA doubling time was < 6 months (study 2). The study's primary endpoint was OS, and secondary outcomes included cancer-specific and disease-free survival, quality of life (QOL), morbidity of

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Best Evidence Yet: Ejaculation Reduces Prostate Cancer Risk! *(Continued from page 2)*

monthly frequency of ejaculation from the ages of 20 to 29 years and 40 to 49 years, and during the previous year. A lifetime average was then computed from these reports.

After potential confounders were controlled for, the risk for prostate cancer was 20% lower in men who ejaculated at least 21 times a month than in men who ejaculated 4 to 7 times a month. The 20% risk reduction was seen at ages 20 to 29 and 40 to 49, and for the lifetime average (P trend <0.0001 for all).

At ages 40 to 49, most men (38.0%) reported eight to 12 ejaculations per month; only 8.8% reported at least 21 ejaculations per month. “We shouldn’t dwell on the exact numbers, but instead should focus on the dose–response relation,” Dr. Rider advised. She summarized: “Safe sexual activity could be good for prostate health.”

Notably, there was no association between ejaculation frequency and the risk for high-grade, advanced, or lethal disease, she reported.

ADT & Cognitive Decline *(Continued from page 3)*

twice as likely to experience cognitive impairment at one-year follow-up.

Researchers also reported for the first time a possible genetic link among individuals experiencing cognitive impairment during ADT. It was found that men who have a particular version of the GNB3 gene were 14 times more likely to suffer from cognitive problems following ADT.

“Studies like ours show the importance of identifying genetic predictors of cognitive impairment. This information can be used to further personalize cancer care based on patients’ unique characteristics and to find patients who may be prone to be intolerant

The reason for this exception is not known.

These results are an update of the last major report from the Health Professionals Follow-up Study, which was published about 10 years ago (JAMA 2004; 291: 1578–86). At that time, investigators concluded that “high ejaculation frequency may possibly be associated with a lower risk of total and organ-confined prostate cancer.”

Many other studies have likewise reported that ejaculation frequency might be tied to prostate cancer risk, with more orgasms being protective. “But these new data have three outstanding strengths,” Dr. Rider said. First, the study is prospective, whereas most other studies have been retrospective, and the data are long term. Second, the study involves the largest cohort of men to date. And third, the study has specific information on ejaculation, she explained.

Whereas previous studies have tended to rely on “proxies” for ejaculation,

of this standard type of treatment,” said Mayer Fishman, MD, PhD, Senior Member of Moffitt’s Genitourinary Oncology Program.

The results of this study may have implications for physicians trying to decide on the best therapeutic options for their patients. “The risk of cognitive impairment should be considered when deciding whether or not to receive ADT for prostate cancer,” said Brian Gonzalez, PhD, Postdoctoral Fellow in the Health Outcomes and Behavior Program at Moffitt.

Dr. Gonzalez is corresponding author of the Journal of Clinical Oncology article.

The ASCO Post, 14 May 2015

such as age at marriage, number of children, and number of sex partners, the Health Professionals Follow-up Study investigators were bold; they explicitly asked about ejaculations from sexual intercourse, masturbation, and nocturnal emissions.

The average age of the men in the study was about 59 years, and they had undergone an

MP-MRI Avoids Biopsies *(Continued from page 1)*

gorithms, have improved the imaging modality’s ability to detect prostate cancer. However, whether the decision to biopsy could rest on MP-MRI results remains unclear.

Using a commercial software package, Haddad and colleagues developed a decision-tree model to compare the cost of two different clinical strategies for men with suspected prostate cancer and a prior negative biopsy: MP-MRI (biopsy performed only in the case of abnormal images) versus TRUS-guided biopsy in all cases.

The outcomes of interest included cost, number of biopsies, and cancers detected. Costs were based on Medicare reimbursement rates and incorporated costs associated with sepsis and minor complications.

The cost of a single TRUS-guided biopsy averaged \$904 and included physician reimbursement, pathology cost, loss of one day of work, and the cost of complications. Cost assumptions for the MRI consisted of MRI (professional and technician costs), cost of a TRUS-guided biopsy, and loss of one half-day of work, resulting in a total cost for MRI plus TRUS-guided biopsy of \$1,570.

A baseline model with 24% prostate cancer incidence showed that TRUS-guided

average of five PSA tests by 2008. Most of the men were married, but the men who reported at least 21 ejaculations per month at ages 40 to 49 were more likely to be divorced than less robust ejaculators (11.8% vs 4-7%).

Presented at 2015 AUA Annual meeting, abstract PD6-07

Medscape Medical News
17 May 2015

biopsy as the initial strategy led to biopsies in all 100 cases and a cancer miss rate of 3.6 (20.4 vs. a baseline of 24). The MRI strategy resulted in 26.9 biopsies per 100 cases and eight missed cancers (16 detected vs. 24).

If the baseline prostate cancer rate were lowered to 10%, the RP-MRI arm led to biopsies in 18.2 cases, avoidance of 81.8 biopsies (versus initial TRUS-guided biopsy), and detection of 6.7 (3.3 missed). Initial TRUS-guided biopsy detected 8.5 cancers and missed 1.5. Total cost for 100 cases was \$90,400 for TRUS-guided biopsy and \$79,400 for MP-MRI.

Increasing the baseline cancer rate to 40% led to 36.8 biopsies per 100 cases in the RP-MRI arm, avoidance of 63.2 biopsies versus initial TRUS-guided biopsy, detection of 26.6 cancers, and 13.4 missed cancers (vs. six missed cancers with upfront TRUS-guided biopsy). Total cost of MP-MRI increased to \$97,100 for 100 cases.

Presented at the 2015 AUA annual meeting, abstract MP1711.

OnLive, 16 May 2015



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 *Hot SHEET* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

a1p1c1 The concern about over-diagnosis and over-treatment of prostate cancer is leading to tests aimed at selecting the right men for prostate biopsy. The study by McKiernan and co-workers using a urine test for EXO106 was able to detect all but 5% of high grade cancers of Gleason 4+3 or higher. If validated the test could eliminate many men from a biopsy that would most likely find a cancer that is relatively low-risk. Savings from avoiding biopsies would offset the added cost of doing the test. Of course more validation is needed, but the early results are encouraging.

The Bottom Line: A urine test for an exosomal mRNA might help to identify those men most likely to need a biopsy because of having a higher-grade cancer.

a2p1c2 Debate continues on the potential value of multi-parametric MRI (MP-MRI) guided biopsies for evaluating men for prostate cancer. Other studies have shown mixed results with an inaccuracy rate of about 30%, including missing high-grade disease. The study by Haddad and co-workers used mathematical modeling to estimate the cost implications and accuracy based on a number of assumptions. The current problem is that relying on this method will be a trade-off because it will reduce the number of biopsies while missing a certain number of important cancers. Better evidence is available supporting MP-MRI for men under consideration for a repeat biopsy after the first one was negative. For now, more data are needed to

prove that this method can replace random core biopsies as a first evaluation for a man suspected of having prostate cancer.

The Bottom Line: MP-MRI guided biopsies as a first line approach for men undergoing evaluation still needs better proof that is preferable to random core biopsies.

a3p1c3 One of the important advances in the treatment of men with locally advanced/high-risk prostate cancer has been the recognition that adding ADT to external RT significantly improves survival. Now additional data have found that adding docetaxel chemotherapy after completing RT adds a small but significant benefit. Sandler and co-workers found that men receiving chemotherapy had a 4% higher survival at four years compared to the men getting RT + ADT without the docetaxel. Although the difference is relatively small, one might expect increasing benefits with longer follow-up. Docetaxel is generally well tolerated, but added side effects do occur. Nevertheless, since the study was well designed, men with high-risk disease should at least be offered the addition of docetaxel to their treatment plan.

The Bottom Line: Men with high-risk, locally advanced prostate cancer appear to have a significantly higher survival rate if they receive docetaxel plus RT + ADT.

a4p2c2 Once again, statins are being discussed for their potential to help men with prostate cancer. Numerous uncontrolled studies have suggested that men on one of these therapies had better outcomes following treat-

ment for prostate cancer compared to men not taking them. This latest study by Kantoff et al is important because it provides some understanding of the mechanism by which they might work. Statins reduce the levels of an important protein that helps testosterone to enter into cells. Less testosterone means less cancer cell growth. More studies are needed in this area and most importantly, a prospective study is critical to proving that men really benefit and identifying those men most likely to benefit.

The Bottom Line: Further evidence shows a potential benefit of statins in men on ADT but we need to wait for a properly conducted randomized study before recommendations can be made.

a5p2c3 The health benefits of sexual activity have been a topic of discussion for a very long time. Some studies have found more is bad and others have found the opposite. Unfortunately, most of them were retrospective, which creates considerable uncertainty about their conclusions. Now a new, large, prospective study provides additional information that might be more valid. Rider and co-workers reported on men in the Physicians Health Study, looking specifically at total ejaculations that include masturbation rather than only looking at frequency of intercourse. They found that more appears to be better with a significantly lower risk of developing prostate cancer. Although prospective, it still leaves many unanswered questions such as the impact of time;

must men have a large number of ejaculations over many years to achieve the benefit, at what age is the high frequency most helpful, and as men reach their 50's, 60's and 70's, what is the optimal number of ejaculations that will sustain this benefit? Those questions may not get answered any time soon. For now, the best we can say to young men as they age is having frequent ejaculations does have a potential health benefit.

The Bottom Line: Having frequent ejaculations may lower a man's risk of prostate cancer.

a6p3c2 The study on olaparib by Mateo et al provides exciting evidence for the growing potential for genetic studies to improve results of men with prostate cancer. The authors used this drug in men with mCRPC and tested for the presence of two genes. If present, men had a much higher response rate to the medication. Other genetic variants have also been able to identify which men do not respond to the Abiraterone. The question why some men to respond or do not respond to various therapies has been a major challenge in trying to improve the success of various treatments. This is just one study that helps explain the variation in responses to both new and older therapies.

The Bottom Line: The use of genetic markers is likely to help improve response rates to various therapies by identifying those men with the greatest chance of responding or not responding to different therapies.

(Continued on page 8)

TOAD Phase III Trial (Continued from page 5)

treatment, and complications from therapy.

Patient characteristics between the early and delayed ADT groups were very similar in Groups 1 and 2, thus data was analyzed by pooling results from both groups. Five year OS was better with immediate vs. delayed ADT (85.6 vs. 76.4%, respectively). The unadjusted hazard ratio [HR (95% confidence interval)] for OS between groups was 0.55 (0.30–1.00, p=0.05) in favor of immediate ADT. The adjusted HR demonstrated a trend toward improvement with immediate treatment, HR 0.54 (0.27–1.06; p=0.074). Median OS was not reached in either group after eight years of follow-up. Prostate cancer deaths were not significantly reduced, and results for all of the secondary endpoints were inconclusive, and longer follow-up will be required to determine if immediate ADT is favored compared with delayed ADT.

This study suggests that the use of early ADT for men with BCR, and those unfit for curative treatment receiving immediate ADT may achieve a 10% improvement in OS at 5 years vs. delayed ADT. This benefit may be delivered with a tolerable side effect profile, though men treated with immediate ADT have a significantly higher risk of ADT-associated side effects than men treated with delayed ADT. Ultimately the study provides evidence of benefit to early treatment with ADT in this population, and does so in a randomized, controlled trial. The difficulty that the team had with accrual makes it unlikely that this type of study will be repeated. As such, we eagerly await future data to determine the secondary endpoint outcomes assessed by this trial.

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UroToday.com, 9 June 2015

Doctor Chodak's Bottom Line (Continued from page 7)

a7p3c4 Although androgen deprivation therapy (ADT) has clearly been an important advance in the treatment of men with prostate cancer, over time, a growing number of side effects have been identified. Perhaps the most significant one is the metabolic syndrome, which unfortunately, not enough doctors routinely monitor. The report from the Moffitt Center adds information to other reports that have demonstrated impairment in cognitive ability from this therapy. This study found a gene that may predict for an increased risk of developing this side effect. If substantiated in additional studies, it

could be used in different ways. One would be to delay ADT in men who have this gene when they have a rising PSA but non-metastatic disease since there is no clear proof it increases survival in that setting. A second option would be to develop interventions that attempt either to treat or prevent the cognitive problems that appear to develop. Either way, this side effect should be routinely discussed when offering ADT therapy to patients.

The Bottom Line: A possible genetic link to developing cognitive problems from ADT provides an important new understanding of who is at risk for this side effect.



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