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Affected by Prostate Cancer?



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Hot SHEET

Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

Weak Evidence Favors Usage of Intermittent Androgen Deprivation Therapy for Advanced Prostate Cancer

For men with advanced or recurrent prostate cancer, intermittent androgen deprivation therapy (IADT) may be just as good as standard continuous ADT in terms of survival and quality of life, a new meta-analysis suggests – but the authors say the level of evidence is weak.

The research team pooled data from 22 articles reporting on 15 randomized controlled trials with 6,856 men. The studies, published between 2000 and 2013,

addressed a variety of disease stages: metastatic hormone sensitive cancer in six trials, mixed stages in four trials, locally advanced disease in one trial, and recurrence after primary radical therapy in two trials.

There was no significant difference between IADT and continuous ADT for overall survival, a primary outcome, in data from eight trials with 5,352 men (hazard ratio 1.02). There were “minimal differences” in self-reported quality of life, another primary outcome, with most trials showing an improvement in physical and sexual functioning with IADT.

There were no differences for the secondary outcomes of cancer-specific survival (in data pooled from five trials with 3,613 men; HR 1.02) or progression-free survival (in four trials with 1,774 men; HR 0.94). Treatment duration and off-treatment periods varied widely across the studies, however, and the criteria for stopping and restarting therapy varied as well.

And as reported online in *JAMA Oncology* on September 17, all but one study had an unclear or high risk of bias. “The level of evidence is not the most optimal” for

(Continued on page 6)

Fewer, Larger Radiotherapy Doses Prove Effective for Prostate Cancer Patients

Giving fewer but higher doses of radiotherapy (RT) is as effective at treating prostate cancer as giving lower doses for a longer period, according to new research presented at the 2015 European Cancer Congress. The results could mean men need fewer trips to the hospital over four weeks (rather than seven and one-half) without reducing the quality and impact of their prostate cancer treatment.

The Cancer Research UK funded CHHiP trial – the largest randomized treatment trial ever undertaken in localized prostate cancer led by The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust – gave 3,216 men with prostate cancer from across the UK different schedules of RT. Some men received standard RT of 74 Gray (Gy) over 37 days (two Gy a day) while others were given either 60 Gy delivered over 20 days or 57 Gy over 19 days (three Gy a day).

The researchers then followed these men for five years and, overall, found that giving patients 60 Gy over 20 days was as effective as the standard treatment – in terms of both controlling the disease and for long-term side effects. Some short-term side effects of the higher daily RT doses during and immediately after RT were higher than for standard RT, but these – including bowel and bladder problems – were not long lasting. There was no difference in the side effects after six months or during the next five years.

Lead investigator Professor David Dearnaley, professor of uro-

(Continued on page 4)

Study Raises Questions about Androgen Deprivation for Certain Prostate Cancer Cases

Men with unfavorable-risk prostate cancer and moderate or severe comorbidities had significantly decreased overall and cardiac mortality when treated with radiotherapy (RT) alone vs. RT and androgen deprivation therapy (ADT), according to a study described in a research letter in *JAMA*. In the letter, D’Amico et al present long-term follow-up to their 2008 randomized trial that showed that six months of ADT + RT vs. RT alone prolongs survival and is the standard treatment for unfavorable-risk prostate cancer.

The new findings build on a post-randomization hypothesis-generating analysis sug-

gesting that men with moderate or severe comorbidity had no increased survival from combined therapy. “Using updated data from our randomized trial, we compared overall survival and mortality from prostate cancer, cardiac, or other causes in all men and those within comorbidity subgroups by randomized treatment group,” the authors explained. Information collected before randomization was used to assign a comorbidity score.

A total of 206 men with unfavorable-risk prostate cancer were randomly assigned to receive RT alone or RT plus

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Jonathan McDermed, PharmD
Tom Kirk
Jackie Konieczka
Chuck Strand

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Tom Kirk, President and CEO
Jackie Konieczka, Office Manager
Terri Gibbons Likowski, Chapter Svc. Manager, (877) 978-7866
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2720 S. River Rd., Ste. 112,
Des Plaines, IL 60018

T: (630) 795-1002 / F: (630) 795-1602

Website: www.ustoo.org

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ED Induced by Prostate Biopsy Likely 'Underestimated'

The various degrees of erectile dysfunction (ED) that occur after prostate biopsy with a needle through the rectum wall have probably been underestimated, according to new research published in the August issue of *BJU International* (Vol. 116, p. 164, 2015).

A new study showed a significant decrease in the erectile function (EF) score of most men after biopsy, and the drop was independent of age, cancer diagnosis, and previous biopsy status, report the study authors, led by Katie Murray, MD, from the University of Kansas Medical Center in Kansas City. Although ED was recognized as a complication of prostate biopsy as early as 2001, it has not been well-established by data, unlike potential adverse events such as hematuria, pain, voiding dysfunction, and infection.

In their prospective study, Dr. Murray and her team used a standard test – the International Index of Erectile Function (IIEF-5) – to evaluate 220 men with elevated levels of PSA who underwent a transrectal-ultrasonography-guided prostate biopsy. In the study cohort, median IIEF-5 score was significantly lower one week after biopsy than at baseline (15.5 vs. 18.2; $P < 0.001$). And the score remained significantly lower at four weeks (17.3 vs. 18.4; $P = 0.008$) and 12 weeks (16.9 vs. 18.4; $P = 0.004$). The team does not, however, say that the needle caused physical damage in this nerve-intensive area that led to ED. “The exact cause of this effect is yet to be determined,” they write.

“Psychological stress” likely contributes to the ED, writes Brian Helfand, MD, from the University of Chicago, in an

accompanying editorial. The men in this study who had a benign biopsy had a fairly quick return to baseline in terms of their EF (after one week, as a group), even though some men reported lower scores for up to three weeks. Dr. Helfand points out that a study he was previously involved in showed that a diagnosis of prostate cancer “can influence a man’s erectile function after prostate biopsy.”

“The literature on this subject is mixed, with some studies finding and some not finding that biopsy induces ED,” he adds. Nevertheless, Dr. Helfand suggests that “patients should be counseled on the possibility of relatively short-term (‘acute’) changes in EF.” Dr. Murray and her team say the same thing.

“This single-group study could have been stronger in terms of its evidence,” said Clint Bahler, MD, from Indiana University in Indianapolis, who was not involved in the study but was asked to comment on the findings. “They should have followed another group of [healthy] men with elevated PSA who did not get biopsy to compare, for instance,” he told *Medscape Medical News*. Like Dr. Helfand, Dr. Bahler pointed out that men who had a benign biopsy (67% of the group) had relatively transient ED, compared with those who had cancer detected.

For the men who did not get a diagnosis of prostate cancer, median IIEF-5 score was lower only at the one-week follow-up ($P < 0.001$). But for those with prostate cancer detected, the median score was lower at one week ($P < 0.001$) and at 12 weeks ($P = 0.001$) after biopsy. Notably, there is no detailed breakout of scores for the benign

group. “They should give us the scores for the benign group, but these are censored, which is suspicious,” said Dr. Bahler.

Dr. Helfand, Dr. Bahler, and the investigators all suspect that longer-term ED might be related to a host of factors, including stress, a diagnosis of cancer, and age. As Dr. Murray’s team puts it, “the exact mechanism of this decline in IIEF-5 score for these patients is most likely multifactorial in nature and many factors – including psychogenic causes, fear of results, anxiety related to biopsy, and even anatomical considerations including nerve damage and hematoma – have potential in being related.”

At baseline, the average age was 64 years, and ED status was reported as nonexistent by 39% of the men, as mild by 22%, as mild to moderate by 15%, as moderate by 10%, and as severe by 14%. Age appears to play a role in healthy men in terms of their erections after undergoing prostate biopsy, the investigators report. For men younger than 60 years, median IIEF-5 score was lower only at the one-week follow-up ($P = 0.015$). But for men 60 years and older, scores were lower at one week ($P < 0.001$), four weeks ($P = 0.024$), and 12 weeks ($P = 0.005$).

The investigators also used the International Prostate Symptom Score (IPSS) questionnaire to evaluate the men. They focused on data related to lower urinary tract symptoms, and found that there was a significant change at weeks one and four, but not at week 12. In other words, in this cohort of men, symptoms, on average, improved by week 12.

Medscape Medical News
1 October 2015

Doc Moyad's What Works & What is Worthless Column, Also Known As "No Bogus Science" Column – "Buongiorno! Drinking coffee in Italy - the Moyad experience & More!"

Mark A. Moyad, MD, MPH, University 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 major colon cancer clinical study and now multiple prostate cancer studies are beginning to suggest that coffee could have anti-cancer properties!¹⁻³

I just returned a few hours ago from a brief working trip that took me through Southern Italy (I know... life is real harsh at times, but someone has to be Mark Moyad). And, now I am semi-addicted to coffee because in Italy it is ubiquitous, and you can't escape from it, which is kind of like those attorney ads on TV or on the highway in the US that promise you that you will get paid big money for suing someone or something. Espresso, cappuccino, café Americano... I learned about all of them by trying all of them (again someone has to be me). And apart from the

fact that I had more energy than a five-year old kid after eating a box of sugar, it was incredible that I saw no one use a "to go" cup or simply walk down the street drinking coffee – not a single person in any of the cities I visited?! What the heck is going on?

These Italians stand or sit in a café and drink and talk and then move on. Perhaps it is not the coffee but the underlying comprehensive healthy behavior of the coffee drinker in some of these countries. They appear to regularly socialize, relax, remain strong spiritually, walk constantly, and eat very healthy diets but only in small to moderate portions. For example, I ordered a crab-stuffed ravioli in Rome, a pizza in Naples, Caprese salad in Sorrento, and anchovies in Amalfi that I swear in every case would never even

qualify as an appetizer ("antipasti") in the US, and each single item was considered one full-meal in Italy! This must be the secret (or my continuous IV olive oil pump)! On the other hand, multiple new human studies are also suggesting that coffee (especially the low- or no-calorie caffeinated type) itself has some anti-cancer/anti-inflammatory properties and could reduce insulin over-exposure, which means not only as a preventive but as a way to reduce cancer recurrence.¹⁻³ So, is it the coffee or the average behavior of the coffee drinker that is the secret? It does not even matter because the message of eating a healthy diet but in small portions and moving more and staying skinny is just part of the theme of the coffee drinker. And if many Italians would quit smoking

they would live even better and longer and this is what they can learn from us in America (not smoking). However, then many Italians would struggle with massive weight gain, which is beginning to also occur.

Ahh, it is good to be home – there is no place like the US, but my trip to Italy was a beautiful educational experience reinforcing some of the similar cultural secrets to a better and/or longer life that I have witnessed from traveling throughout the world from Singapore to South Africa to South America over the past 30 years. Now, if we could just get rid of all those attorney ads in the US that don't exist in Italy! Perhaps that is the real secret to a better and long life! Gratz! Marco Anthony Moyad, Gratz!

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Mutation Predicts Poor Chemotherapy Outcome

The presence of the TMPRSS2-ERG mutation in blood may predict how well patients with metastatic castration-resistant prostate cancer (mCRPC) respond to docetaxel, according to study findings presented at the 2015 European Cancer Congress (ECC) in Vienna, Austria.

Òscar Reig, MD, of Hospital Clinic, Barcelona, Spain, and colleagues prospectively evaluated TMPRSS2-ERG in peripheral blood mononuclear cells (PBMC) in 50 men with mCRPC treated with docetaxel. Men with TMPRSS2-ERG had a significantly lower rate of PSA response to docetaxel compared with those who did not have TMPRSS2-ERG (12.5% vs. 68.3%). They also

had a significantly lower median PSA progression-free survival (PFS) (3.1 vs. 7.5 months), and lower median clinical/radiologic PFS (3.1 vs. 8.2 months). In multivariate analysis, TMPRSS2-ERG was independently associated with a 3.7 and 6.3 times higher risk of PSA progression and clinical/radiologic progression, respectively (P < 0.05). "TMPRSS2-ERG predicts [a] low response rate to docetaxel and poor outcome in mCRPC patients," the authors concluded in a study abstract. "These data support its potential role as a biomarker to tailor treatment strategy."

Renal & Urology News
29 September 2015

Silicon and Bone Health

Rodella LF, Bonazza V, Labanca M, et al

J Nutr Health and Aging 2014; 18: 820-826

Objective:

Increasing evidences suggest that dietary silicon intake is positively correlated with bone homeostasis and regeneration representing a potential and valid support for the prevention and improvement of bone diseases like osteoporosis. This review aims to provide the state of art of the studies performed until today in order to investigate and clarify the beneficial properties and effects of silicates on bone metabolism.

Methods:

We conducted a systematic literature search up to March 2013, using two medical da-

tabases (PubMed and the Cochrane Library), to review the studies about silicon consumption and bone metabolism.

Results:

We found 45 articles, but 38 were specifically focused on silicon studies.

Conclusion:

Results of this search showed a positive relationship between dietary silicon intake and bone regeneration.

Higher RT Doses Less Often *(Continued from page 1)*

oncology at The Institute of Cancer Research, London, and Consultant at The Royal Marsden, said, "These data are encouraging news for men. Excellent control rates and a low side effect profile have been seen across the trial. Giving patients larger doses of RT for a shorter time will mean fewer hospital trips and less RT needed overall. These findings are the result of many years of research and should help to further refine treatment."

Dr. Emma Hall, deputy director of the Cancer Research UK-funded Clinical Trials and Statistics Unit at The Institute of Cancer Research, London, which coordinated the study, said, "The technique used to give the RT has led to low levels of side effects even with the higher daily dose. We have also shown that the 20 day schedule is at least as good at controlling disease as the current 37 day schedule."

Professor Malcolm Mason, Cancer Research UK's prostate cancer expert, said,

"These results are great news for men. From a logistical and patient convenience point of view, being able to treat men over a shorter period of time has been a goal for specialists, but the question has always been whether it was safe to do so. This study shows that it is safe and effective, and there should be no reason why this cannot be implemented immediately – it is saving the NHS resources."

He continued, "But there are still questions that need answers. It's not impossible that fewer, but bigger fractions of RT might be still better at controlling the disease, but this would need more data from large clinical trials to answer. We look forward to seeing more research – perhaps by combining this and similar studies. It's also valuable to see the impact of the shorter treatment on side effects. Reassuringly, these are no different to the older, standard treatment."

*Adapted by Medical News Today
28 September 2015*

Prostate Cancer Diagnoses Drop after USPSTF 'Don't Screen' Recommendation

Prostate cancer diagnoses decreased by 28 percent in the first year following the US Preventive Services Task Force (USPSTF) recommendation against regular PSA screening, according to a new analysis published online September 22nd in the *Journal of Urology*. Diagnoses of low-, intermediate-, and high-risk prostate cancers declined significantly during that period, although new diagnoses of nonlocalized disease did not change.

"It is not surprising that new diagnoses of nonlocalized disease have remained the same," explained lead author Daniel A. Barocas, MD, MPH, of the Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN. "Our data go to 2012, so it's really only a year since the guideline was issued," he said. "I would have not expected to see a change at this point in time."

In October 2011, the USPSTF recommended against routine screening for prostate cancer using the PSA test, which has caused considerable controversy among professional organizations, patient advocacy groups, and physicians. Prior to this, the USPSTF had already recommended against routine PSA screening in men older than 75 years, but the new guidelines

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Impact of the CCP Test on Physician and Patient Treatment Selection for Localized PCa

Shore ND, Kella N, Moran B, et al

J Urol 21 September 2015; Epub

Purpose: The CCP test is a validated molecular assay that assesses prostate cancer-specific disease progression and mortality risk when combined with clinicopathologic parameters. The results from PROCEED-1000, a large, prospective registry designed to evaluate the impact of the CCP test regarding shared treatment decision making for newly diagnosed prostate cancer patients, are presented here.

Materials and Methods: Untreated patients with newly diagnosed prostate adenocarcinoma were enrolled and the CCP test was performed on the initial prostate biopsy tissue. A set of four sequential surveys tracked changes relative to initial therapy recommendations (pre-CCP) based on clinicopathologic parameters following: physician review of the CCP test result, physician/patient review of the CCP test results, and a minimum of three-months of clinical follow-up (actual treatment).

Results: 1,206/1,596 patients enrolled in this registry were eligible for analysis. There was a significant reduction in the treatment burden recorded at each successive evaluation ($P < 0.0001$), with mean number of treatments per patient de-

(Continued on page 7)

Appropriateness of Prostate Cancer Imaging among Veterans in a Delivery System without Incentives for Overutilization

Makarov DV, Hu EYC, Walter D, et al

Health Serv Res 30 September 2015; Epub

Objective: To determine the frequency of appropriate and inappropriate prostate cancer imaging in an integrated health care system.

Data Sources/Study Setting: Veterans Health Administration Central Cancer Registry linked to VA electronic medical records and Medicare claims (2004-2008).

Study Design: We performed a retrospective cohort study of VA patients diagnosed with prostate cancer (N = 45,084). Imaging (CT, MRI, bone scan, PET) use was assessed in men with low-risk disease, for whom guidelines recommend against advanced imaging, and in high-risk men for whom guidelines recommend it.

Principal findings: We found high rates of inappropriate imaging among men with low-risk prostate cancer (41 per-

cent) and suboptimal rates of appropriate imaging among men with high-risk disease (70 percent). Veterans utilizing Medicare-reimbursed care had higher rates of inappropriate imaging [OR: 1.09 (1.03-1.16)] but not higher rates of appropriate imaging. Veterans treated in middle [OR: 0.51 (0.47-0.56)] and higher [OR: 0.50 (0.46-0.55)] volume medical centers were less likely to undergo inappropriate imaging without compromising appropriate imaging.

Conclusions: Our results highlight the overutilization of imaging, even in an integrated health care system without financial incentives encouraging provision of health care services. Paradoxically, imaging remains underutilized among high-risk patients who could potentially benefit from it most.

Exploiting Altered Patterns of Choline Kinase-alpha Expression on Human Prostate Tissue to Prognosticate Prostate Cancer

Challapalli A, Trousil S, Hazell S, et al

J Clin Pathol 2015; 68: 703-709

Aims: Malignant transformation results in overexpression of choline-kinase (CHK) and altered choline metabolism, which is potentially detectable by immunohistochemistry (IHC). We investigated the utility of CHK-alpha (CHKA) IHC as a complement to current diagnostic investigation of prostate cancer by analysing expression patterns in normal (no evidence of malignancy) and malignant human prostate tissue samples.

Methods: As an initial validation, paraffin-embedded prostatectomy specimen blocks with both normal and malignant prostate tissue were analysed for CHKA protein and mRNA expression by western blot and quantitative reverse transcriptase PCR (qRT-PCR), respectively. Subsequently, 100 paraffin-embedded malignant prostate tumour and 25 normal prostate cores were stained for both Ki67 (labelling-index: LI) and CHKA expression.

Results: The validity of CHKA-antibody was verified using

CHKA-transfected cells and siRNA knockdown. Immunoblotting of tissues showed good resolution of CHKA protein in malignant prostate, verifying use of the antibody for IHC. Minimal CHKA mRNA was detected by qRT-PCR in normal tissue; conversely high expression in malignant prostate tissues. IHC of normal prostate cores showed mild CHKA expression in only 28% (7/25) of samples with no Ki67 expression. In contrast, CHKA was expressed in all malignant prostate cores along with characteristically low proliferation (median 2% Ki67-LI; range 1–17%). Stratification of survival according to CHK intensity showed a trend towards lower progression-free survival with CHK score of 3.

Conclusions: Increased expression of CHKA, detectable by IHC, is seen in malignant lesions. This relatively simple cost-effective technique (IHC) could complement current diagnostic procedures for prostate cancer and, therefore, warrants further investigation.

RT + ADT in Prostate Cancer Patients with Comorbidity (Continued from page 1)

six months of ADT at three academic and three community-based centers in Massachusetts between 1995 and 2001. At a median follow-up of 16.6 years, 156 (76%) men died; 29 (19%) died of prostate cancer, 39 (25%) of cardiac causes, and 88 (56%) of other causes.

Among men with moderate or severe comorbidity, 46/49 (94%) had died compared to 110/157 (70%) men with no or minimal comorbidity. Survival did not differ in the men receiving RT alone vs. those receiving RT + ADT, “but opposite effects of treatment on survival were observed in the comorbidity subgroups,” the authors reported.

In multivariable analyses, RT alone vs. RT + ADT in men with no or minimal comorbidity was associated with significantly increased overall mortality (hazard ratio [HR] 1.5, 95% CI 1.0-2.2, $P = 0.04$) and prostate cancer mortality (HR 4.3, 95% CI 1.6-11.5, $P = 0.004$), no difference in cardiac mortality (HR 1.7, 95% CI 0.6-4.6, $P = 0.28$), and decreased other-cause mortality (HR 0.6, 95% CI 0.4-1.0, $P = 0.04$).

Conversely, in men with moderate or severe comorbidity, RT alone vs. RT + ADT was associated with significantly decreased overall mortality (HR 0.4, 95% CI 0.2-0.7, $P = 0.001$) and cardiac mortality (HR 0.2, 95% CI 0.1-0.5, $P < 0.001$).

This finding is in contrast to no association with overall mortality at a median follow-up of 7.6 years, as previously reported. In addition, among men with moderate or severe comorbidity, RT alone was associated with no difference in prostate cancer mortality, and increased other-cause mortality.

“The results are hypothesis-generating and require validation,” D’Amico said. Nevertheless, the association of treatment with RT alone with decreased cardiac and overall mortality in men with moderate or severe comorbidity suggests that administering ADT to treat unfavorable-risk prostate cancer in these men should be carefully considered.”

The ASCO Post
22 September 2015

A Phase II Randomized Trial of Lycopene-Rich Tomato Extract Among Men with High-Grade Prostatic Intraepithelial Neoplasia

Gann PH, Deaton RJ, Rueter EE, et al

Nutr Cancer 13 October 2015; Epub

A diverse body of evidence suggests that lycopene might inhibit prostate cancer development. We conducted a six-month repeat biopsy randomized trial among men with high-grade prostatic intraepithelial neoplasia (HGPIN).

Here we report results for serum lycopene, prostate specific antigen (PSA) and insulin-like growth factor (IGF) proteins, histopathological review, and tissue markers for

proliferation minichromosome maintenance protein 2 (MCM-2)] and cell cycle inhibition (p27). Participants consumed placebo or tomato extract capsules containing 30 mg/day lycopene. Pre- and post-treatment biopsies were immunostained and digitally scored. Serum lycopene was determined by LC-MS-MS. In secondary analyses, pathologists blindly reviewed each biopsy to score histological

features. Fifty-eight men completed the trial. Serum lycopene increased by 0.55 $\mu\text{mol/L}$ with treatment and declined 0.29 $\mu\text{mol/L}$ with placebo. We observed no meaningful differences in PSA, IGF-1, or IGF binding protein 3 concentrations between groups, nor any differences in expression of MCM-2 or p27 in epithelial nuclei. Prevalences of cancer, HGPIN, atrophy, or inflammation posttreatment were similar;

however, more extensive atrophy and less extensive HGPIN was more common in the lycopene group. Despite large differences in serum lycopene following intervention, no treatment effects were apparent on either the serum or benign tissue endpoints. Larger studies are warranted to determine whether changes observed in extent of HGPIN and focal atrophy can be replicated.

Prostate Cancer Diagnoses Drop after USPSTF Recommendation

(Continued from page 4)

extended it to all men. PSA testing was given a “D” rating, which means “there is moderate or high certainty that the service has no benefit or that the harms outweigh the benefits.”

Some of the effects of this guideline may be beneficial in terms of reducing harms related to overdiagnosis and overtreatment, Dr. Barocas told *Medscape Medical News*. “But not only are we missing low-risk diagnoses, we are also missing diagnoses of intermediate- and high-risk disease. A delay in the diagnosis for those patients could lead to worse outcomes.”

Previous research has suggested that higher-risk disease could be on the rise because of the decline in screening. One study found that the rate of higher-risk prostate cancer rose slightly but significantly in the United States during 2011 and 2012. The 3% increase in each of those two years coincides

with the changes that were made in USPSTF prostate cancer guidelines in 2009 and 2011. Without screening, many of these cancers will not be detected until they are advanced. Dr. Barocas continued, “Patients are generally not symptomatic until the disease is more advanced and may be difficult to treat.”

But even one year after the recommendations, he noted that they were already seeing reductions in the diagnosis of intermediate- and low-risk disease. “We saw an almost 30% reduction in the diagnosis of intermediate prostate cancer,” he said. “A decline of that magnitude is huge. This shows that we are missing important opportunities to treat these men with curative therapies.” As time goes on, the full impact of the guidelines will become more apparent. “In a year or two, we will have a better idea of the impact that they are having, especially in men

with high-risk disease,” Dr. Barocas said.

Using data from the National Cancer Database, the authors sought to determine whether the number of incident cases of prostate cancer per month has substantially changed since the guideline. They assessed the trend of new prostate cancer cases that were diagnosed each month before and after the draft guideline. The bulk of new cases were diagnosed in men between the ages of 60 and 69 years (43.7%), and the majority were white (80%). There was a small predominance of intermediate-risk disease in localized cases as compared with low- and high-risk disease (32.2% vs. 25.4% vs. 27.0%); 5.4% of men had non-localized disease at diagnosis.

Prior to the introduction of the guideline, the number of monthly diagnoses of prostate cancer ranged from 9,442 to 12,021, and diagnoses were increasing by approximately 45 cases per month (0.4%). In October 2011, however, there was a significant and immediate reduction in estimated diagnoses of incident disease of -1,373 cases, along with a significant change in trend in the periods before and after the guidelines were issued. This represented a relative decrease of 164 cases per month, corresponding to a change of -12.2% ($P < 0.01$) in incidence in the month that immediately followed the publication of the guidelines. After that, there was an ongoing rate of decrease of -1.8% per month ($P < 0.01$).

A year after its release, the number of new diagnoses had declined by 27.9% as compared with the projected trend from the period before the guideline was issued. When looking at the different

subgroups, diagnoses declined in all risk categories. Monthly diagnoses initially decreased -16.9% for low-risk, -12.9% for intermediate-risk, -10.1% for high-risk, and -2.7% for nonlocalized disease. The corresponding monthly changes thereafter were -2.7, -1.9, -1.4 and -0.1%, respectively (P -interaction < 0.01).

“This study clearly shows how important it is to utilize PSA for appropriately managing various stages of prostate cancer, including initial diagnosis, and to avoid overutilization,” commented Khurshid Guru, MD, associate Professor of oncology in the Department of Urology at Roswell Park Cancer Institute, Buffalo, New York, who was approached by *Medscape Medical News* for an independent comment.

Dr. Barocas and his colleagues agree. They call for more research that focuses on screening paradigms that will minimize harms but at the same time maximize the potential benefits of screening and take into account individual patient risk factors and preference.

Medscape Medical News
22 September 2015

No Bogus Science

(Continued from page 3)

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Intermittent ADT (Continued from page 1)

recommending an intervention,” said lead author Dr. Sindy Magnan of University Laval, Quebec, Canada, in email to Reuters Health. “We currently do not know the optimal way to manage these periods of intermittence,” Dr. Magnan said. “This needs to be clarified in the future.”

Dr. Christopher J. Sweeney, of Harvard Medical School and Dana Farber Cancer Institute, Boston, wrote a companion editorial. In a phone interview, he praised the paper for its exhaustiveness and adherence to sound methodological principles. But, he said, “The authors take away clinical judgment and nuance in caring for patients. We really need to tai-

lor the treatment to the patient and how a patient responds to therapy. Their results may apply to most people, most of the time, but they cannot guide best individual treatment decisions for individuals.”

Dr. Magnan responded by email, “The type of study we conducted is the best level of evidence that someone (a clinician, a patient, a stakeholder) can have on the effect of an intervention to base a decision to use or not use an intervention. . . . Our clinical judgment at the bedside is paramount when caring for a patient, but it should always be based on the best level of evidence.”

Reuters Health
2 October 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 Improvements in radiation therapy techniques are making it possible to deliver higher doses of radiation per dose thereby completing the therapy in a shorter amount of time. What remains unknown so far is whether the long-term survival rates will be at least as good as the conventional approach. Early results of an ongoing randomized trial comparing the standard 37 treatments to 19 or 20 were recently presented at the European Cancer Congress. The investigators reported similar long-term toxicity and similar rates of disease progression. Important issues for readers to note are that the patients did receive hormone therapy, it included an undefined number of low-risk patients, and this was a pilot trial, not designed to assess long-term survival. Details of the study can be reviewed at <https://clinicaltrials.gov/ct2/show/NCT00392535>. That means it is still too early to know for certain if the shorter course of therapy is better for patients but hopefully that study will be forthcoming.

The Bottom Line: Early results suggest that 19 or 20 days of XRT may be as good as the standard 37 days but more work is needed before that conclusion can be made.

a2p1c2 The technique of meta-analysis has been suggested as a way to combine the results from several randomized studies in which the outcomes were inconsistent. The idea is that by increasing the number of patients under evaluation, the ability to detect small but significant differences in outcome is increased. That technique was used in a large number of

studies assessing the impact of continuous vs. intermittent androgen deprivation therapy (ADT) in men with treated or untreated prostate cancer. The authors acknowledge a high likelihood of bias in all but one of the studies. What kinds of problems may have occurred that could limit the reliability of the results? First, the studies did not include homogeneous groups of patients. For example, some men had recurrent disease and some had never received local therapy. Combining them into a single group requires a careful assessment that the groups behave similarly and it is unclear if the authors did it. Another problem is that the method for intermittent ADT is not standardized. Readers of the *Hot SHEET* should always be on the alert when they read the results of a meta-analysis because it is very easy to reach incorrect conclusions.

The Bottom Line: This meta-analysis does not prove that intermittent ADT is equivalent to continuous therapy.

a4p2c1 When the USPTF accumulated its data evaluating the risks and benefits of screening with PSA, they weighed the potential risks against the potential benefits. Ultimately, they reached the conclusion that the harms outweighed the benefits. Potentially, the study by Murray et al might have added fuel to the downside impact of screening. In this study, the authors suggest that men undergoing a prostate biopsy had a decrease in sexual function up to 12 weeks later. But the results differed according to the patient's age with the younger men recovering very quickly. Although

this study was randomized, several factors were lacking as pointed out by the two commentaries accompanying the article. First, the authors did not assess changes in a comparable cohort of men who did not undergo a biopsy. Second, the results were markedly different in the men diagnosed with prostate cancer vs. those without cancer. The latter group only had a decrease in their sexual function questionnaire at one week but no difference at 12 weeks. A third factor not mentioned by the commentators was whether the results varied depending on the initial IEFF score. It is possible that change in IEFF score was dependent on the initial score, meaning that men with a score above a certain number had different effect than those below that number. Lastly, even if a difference is real, it is completely unclear whether the effect was caused by a psychological change after a man was given a diagnosis of prostate cancer. It would have been helpful to know if all the men were informed of their biopsy results before the one-week assessment began.

The Bottom Line: More work is needed to know whether a prostate biopsy truly has a negative short-term impact on erectile function, and if that is true, why that occurs.

a6p3c1 One of the most important challenges in cancer therapy is trying to understand why some individuals respond to a particular therapy and others do not. If that could be answered, individualized treatments could be given to men most likely to respond while avoiding treat-

ments for men least likely to respond thereby avoiding wasted time and money. The study by Reig and co-workers shows promise as a way to identify which men should or should not receive docetaxel chemotherapy. They measured TMPRSS2-ERG mutation in blood of men with metastatic castration resistant disease and found that those men who had the mutation did not respond well to the chemotherapy. This information could be used to lower cost and patient morbidity. Hopefully other important markers will become available in the near future that will enhance the ability of doctors to tailor therapy that is more effective.

The Bottom Line: A mutation of TMPRSS2-ERG may become an important method for identifying which men should not receive docetaxel therapy when their cancer has progressed.

Impact of CCP Test

(Continued from page 4)

creasing from 1.72 pre-CCP test to 1.16 in actual follow-up. The CCP test caused a change in actual treatment in 47.8% of patients. Of these changes, 72.1% were reductions and 26.9% were increases in treatment. For each clinical risk category, there was a significant change in treatment modality (intervention vs. non-intervention) pre-CCP to post-CCP testing ($P = 0.0002$).

Conclusions: The CCP test has a significant impact in assisting physicians and patients reach personalized treatment decisions.

Testosterone Levels Improve in Obese Men Following a Common Weight-Loss Operation

A common weight-loss operation called sleeve gastrectomy can make testosterone levels normal in obese men, according to new findings presented at the 2015 Clinical Congress of the American College of Surgeons. Surgeons from Stanford University in California reported that after undergoing this bariatric surgical procedure, obese patients with low testosterone levels experienced a measureable increase in their testosterone levels over a 12 month-period following the operation.

"When men are obese, they have low testosterone. Low testosterone is known to impact sexual quality of life, but it's also an independent cardiac risk factor. Men with low testosterone have more cardiac events than men with normal testosterone," according to study coauthor John Morton, MD, MPH, FACS, chief, bariatric and minimally invasive surgery, Stanford

University School of Medicine. "Low testosterone also increases the risk of sarcopenia, a loss of muscle that accelerates the aging process, so it has an impact on many different levels."

The aim of the study was to investigate the effect of surgical weight loss following sleeve gastrectomy on serum testosterone, DHEA (a precursor to testosterone), and PSA. This clinical study involved 24 obese male patients undergoing gastric sleeve surgery, also called sleeve gastrectomy, at Stanford Hospital. Serum testosterone, DHEA, and PSA were measured before and at three, six, and 12 months after the procedure.

The researchers found that the study group experienced a significant increase in average serum testosterone after undergoing sleeve gastrectomy. At 12 months, testosterone had increased on average from 295 to 423 ng/dL.

The normal range for circulating testosterone is 300 to 1000 ng/dL. A person is diagnosed with low serum testosterone when the level drops below 300 ng/dL.

Before the procedure, 63 percent of participants had low testosterone and afterwards, only 41 percent did. The average BMI was 46 before surgery and 31 after the operation. In addition, DHEA also rose, from 12.8 to 39.6 ng/mL, and serum PSA concentration rose over 12 months from 0.62 to 0.75 ng/mL with no change in PSA mass, which is a marker for prostate cancer progression.

"More men should seek surgical care for obesity as they carry more risk from their weight--low testosterone causes further weight gain, increases cardiac risk, and decreases quality of life. And sleeve gastrectomy can improve all of those comorbidities," Dr. Morton said.

Sleeve gastrectomy has never

been studied in this way before. Sleeve gastrectomy, which was introduced about 10 years ago, has replaced gastric bypass as the new gold standard in weight-loss operations. It's a shorter, lower-risk procedure.

"When you are obese, your fat becomes converted to estrogen, which will compete with testosterone and drive it down," Dr. Morton said.

"When patients are losing weight, they lose that estrogen, which causes natural testosterone stores to rise."

"The take home message is that if you are an obese man with low testosterone your therapy should be weight loss not testosterone replacement, and a successful way to achieve meaningful weight loss is through a bariatric operation," Dr. Morton concluded.

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