

INSIDE THIS ISSUE

Pg #

POM Loses Bid to Claim Health Benefits	1
MRI/Ultrasound Biopsy & High-Risk Disease	1
PDE5 Use & Risk of BCR after RP	1
Positive Surgical Margins & Mortality	2
Bone Complications from Long-Term ADT	2
Prostate Biopsies May Be More Accurate at Academic Centers	3
Doc Moyad's "No Bogus Science" Column – "Dietary Supplements and Jim Harbaugh"	3
Lap vs Mini-Lap Robot-Assisted RP & Scars	4
Providing Clinicians & Patients with Actual Prognosis: Cancer Vs Non-Cancer Mortality	5
Duration of ADT before RT—How Long?	6
Docs 'Astonished' about PDE5 Drugs & BCR	6
Doctor Chodak's Bottom Line	7



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HOTSHEET

MARCH 2015

POM WONDERFUL LOSES BID TO TOUT HEALTH BENEFITS IN DRINK ADS

Pomegranate juice maker POM Wonderful cannot advertise that its pomegranate drinks treat or prevent heart disease or other ailments unless it has proof, a U.S. appeals court said Friday, upholding an order by the Federal Trade Commission.

The U.S. Court of Appeals for the D.C. Circuit largely upheld a 2010 order by the Federal Trade Commission, which found that POM Wonderful's advertising was misleading in claiming its products would treat or reduce the risk of diseases ranging from heart disease to prostate cancer to erectile dysfunction. The advertisements that the FTC challenged appeared in Parade, Fitness and Prevention magazines, as well as online, and on product tags, the FTC said.

"Many of those ads mischaracterized the scientific evidence concerning the health benefits of POM's products with regard to those diseases. The FTC Act proscribes – and the First Amendment does not protect – deceptive and misleading advertisements," the court said in its ruling. But the appeals court said the FTC went too far in requiring two human clinical trial studies to support any health claims in advertising, saying there was "inadequate justification" for that demand.

(Continued on page 4)

MR/ULTRASOUND BIOPSY DETECTS MORE HIGH-RISK PROSTATE CANCERS

A targeted fusion-guided approach to prostate biopsy improves detection rates of high-risk cancers while finding fewer low-risk cancers when compared with the standard approach of 12 core biopsy that is currently used in clinical practice, according to a study published in the *Journal of the American Medical Association* (JAMA Vol. 313, pp. 390–397, 2015). However, there are no clinical outcome data as yet. The new approach electronically superimposes magnetic resonance images (MRIs) onto standard transrectal ultrasound images in real time, and thus provides a three-dimensional map of the prostate.

In contrast, the standard approach of taking 12 core samples seems to rely a lot on luck. "If any cancer is there, hopefully one of those 12 biopsies will catch that cancer. But you don't know. You could easily get an edge of a tumor or miss it altogether. That's been a dilemma for a long time," stated lead author M. Minhaj Siddiqui, MD, assistant professor of surgery at the University of Maryland School of Medicine and director of urologic robotic surgery at the Marlene and Stewart Greenebaum Cancer Center.

Another issue is that "biopsies come into the prostate from the back and miss cancer at the front, so they aren't even

(Continued on page 5)

PDE5 USE AND BIOCHEMICAL RECURRENCE AFTER RADICAL PROSTATECTOMY

Men who used phosphodiesterase type 5 (PDE5) inhibitors after radical prostatectomy (RP) had a significantly greater risk of PSA recurrence of prostate cancer compared with nonusers, German investigators reported.

During a median post-RP follow-up of 5 years, the biochemical relapse-free survival was 84.7% in PDE5 users and 89.2% in nonusers. In a multivariate analysis, PDE5 use after RP was an independent predictor of biochemical recurrence (BCR), as reported online in *The Journal of Urology*.

Following RP for localized prostate cancer, a substantial proportion of men who were sexually potent prior to surgery have erectile dysfunction that ranges from transient to permanent. Multiple studies of PDE5 inhibitors such as sildenafil (Viagra) have shown that postoperative use leads to higher rates of

(Continued on page 4)



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TOM KIRK
JACKIE KONIECZKA
CHUCK STRAND

US TOO INTERNATIONAL STAFF:

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JACKIE KONIECZKA, OFFICE MANAGER
TERRI GIBBONS LIKOWSKI, CHAPTER SERVICES MANAGER, PHONE +1 (877) 978-7866 (TOLL-FREE)
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2720 S. RIVER RD., STE. 112, DES PLAINES, IL 60018
PHONE: (630) 795-1002 / FAX: (630) 795-1602

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DETERMINANTS AND EFFECTS OF POSITIVE SURGICAL MARGINS AFTER PROSTATECTOMY ON PROSTATE CANCER MORTALITY: A POPULATION-BASED STUDY

Retèl VP, Bouchardy C, Usel M, et al
BMC Urol 5 November 2014; Epub

Background: The objective of this population-based study was to assess patient, physician and tumour determinants associated with positive surgical margins after prostatectomy, and to assess the effects of positive surgical margins on prostate cancer-specific survival.

Methods: We included 1,254 prostate cancer patients recorded at the Geneva Cancer Registry who had radical prostatectomy during 1990–2008. To assess factors associated with positive margins, we used logistic regression. We assessed the effects of positive margins on prostate cancer-specific survival (PCSS) by Cox proportional hazard models accounting for numerous other prognostic factors including prostate and tumour volume, the total percentage of tumour, radiotherapy, surgical approach and surgeon's caseload.

Results: Among men undergoing prostatectomy, 479 (38%) had positive margins. In the multivariate logistic regression analysis, period, clinical- and pathological T stage, PSA level, Gleason score and percentage of tumour in the prostate were significantly associated to positive margins. Ten-year PCSS was 96.6% for the negative margins group and 92.0% for the positive margins group (log rank $p = 0.008$). In the Cox survival analysis adjusted for tumour characteristics, surgical margin status per se was not an independent prognostic factor while age, pathological T, PSA level and Gleason score remained associated with PCSS.

Conclusions: More aggressive tumour characteristics were strong determinants for positive margins. Furthermore, surgical margin status per se was not an independent prognostic factor for PCSS after adjusting by the gravity of the disease in the multivariate analysis.

BONE COMPLICATIONS AMONG PROSTATE CANCER SURVIVORS: LONG-TERM FOLLOW-UP FROM THE PROSTATE CANCER OUTCOMES STUDY

Morgans AK, Fan K-H, Koyama T, et al
PCAN 17: 338–342, 2014

Background: To assess the relationship between androgen deprivation therapy (ADT) exposure and self-reported bone complications among men in a population-based cohort of prostate cancer survivors followed for 15 years after diagnosis.

Methods: The Prostate Cancer Outcomes Study enrolled 3,533 patients diagnosed with prostate cancer between 1994 and 1995. This analysis included participants with non-metastatic disease at the time of diagnosis that completed 15-year follow-up surveys to report development of fracture, and use of bone-related medications. The relationship between ADT duration and bone complications was assessed using multivariable logistic regression models.

Results: Among 961 surviving men, 157 (16.3%) received prolonged ADT (>1 year), 120 (12.5%) received short-term ADT (≤ 1 year) and 684 (71.2%) did not receive ADT. Men receiving prolonged ADT had higher odds of fracture (OR 2.5; 95% confidence interval (CI): 1.1–5.7), bone mineral density testing (OR 5.9; 95% CI: 3.0–12) and bone medication use (OR 4.3; 95% CI: 2.3–8.0) than untreated men. Men receiving short-term ADT reported rates of fracture similar to untreated men. Half of men treated with prolonged ADT reported bone medication use.

Conclusions: In this population-based cohort study with long-term follow-up, prolonged ADT use was associated with substantial risks of fracture, whereas short-term use was not. This information should be considered when weighing the advantages and disadvantages of ADT in men with prostate cancer.

PROSTATE BIOPSIES MAY BE MORE ACCURATE AT ACADEMIC CENTERS

Men may get more accurate prostate cancer biopsies at an academic medical center than at a community hospital, say Canadian researchers. The researchers analyzed follow-up biopsies done at Princess Margaret Cancer Center at the University of Toronto for 375 men being monitored with active surveillance. The researchers found that tumors initially biopsied at non-academic facilities were much more likely to be reclassified than those taken at a major medical center.

“Men having external initial biopsies were 3-4 times more likely to have grade or volume reclassification,” said lead author Dr. Lih-Ming Wong. Ultimately, 13.8% of men who had the first biopsy done at St. Margaret were reclassified as high-risk, compared with 26.8% of men initially biopsied elsewhere.

The study found that 19.7% of men initially evaluated elsewhere were reclassified from “low-risk” to “aggressive” tumor growth on the second biopsy, compared with 7.5% of men who got their first biopsy at the academic medical center. In addition, 20.3% of men first tested elsewhere were reclassified as high-risk because at least half of the tissue sampled was malignant, compared with 8.5% of the men biopsied both times at the Princess Margaret Cancer Centre, the researchers reported December 9 online in *Prostate Cancer and Prostatic Disease*.

Some men waited longer than the recommended six months to get a second biopsy, leading to reclassification as high-risk because of the delay. Still, the findings highlight the importance of seeking out the right specialists to do the original biopsy. Men should go where the most procedures are done, which is often an academic medical center, Wong said.

If it’s at all possible, men should travel to an academic medical center for a biopsy, especially if they have already found an abnormal result at a community hospital closer to home, said Dr. Jay Ciezki at the Cleveland Clinic’s Taussig Cancer Institute in Ohio. Even though the study was done at a single site in

(Continued on page 4)

DOC MOYAD’S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS “NO BOGUS SCIENCE” COLUMN

“Dietary Supplements can be messy and so can being friends with Coach Jim Harbaugh?”

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:

When purchasing a dietary supplement, especially herbal products, be careful and look for some kind of seal of approval (NSF, USP, NPA...) and single standardized ingredient. Otherwise you could be getting everything but the ingredient you wanted in the bottle! Yikes!

I especially love life right now! Jim Harbaugh is the new coach of the University of Michigan football team and I am 50-years old! Coach Harbaugh and I were friends in grade school in Ann Arbor, so of course I am excited for me, and him, and our team! Okay, we were not exactly best friends back then because during a flag football game in 4th grade, I was about to score a touchdown and he tackled me real hard, and my face went right into the ground, and it hurt like DOUBLE TOOTHPICKS! I really hated him for making my face part of the dirt on the field, but now I am grateful he did this so I can tell this story about him (hopefully we will be best friends soon and go bowling – no more flag tackle to the dirt football!)

Speaking of dirt (how about that segue!), you have probably been reading the NY Times and all the other articles that are questioning the quality control of many herbal products sold in major stores!¹ Whether or not the test results are completely accurate does not matter, because herbal dietary supplements have a history of being a mess for several reasons. First of all, there are many health claims on products that have no research to support them. Second of all, most of the well-designed studies on herbals used only one ingredient (like American ginseng and its ability to reduce cancer fatigue). Few studies support the efficacy of 10-15 ingredients in a bottle, products with which allows companies to charge higher prices and increase the possible risk of liver toxicity. Lastly, some products do not have a standardized active ingredient, so you

have no idea if you are getting the right amount of the ingredient.

For example, when it comes to the study by Mayo Clinic evaluating ginseng for cancer fatigue, researchers used a ginseng from Wisconsin that in general had only 3-5% ginsenosides (the active ingredient).² So, how do we resolve up this mess? Do not take any supplements unless you really think you need them for some medical condition (like fatigue from cancer treatment) while at the same time working with health care professionals you trust (MD, RN, PA, pharmacist, etc.). Then then look for only one compound that has a standardized active ingredient. Next, look for a seal of approval like NSF (many professional athletic organizations require this one) or USP or NPA on the label or web-site. Also check out other sites such as www.consumerlabs.com for the latest in testing results (fees may apply) .

Demand proof of quality control from the company or some transparency. Do not take a multivitamin with an herbal ingredient in it because in the largest studies ever completed (like the Centrum Silver studies) showed no herbal products in these multivitamins. And, there is rarely a relationship between price and quality. In other words, some of the least expensive products have great quality control and some of the more expensive do not; but do your own research. Finally, I have to go wait by the phone in case Coach Harbaugh calls and wants to go bowling or get a few beers! I can’t wait to see him and I hope he gives me a big handshake and a big hug! I really hope he does not push me into the dirt again. But if he did, that would be awesome because I could sell that story to some tabloid magazine and make a lot of money!

References:

1. O’Connor A. NY times, 02/03/15.
2. Barton DL, Liu H, Dakhil SR, et al. J Natl Cancer Inst 105:1230-1238, 2013.

ACADEMIC CENTERS

(Continued from page 3)

Toronto, the findings should be applicable in the U.S. because the difference in expertise between academic medical centers and local hospitals is widespread, said Ciezki, who was not involved in the research.

One shortcoming of the study, however, is the type of biopsy involved, said Dr. Leonard Marks, a urologist at the University of California, Los Angeles Medical Center and Jonsson Comprehensive Cancer Center. It relied on conventional ultrasound-guided biopsies, which are much less accurate than the targeted biopsies guided by MRI images used at UCLA and a growing number of other academic medical centers, said Marks, who was not involved in the study.

“Ultrasound-guided biopsy is blind; it doesn’t see cancer,” Marks said. “If you do it the modern way using MRI, the imaging tells you where to go with the needle to get the tissue you need. That MRI imaging is sophisticated and probably wouldn’t be too widely available outside of academic medical centers.”

Reuters Health, 16 January 2015

POM WONDERFUL

(Continued from page 1)

POM said it was pleased with this portion of the decision. “We are grateful that the court substantially reduced the requirement that the FTC tried to enforce on us to conduct multiple double-blind, placebo-controlled studies,” the company said in a statement.

The FTC said the decision was a victory for consumers. “It is in keeping with established law that advertisers who market products for serious health conditions must have rigorous science to back up those claims,” wrote FTC Chairwoman Edith Ramirez in a statement. “The court specifically recognized that this applies to food and dietary supplement marketers such as POM.”

The advertisements that most concerned the FTC were discontinued in 2005 and others were halted in 2007, said lawyer Thomas Goldstein when he argued for POM Wonderful before the judges in May 2014.

Reuters, 30 January 2015

RETROPUBLIC, LAPAROSCOPIC AND MINI-LAPAROSCOPIC

RADICAL PROSTATECTOMY: A PROSPECTIVE ASSESSMENT OF PATIENT SCAR SATISFACTION

Quattrone C, Cicione A, Oliveira C, et al

World J Urol 26 October 2014; Epub

Purpose: To compare patient scar satisfaction after retropubic, standard laparoscopic, mini-laparoscopic (ML) and open radical prostatectomy (RP).

Methods: Patients undergoing RP for a diagnosis of localized prostate cancer at a single academic hospital between September 2012 and December 2013 were enrolled in this prospective nonrandomized study. The patients were included in three study arms: open surgery, VLP and ML. A skin stapler was used for surgical wound closure in all cases. Demographic and main surgical outcomes, including perioperative complications, were analyzed. Surgical scar satisfaction was measured using the Patient and Observer Scar Assessment Questionnaire (POSAS) and the two Body Image Questionnaire (BIQ) scales, respectively, recorded at skin clips removal and either at 6 months after surgery.

Results: Overall, 32 patients were enrolled and completed the 6 month of follow-up. At clips removal, laparoscopic approaches offered better scar result than open surgery according to the POSAS. However, at 6 months, no differences were detected between VLP and open, whereas ML was still associated with a better scar outcome ($p = 0.001$). This finding was also confirmed by both BIQ scales, including the body image score (ML 9.8 ± 1.69 , open 15.73 ± 3.47 , VLP 13.27 ± 3.64 ; $p = 0.001$) and the cosmetic score (ML 16.6 ± 4.12 , open 10 ± 1.9 , LP 12.91 ± 3.59 ; $p = 0.001$). Small sample size and lack of randomization represent the main limitations of this study.

Conclusions: ML RP offers a better cosmetic outcome when compared to both open and standard laparoscopic RP, representing a step toward minimal surgical scar. The impact of scar outcome on RP patients' quality of life remains to be determined.

PDE5 INHIBITORS AND BCR

(Continued from page 1)

potency preservation.

Preclinical studies have suggested a beneficial effect of PDE5 inhibitors on the risk of cancer recurrence. One recent study showed a lower risk of prostate cancer among men who used PDE5 inhibitors versus those who did not. However, limited clinical data have accumulated regarding the impact of post-RP PDE5 use on oncologic outcomes, Derya Tilki, MD, of University Hospital Hamburg-Eppendorf in Germany, and co-authors reported.

To examine the relationship of PDE5 use and BCR after RP, Tilki and colleagues retrospectively reviewed records of 4,752 consecutive men who underwent bilateral nerve-sparing RP at the Hamburg center from January 2000 through December 2010. They excluded patients who received neoadjuvant or adjuvant hormonal therapy and those who received adjuvant radiation therapy.

The patients had a median age of 64. Final pathologic results showed that 86.2% of the study population had pathologic T2 disease. A fourth of the patients used PDE5 inhibitors after RP.

The multivariate analysis showed that PDE5 use increased the hazard for BCR by almost 40% (HR 1.38, 95% CI 1.11-1.70, $P = 0.0035$). The analysis showed no association between BCR and age, body mass index, or smoking. A propensity-matched analysis involving 1,102 pairs of men (PDE5 user versus nonuser) showed a significantly inferior BCR-free survival in men who used PDE5 inhibitors ($P = 0.005$).

MedPage Today, 24 January 2015



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MR/ULTRASOUND BIOPSY DETECTS MORE HIGH-RISK PROSTATE CANCERS

(Continued from page 1)

that good at identifying all the cancer,” commented Anthony Zietman, MD, the Jenot and William Shipley Professor of Radiation Oncology at Harvard Medical School and Massachusetts General Hospital, in Boston, MA, who was not involved in the study. He added, however, that biopsies “are good at telling us how nasty the cancer they find is,” referring to the Gleason grade.

The 15-year survival rate for men diagnosed early with prostate cancer is 94%. But there is much concern about over-treatment, because many men diagnosed with prostate cancer undergo radical prostatectomy (RP) to treat cancers that would never have advanced.

“Because many men are overtreated, perhaps the most pressing issue in management is identifying aggressive cases. As functional and molecular imaging approaches advance, they become appealing means by which to uncover more aggressive cases,” commented Martin Pomper, MD, PhD, William R. Brody Professor of Radiology at Johns Hopkins Medical School, in Baltimore, MD, who was not involved in the study. Dr Siddiqui et al, “hypothesized that multiparametric MR-targeted biopsy, a functional imaging approach, would prove superior at identifying high-risk prostate cancer than the conventional, random sampling approach. And that is precisely what they found in their prospective study.”

The study began in 2007, at the NIH, enrolling 1,003 men referred for biopsy following detection of elevated PSA or abnormal findings on digital rectal examination (DRE). Some of the men had had negative results on standard biopsies but were still concerned about high PSA or abnormal DRE. Participants agreed to undergo targeted and standard biopsies, performed at the same time.

Targeted biopsy detected 461 prostate cancer cases, and standard biopsy found 469. Risk categorization “demonstrated exact agreement” between the two strategies for 690/1,003 (69%) of the men.

Although targeted and standard biopsies detected approximately the same number of cancers, the targeted approach found 30% more high-risk cancers (173 targeted vs. 122 standard, $P < 0.001$) and

17% fewer low-risk cancers (213 vs. 258, $P < 0.002$). Standard biopsy cores plus targeted biopsies diagnosed an additional 103 cases (22%), of which 83% were low-risk, 12% intermediate-risk, and 5% high-risk.

It would take 200 standard biopsies combined with targeted biopsy to diagnose one additional high-risk cancer, the researchers estimated. Standard biopsy would find 17 more low-risk cancers for every additional high-risk cancer. Adding standard biopsy to targeted biopsy did not alter the Gleason score in 857 cases (85%), and of those whose risk category changed, 86 (9%) went from no cancer to low-risk cancer, and 19 (2%) went from no cancer or low- or intermediate-risk to higher risk.

By comparing biopsy specimens to tissue removed from 170 men treated by RP, the sensitivity of targeted biopsy was 77% vs. 53% for standard biopsy. Specificities were similar (targeted, 68%, vs standard, 66%).

The fused approach might calm fears in some patients, Dr Siddiqui said. “We found that the low-risk, low-volume cancer that’s not aggressive doesn’t show up on MRI. Targeted biopsy doesn’t even catch those; it decreases the rate of diagnoses of low-risk prostate cancers by 17%. And that’s helpful,” he said.

The new approach will influence active surveillance, according to Dr Siddiqui. “A provider can feel more confident telling someone with a low-risk diagnosis based on targeted biopsy that the chances are there’s not something hiding in the prostate you’re missing. Now we are no longer relying on 12 random pieces.”

Dr Pomper, who was not involved in the research, commented to Medscape Medical News: “This study is an important step toward identifying patients who would be more likely to benefit from definitive therapy and shows that MR guidance alone provides the best decision guide with respect to performing surgery. As duly noted by the authors, that this result portends lower morbidity or mortality remains to be seen, but it certainly makes sense that ferreting out the most aggressive cases – and treating them appropriately – will do just that.”

Limitations of the study include the mix of situations that prompted men to participate and the fact that the study did not assess clinical endpoints such as recurrence and mortality. Patients with no visible lesions on MRI were excluded, which may explain the lower detection of low-risk cancers.

In an accompanying editorial, Lawrence H. Schwartz, MD, from the Department of Radiology, Columbia University College of Physicians and Surgeons and New York Presbyterian Hospital, in New York, and Ethan Basch, MD, from the Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, applaud targeted fusion biopsy. However, they caution against wide adoption until further studies demonstrate clear “benefits on quality of life, life expectancy, or, ideally, both.”

Study coauthors Dr Choyke and Dr Pinto hold a patent related to the MR/ultrasound fusion biopsy platform, and Dr Wood holds several patents related to imaging and prostate biopsy.

Medscape Medical News, 27 January 2015

PROVIDING CLINICIANS AND PATIENTS WITH ACTUAL PROGNOSIS: CANCER IN THE CONTEXT OF COMPETING CAUSES OF DEATH

Howlader N, Mariotto A, Woloshin S, et al

J NCI Monogr 2014; 49: 255-64

Objective: To compare cancer and actual prognosis in the United States for four leading cancers—lung, breast, prostate, and colon—by age, comorbidity, and cancer stage and to provide templates to help patients, clinicians, and researchers understand actual prognosis.

Method: Using population-based registry data from the Surveillance, Epidemiology, and End Results (SEER) Program, we calculated cancer prognosis (relative survival) and actual prognosis (five-year overall survival and the “crude” probability of dying from cancer and competing causes) for three important prognostic determinants (age, comorbidity (Charlson-score from 2012 SEER-Medicare linkage dataset) and cancer stage at diagnosis).

(Continued on page 8)

DURATION OF ANDROGEN SUPPRESSION BEFORE RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER: RADIATION THERAPY ONCOLOGY GROUP RANDOMIZED CLINICAL TRIAL 9910

Pisansky TM, Hunt D, Gomella LG, et al
J Clin Oncol 22 December 2014; Epub

Purpose: To determine if prolonged androgen suppression (AS) before radiotherapy (RT) improves survival and disease control in prostate cancer (PCa).

Patients and Methods: One thousand five hundred seventy-nine men with intermediate-risk PCa were randomly assigned to eight weeks of AS followed by RT with an additional eight weeks of concurrent AS (16 weeks total) or to 28 weeks of AS followed by RT with an additional eight weeks of AS (36 weeks total). The trial sought primarily to detect a 33% reduction in the hazard of PCa death in the 28-week assignment. Time-to-event end points are reported for up to 10 years of follow-up.

Results: There were no between-group differences in baseline characteristics of 1,489 eligible patients with follow-up. For the 8- and 28-week assignments, 10-year disease-specific survival (DSS) rates were 95% (95% CI, 93.3–97.0%) and 96% (95% CI, 94.6–98.0%; hazard ratio [HR], 0.81; $P = 0.45$), respectively, and 10-year overall survival rates were 66% (95% CI, 62.0–69.9%) and 67% (95% CI, 63.0–70.8%; HR, 0.95; $P = 0.62$), respectively. For the 8- and 28-week assignments, 10-year cumulative incidences (CIs) of locoregional progression were 6% (95% CI, 4.3–8.0%) and 4% (95% CIs, 2.5–5.7%; HR, 0.65; $P = 0.07$), respectively; 10-year distant metastasis CIs were 6% (95% CI, 4.0–7.7%) and 6% (95% CI, 4.0–7.6%; HR, 1.07; $P = 0.80$), respectively; and 10-year BCR CIs were 27% (95% CI, 23.1–29.8%) and 27% (95% CI, 23.4–30.3%; HR, 0.97; $P = 0.77$), respectively.

Conclusion Extending AS duration from eight weeks to 28 weeks before RT did not improve outcomes. A lower than expected prostate cancer death rate reduced ability to detect a between-group difference in DSS. The schedule of 8 weeks of AS before RT plus 8 weeks of AS during RT remains a standard of care in intermediate-risk prostate cancer.

DOCS ‘ASTONISHED’ ED DRUGS TIED TO PROSTATE CANCER RETURN

Sometimes a scientific hypothesis is all wrong but scientific understanding moves forward anyway. That might be the case in a study of men with prostate cancer. In the study, researchers found an association between the use of erectile dysfunction (ED) drugs after radical prostatectomy (RP) and biochemical recurrence (BCR). They were surprised by the findings; they expected the opposite results because they had hypothesized that the drugs would be protective because multiple lab studies and an observational clinical study suggested an anticancer effect in the prostate.

“We still advise our patients to use PDE5 [phosphodiesterase type 5] inhibitors on demand,” said lead researcher Uwe Michl, MD, from the Martini-Klinik Prostate Cancer Center in Hamburg, Germany. “PDE5 inhibitors are effective in treating ED following nerve-sparing RP, assuming that there are still some spontaneous but insufficient erections.”

The findings about cancer risk are not entirely novel. Sildenafil was associated with an increased risk for melanoma in 25,000 men in the Health Professionals’ Follow-up Study (HPFS), as reported by Medscape Medical News. Dr Michl reported that his team is hoping to work with the HPFS investigators to evaluate their data with respect to prostate cancer.

In their study, the German researchers reviewed data on 4752 consecutive men who had undergone RP from 2000 to 2010 at the Martini-Klinik, which is one of the world’s largest centers for prostate cancer. After surgery, about a quarter of the men (23.4%) were treated with a PDE5 inhibitor for ED using the drugs sildenafil (Viagra), vardenafil (Levitra), and/or tadalafil (Cialis). The other 76.6% of the men did not receive a PDE5 inhibitor.

The two patient groups were comparable on most clinical parameters. Five-year BCR-free survival estimates were lower in the treated than in the untreated group (84.7% vs. 89.2%; $P = 0.0006$). In other words, ED treatment with a PDE5 inhibitor was associated with a significant reduction in the rate of being free of recurrence. The median follow-up in the study was 60.3 months.

On multivariate regression analysis, the use of PDE5 inhibitors was an independent risk factor for BCR (hazard ratio [HR], 1.38; $P = .0035$), Dr Michl and his colleagues report. Notably, the team found no significant association between BCR and age, body mass index (BMI), or smoking in that analysis. These three variables are known risk factors for ED and have been associated with BCR after RP.

On propensity score matched analysis (parameters included PSA, Gleason score, and tumor stage), biochemical recurrence-free survival was significantly worse in the treated than in the untreated group ($P = 0.005$). “Correction for several confounders did not change these results,” Dr Michl said.

The study is the first of its kind. No other research has looked at the use of these drugs after prostate cancer surgery and their impact on BCR. “Our results need to be interpreted with caution,” Dr Michl and his colleagues write in their study, which was published in the February issue of *The Journal of Urology* (Vol. 193, pp. 479–483, 2015).

The researchers speculate about possible mechanisms behind the adverse outcome. “The effects of sildenafil and other selective PDE5 inhibitors on the immune system, on autonomic nerve development as well as on angiogenesis, are conceivable causes of our findings,” they write. There have also been multiple reports from labs that these drugs might thwart cancer prostate cancer growth and postpone metastasis. In fact, lab evidence on ED drugs in prostate and other cancers has prompted some investigators to call for the “repurposing” of PDE5 inhibitors for adjuvant chemotherapy.

PDE5 inhibitors have “revolutionized” the treatment of ED, the researchers report. But right now, they say, it is not known whether that is a good or a bad thing for men who have undergone surgery for prostate cancer and use these drugs. More study is needed, and men and their doctors await more data.

Medscape Medical News, 27 January 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 *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.

a2p1c2 Much has been written about the overtreatment of prostate cancer and many investigators are searching for methods to reduce this problem. One way is to avoid diagnosing a non-life threatening cancer without reducing the detection or more aggressive tumors. Using MRI to target biopsies may provide a partial solution to this problem. A large prospective study done at the NIH compared conventional 12-core ultrasound guided random biopsies to focal biopsies done based on MRI. The latter detected more high-grade cancers and omitted finding some of the low risk cancers. However, MRI alone will miss some high-grade cancers so it remains unclear whether the two need to be combined to avoid missing significant disease. Although progress is being made, the ultimate benefits of using MRI to perform prostate biopsies still have yet to be defined. There may be a role for MRI to be used now in evaluating men for active surveillance (AS) because it may identify men with higher risk cancers than were detected by the initial biopsy.

The Bottom Line: Research with MRI-guided biopsies is progressing but questions still remain as to whether it should be done in place of or in conjunction with ultrasound guided random biopsies.

a3p1c3 Is the use of PDE5 inhibitors to help improve sexual function after radical prostatectomy (RP) harmful to patients? That is the subject of a provocative paper by Michi and co-workers from a center in Germany. They conducted a retrospective analysis of nearly 4,800 men that were treated by RP between 2000-2010. About one-quarter of the men used one of these drugs and the remainder did not. They found a statistically higher biochemical recurrence (BCR) rate in the men using any of these drugs. Should these results deter men from using a PDE5 in the future? The answer is a definite NO. This study does not prove a true risk for patients. The authors acknowledge some of the methodological limitations of their analysis. The study was retrospective and there was no determination whether the effect was

similar for all the PDE5 inhibitors available. Another limitation is that there was no attempt to quantify the amount of drug needed to raise a man's risk or prove that the risk applied to men who ingested very small amounts of the drug.

The Bottom Line: Until a well-designed study is conducted, men do not need to avoid taking a PDE5 inhibitor to help improve their sexual function.

a4p2c1 What is the significance of finding a positive surgical margin (PSM) after RP? That question is partly addressed in the study by Retel and co-workers who conducted a multivariate analysis of men undergoing RP over an 18-year period. They found nearly 40% of the men had a PSM; however, it was not a significant predictor of prostate cancer mortality. Factors associated with mortality included age, pathological T stage, PSA level and Gleason score. It is unclear from the abstract whether the authors conducted additional analysis of the PSM group to determine if a subset of them were at greater risk of dying from their disease. For example, if a man had a PSM and a Gleason score of 8, was he more likely to die from his disease compared to a man with a negative margin and the same Gleason score? Other studies have found a higher risk of recurrence when the margin was positive. One of the limitations of this study is that some men received adjuvant RT and some received it for BCR. These two groups were combined together for the analysis, which could provide a misleading result. The amount of RT also was not defined but if different doses were used it could have impacted on the results. Lastly, since the men were not randomized, the use of RT in some cases may have biased the results.

The Bottom Line: Although this study found margin status to be less predictive of cancer mortality, other studies have found different results so more work is needed to define the significance of a positive margin.

a5p2c3 For years, many men with a ris-

ing PSA were started on ADT without evidence of a true improvement in survival or reduction in metastases. Over time, the side effects of this long-term use have been increasingly recognized. One of them is osteoporosis possibly leading to fracture. Morgans, et al looked at this risk in men followed for 15 years in the Prostate Cancer Outcomes Study, a non-randomized cohort of men followed after a diagnosis of non-metastatic disease. Patients on ADT for more than one year were about 2.5 times more likely to develop a fracture and 4.3 times more likely to be on bone medication. What we do not know about this cohort is how many of the men were taking ADT because of metastatic disease, which is appropriate vs. taking it for a rising PSA, which still has unproven benefit. For those taking it appropriately, the use of bone medication is important because it does reduce the risk of fracture.

The Bottom Line: Long-term use of ADT does increase the risk of fracture and the need for bone medication so it should be limited to men that clearly will benefit from protection against this risk, namely those with metastatic disease. The benefit in men with a rising PSA remains unknown.

a6p3c1 Are men better off having their biopsy at a University hospital compared to a community practice? That question was addressed by a Canadian study that found men were significantly more likely to have their cancer upgraded if the initial biopsy was done in the community rather than at a University center. Several concerns are raised about this study. First, it was not randomized, which means the results would need to be confirmed by another properly done trial. Second, the analysis was limited to a single academic center in Canada and it is unclear how those results would be affected if done in the US or at other academic centers in Canada. A third concern is whether the same number of cores was being used by all the community biopsies because this could influence the findings on the repeat study. The other

(Continued on page 8)

DOCTOR CHODAK’S BOTTOM LINE (Continued from page 7)

question raised by one of the commentators is whether MRI guided biopsies would give more accurate results how that would influence the difference between community-based and University-based centers.

The Bottom Line: Better studies are needed to determine if there is truly a significant difference in the accuracy of prostate biopsies between community and academic physicians.

a9p5c3 Counseling patients about their prognosis is vital to help men select their therapy. Unfortunately, few randomized studies have been done comparing different therapies. Consequently, doctors must select from a wide range of uncontrolled trials. Are the results cited consistent? Are they applicable to men at different ages? Doctors recognize that older or less healthy individuals will have a shorter OS than healthier patients. The paper by Howlader and co-workers makes a case for studies reporting both OS and DSS in order to reduce potential bias that occur by only reporting OS. The only way to eliminate that need is to conduct future randomized trials comparing different therapies.

The Bottom Line: Studies reporting outcomes for various prostate cancer therapies may be misleading when only OS is reported. Including DSS may reduce that bias.

a10p6c1 Well-done studies have established the value of combining radiation therapy (RT) and androgen deprivation therapy (ADT) for men with intermediate and high-risk disease. Studies have continued to search for the optimum duration of the ADT. A large, recent study compared a total of 16 weeks to 36 weeks in men with intermediate risk prostate cancer. With 10 years of follow-up, no difference could be detected in overall survival (OS), disease specific survival (DSS), loco-regional progression, or metastatic disease-free survival. On the basis of this study, men with intermediate risk prostate cancer will achieve the best survival by combining RT with a total of 16 weeks of ADT.

The Bottom Line: Men with intermediate risk prostate cancer can derive a survival benefit with 16 weeks of ADT with RT that does not improve with longer duration of ADT.

PROVIDING ACTUAL PROGNOSIS

(Continued from page 5)

Result: For younger, healthier, and earlier stage cancer patients, cancer and actual prognosis estimates were quite similar. For older and sicker patients, these prognosis estimates differed substantially. For example, the five-year overall survival for an 85-year-old patient with colorectal cancer is 54% (cancer prognosis) versus 22% (actual prognosis) – the difference reflecting the patient's substantial chance of dying from competing causes. The corresponding five-year chances of dying from the patient's cancer are 46% versus 37%. Although age and comorbidity lowered actual prognosis, stage at diagnosis was the most powerful factor: The five-year chance of colon cancer death was 10% for localized stage and 83% for distant stage.

Conclusion: Both cancer and actual prognosis measures are important. Cancer registries should routinely report both cancer and actual prognosis to help clinicians and researchers understand the difference between these measures and what question they can and cannot answer. We encourage them to use formats like the ones presented in this paper to communicate them clearly.

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