Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

FEBRUARY 2013

UPDATED TOOL NOW AVAILABLE TO PREDICT PROSTATE CANCER SPREAD

Prostate cancer experts at Johns Hopkins have developed an updated version of the Partin Tables, a tool to help men diagnosed with prostate cancer and their doctors to better assess their chance of a surgical cure. The updated tool, based on a study of more than 5,600 men treated at Johns Hopkins from 2006 to 2011, is published in the January issue of the *British Journal of Urology International*.

"The first thing most men want to know when they learn they have prostate cancer is their prognosis – whether it can be cured," says Alan W. Partin, MD, PhD, professor and director of Urology at the Johns Hopkins University School of Medicine, and creator of the Partin Tables. "The Partin Tables are a statistical model to show the probability that the cancer is confined to the prostate and therefore is likely to be cured with surgery," he says.

The model is based on a patient's PSA level, Gleason Score, and clinical stage.

Treatment decisions for prostate cancer are very complex and depend on a variety of factors, including whether the cancer is confined to the prostate or whether it has spread to the edge of the gland, seminal vesicles, lymph nodes or elsewhere in the body. Data for the Partin Tables, first published in 1993, have

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BAYER SUBMITS NEW DRUG APPLICATION FOR RADIUM (RA-223 DICHLORIDE) FOR THE TREATMENT OF CASTRATION-RESISTANT PROSTATE CANCER (CRPC) WITH BONE METASTASES

Bayer HealthCare announced in December 2012 that the company has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) seeking approval for radium-223 dichloride (radium-223), an investigational compound for the treatment of castration-resistant prostate cancer (CRPC) patients with bone metastases.

"If approved, radium-223 has the potential to play a key role in the treatment of men with CRPC that has metastasized to the bone," said Pamela A. Cyrus, MD, Vice President and Head of U.S. Medical Affairs, Bayer HealthCare Pharmaceuticals. "The development of a compound like radium-223 is an example of Bayer's commitment to investing in approaches to treat hard-to-treat cancers."

Radium-223 (proposed trade name Alpharadin) was granted fast track designation by the FDA. The fast track process is designed to facilitate the development and expedited review of drugs to treat serious diseases and fill an unmet medical need. Fast track designation must be requested by the drug company and can be initiated at any time during the drug development process.

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HOW PROSTATE CANCER THERAPIES COMPARE BY COST AND EFFECTIVENESS

The most comprehensive retrospective study ever conducted comparing how the major types of prostate cancer treatments stack up to each other in terms of saving lives and cost effectiveness was recently reported by a team of researchers at the University of California, San Francisco (UCSF).

Appearing online ahead of print in the *British Journal of Urology International*, the work analyzed 232 papers published in the last decade that report results from clinical studies following men with low-, intermediate- and high-risk forms of prostate cancer who were treated with one or more of the standard treatments – radiation therapy (RT), radical prostatectomy (RP), androgen deprivation therapies (ADT) and brachytherapy (BT).

The analysis shows that for men with low-risk prostate cancer, the various treatments vary only slightly in terms of survival – the odds of which are quite good for men with this type of cancer, with a 5-year cancer-specific survival rate of nearly 100 percent. But the cost of RT is significantly higher than RP for low-risk prostate cancer, they found.

For intermediate- and high-risk cancers, both survival and cost generally favored RP over other forms of treatment – although combination external-beam RT

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POTENTIAL IMPACT OF ADDING GENETIC MARKERS TO CLINICAL PARAMETERS IN PREDICTING PROSTATE BIOPSY OUTCOMES IN MEN FOLLOWING AN INITIAL NEGATIVE BIOPSY: FINDINGS FROM THE REDUCE TRIAL

Kader AK, Sun J, Reck BH, et al

Eur Urol 62: 953-61, 2012

Background: Several germline single nucleotide polymorphisms (SNPs) have been consistently associated with prostate cancer (PCa) risk.

Objective: To determine if there is an improvement in PCa risk prediction by adding these SNPs to existing predictors of PCa.

Design, Setting, and Participants: Subjects included men in the placebo arm of the randomized Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial in whom germline DNA was available. All men had an initial negative prostate biopsy and underwent study-mandated biopsies at 2 yr and 4 yr. Predictive performance of baseline clinical parameters and/or a genetic score based on 33 established PCa risk-associated SNPs was evaluated.

Outcome Measurements and Statistical Analysis: Area under the receiver operating characteristic curves (AUC) were used to compare different models with different predictors. Net reclassification improvement (NRI) and decision curve analysis (DCA) were used to assess changes in risk prediction by adding genetic markers.

Results and Limitations: Among 1654 men, genetic score was a significant predictor of positive biopsy, even after adjusting for known clinical variables and family history ($p=3.41\times10(-8)$). The AUC for the genetic score exceeded that of any other PCa predictor at 0.59. Adding the genetic score to the best clinical model improved the AUC from 0.62 to 0.66 ($p<0.001$), reclassified PCa risk in 33% of men (NRI: 0.10; $p=0.002$), resulted in higher net benefit from DCA, and decreased the number of biopsies needed to detect the same number of PCa instances.

The benefit of adding the genetic score was greatest among men at intermediate risk (25th percentile to 75th percentile). Similar results were found for high-grade (Gleason score ≥ 7) PCa. A major limitation of this study was its focus on white patients only.

Conclusions: Adding genetic markers to current clinical parameters may improve PCa risk prediction. The improvement is modest but may be helpful for better determining the need for repeat prostate biopsy. The clinical impact of these results requires further study.

TARGETED PROSTATE CANCER BIOPSIES MIGHT IMPROVE CARE

Researchers at the University of California, Los Angeles, say prostate tumors can be diagnosed using "image-guided targeted biopsy" – the direct sampling of tumors in tissue using both MRI and real-time 3-dimentional ultrasound (3D-US). The UCLA team says this targeted form of biopsy is much more accurate than conventional "blind" biopsies that do not enable doctors to actually see the tumors. They suggested the new procedure may improve early detection of prostate cancer and result in fewer biopsies overall.

"Early prostate cancer is difficult to image because of the limited contrast between normal and malignant tissues within the prostate," study senior author Dr. Leonard Marks, a professor of urology and director of the UCLA Active Surveillance Program, said in a university news release. Of the 1 million prostate biopsies performed in the US every year, approximately 75 percent are negative for prostate cancer. Men who remain suspect for harboring prostate cancer undergo a repeat biopsy at some point when the PSA test continues to rise.

The problem with this approach, according to Dr. Warren Bromberg, chief of urology at Northern Westchester Hospital in Mount Kisco, NY, who was not involved in the study, is "insignificant cancers are detected as often as significant ones, there is always the fear that a cancer was missed, and there are risks of infection, pain and bleeding."

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2-WEEKLY VERSUS 3-WEEKLY DOCETAXEL TO TREAT CASTRATION-RESISTANT ADVANCED PROSTATE CANCER: A RANDOMISED, PHASE 3 TRIAL

Kellokumpu-Lehtinen P-L, Harmenberg U, Joensuu T, et al

The Lancet Oncology, 4 January 2013, Epub

Background: Docetaxel administered every 3 weeks is a standard treatment for castration-resistant advanced prostate cancer. We hypothesised that 2-weekly administration of docetaxel would be better tolerated than 3-weekly docetaxel in men with advanced castration-resistant prostate cancer (CRPC), and did a prospective, multicentre, randomised, phase 3 study to compare efficacy and safety.

Methods: Eligible men had advanced prostate cancer (metastasis, a PSA result of more than 10·0 ng/mL, and WHO performance status score of 0–2), had received no chemotherapy (except estramustine), had undergone surgical or chemical castration, and had been referred to a treatment centre in Finland, Ireland, or Sweden. Enrollment and treatment were done between March 1, 2004, and May 31, 2009. Randomisation was done centrally and stratified by centre and WHO performance status score of 0–1 vs 2. Men were assigned 75 mg/m^2 docetaxel intravenously (IV) on day 1 of a 3-week cycle, or 50 mg/m^2 docetaxel IV on days 1 and 15 of a 4-week cycle. 10 mg oral prednisolone was administered daily to all men. The primary endpoint was time to treatment failure (TTTF). We assessed data in the per-protocol population. This study is registered with ClinicalTrials.gov, number NCT00255606.

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TREATMENT COST AND EFFECTIVENESS *(Continued from page 1)*

and BT together were comparable in terms of quality of life-adjusted survival for high-risk prostate cancer.

"Our findings support a greater role for surgery for high-risk disease than we have generally seen it used in most practice settings," said urologist Matthew Cooperberg, MD, MPH who led the research. Cooperberg is an assistant professor of urology and epidemiology and biostatistics in the UCSF Helen Diller Family Comprehensive Cancer Center.

There are multiple types of treatment for this form of the disease, including open, laparoscopic or robot-assisted RP; RT (dose-escalated 3-dimensional conformal RT, intensity-modulated RT); BT; ADT; and combinations of each. Many men with low-risk prostate cancer do not need any of these treatments, and can be safely observed (using active surveillance, or AS) at least initially.

Treatment plans for localized prostate cancer often vary dramatically from one treatment center to another. As Cooperberg put it, one person may have RP, while someone across town with a very similar tumor may have RT, and a third may undergo AS. Men may respond equally well to any treatment regimen.

"There is very little solid evidence that one [approach] is better than another," said Cooperberg. The motivation for the new study, however, was that there are also few data examining the differences in terms of cost-effectiveness – the price to the health care system for every year of life gained, with adjustment for complications and side effects of treatments.

The new study was the most comprehensive cost analysis ever, and it compared the costs and outcomes associated with the various types of treatment for all forms of the disease, which ranged from $19,901 for robot-assisted RP to treat low-risk disease, to $50,276 for combined RT for high-risk disease.

The study did not consider two other approaches for dealing with prostate cancer: AS and proton therapy, the latter of which is much more expensive and has been shown not to be cost-effective in multiple studies, said Cooperberg.

The work was supported by the National Cancer Institute, a component of the National Institutes of Health through grant #5RC1CA146596, and by the US Agency for Healthcare Research and Quality through grant #1U01CA88160.

Science Daily, 4 January 2013

ASSOCIATIONS OF ADIPONECTIN AND LEPTIN WITH STAGE AND GRADE OF PSA-DETECTED PROSTATE CANCER: THE PROTECT STUDY

Burton A, Martin RM, Holly J, et al

Cancer Causes Control, 8 December 2012; Epub ahead of print

Purpose: Obesity has been associated with an increased risk of advanced and fatal prostate cancer; adipokines may mediate this association. We examined associations of the adipokines leptin and adiponectin with the stage and grade of PSA-detected prostate cancer.

Methods: We conducted a nested case-control study comparing 311 men with mainly locally advanced (≥T3, N1, or M1 cases) vs. 413 men with localized (T ≤ 2 & NX-0 & M0 controls) PSA-detected prostate cancer, recruited 2001-2009 from 9 UK regions to the ProtecT study. Associations of body mass index and adipokine levels with prostate cancer stage were determined by conditional logistic regression and with grade (Gleason score ≥7 vs. ≤ 6) by unconditional logistic regression.

Results: Adiponectin was inversely associated with prostate cancer stage in overweight and obese men (OR 0.62; 95 % CI 0.42-0.90; p = 0.01), but not in normal weight men (OR 1.48; 0.77-2.82; p = 0.24) (p for interaction 0.007), or all men (OR 0.86; 0.66-1.11; p = 0.24). There was no compelling evidence of associations between leptin or leptin to adiponectin ratio and prostate cancer stage. No strong associations of adiponectin, leptin, or leptin:adiponectin ratio with grade were seen.

Conclusions: This study provides some evidence that adiponectin levels may be associated with prostate cancer stage, dependent on the degree of a man's adiposity. Our results are consistent with adiponectin countering adverse effects of obesity on prostate cancer progression.

UPDATED PARTIN TABLES

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been based on the outcomes for more than 20,000 men who underwent radical prostatectomy (RP) at Johns Hopkins over the past three decades. This represents the third update of the data.

"Twenty years ago, before widespread adoption of PSA for early detection, many men were diagnosed with prostate cancer after their cancer had spread. Today, the vast majority of men are diagnosed when the cancer is still confined to the prostate, giving them a much better chance of a cure with a surgical removal of the prostate," says Partin.

John B. Eifler, MD, the lead author of the article who worked with Partin on the revision, says the new Partin Tables show that certain categories of men who were previously not thought to have a good prognosis actually could be cured with surgery. "We now have a better understanding of intermediate risk and see that more men now fall into that category, instead of the higher risk group," says Eifler.

For example, men with a biopsy Gleason Score of 8 and above previously were not thought to be good candidates for surgery because of the likelihood that the cancer had spread. The new data show a higher probability of a cure with surgery even if a man's Gleason score is 8. Scores of 9 and 10 are still considered high risk, indicating that the cancer likely has spread.

"The updated Partin Tables will significantly improve the ability of physicians to counsel patients on the extent of their disease and help them make treatment decisions, such as whether surgery is warranted and, if so, whether lymph nodes also should be removed during surgery," Partin says. "If there is a high probability that the cancer has spread, treatment options include radiation, chemotherapy and hormonal therapy."

To access the updated Partin Tables and calculate your probability of cancer spread, go to http://urology.jhu.edu/prostate/partintables.php and input your PSA, Gleason Score and clinical stage results, and click on "find results."

Science Daily, 3 January 2013

BE PREPARED

by Ray Marsh, member of PCaSO, an Us TOO group in the United Kingdom

Even if you weren't a Boy Scout, you surely know the motto. But you're unlikely to know that my school motto, being "Goreu Arf Arf Dysg" roughly translates in *your* language as "Knowledge Is the Best Weapon" or loosely, and perhaps more appropriately, "Knowledge Empowers" – which happens to be the title of our support group's acclaimed Information Booklet.

Although the "Questions You May Wish to Ask" in the PCaSO booklet is specifically geared to prostate cancer, the general NHS (the United Kingdom's National Health Service) leaflet that discusses these matters is in some respects more comprehensive. I suggest that it's crucial to acquire as much information as you can muster on your condition and its possible treatments so that you can monitor your optimum progress, but not with which to confront your medical adviser.

We all, but I particularly, have the greatest respect for medical practitioners and the expertise that they have acquired from a long, rigorous and very arduous training, far above, it seems to me, any other profession. Possibly paradoxically, because of that respect, I do not demand that they be infallible in circumstances which require not only expertise and experience, but also judgment.

You might have seen an article in the Us TOO *HotSheet* showing an analysis of primary treatments over a large sample of prostate cancer sufferers. This showed a significant bias towards the specialism of the advising medic. Also, your treatment involves clerical procedures, and who should prejudice his health and life on the assumption that these procedures are not prone to error? I do not suggest that you query the validity of medical advice you are given, but suggest that you should ask yourself whether it is the best option for you at your particular stage.

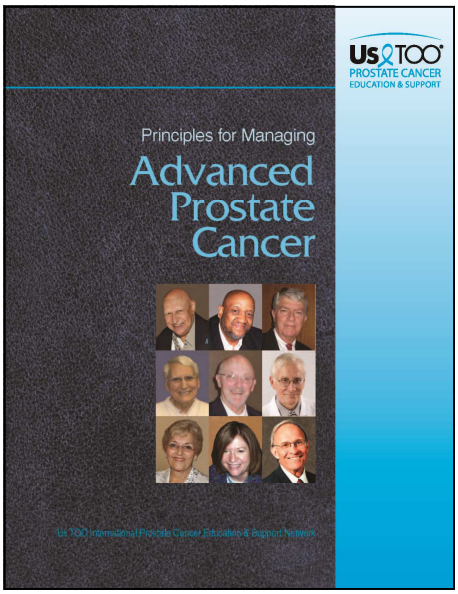
Among the sources of information is, of course, PCaSO, where we have very hard-working trustees who, as non-medics, are incredibly knowledgeable on prostate cancer and the treatment options, and are involved at the national level in setting treatment policies. While you are asking questions, you might come to the stage of asking yourself two important ones, viz. (I imagine that I can safely use that expression to our generation!):

- Should I ask for a second opinion on the treatment now advised?
- Should that option be from a specialist prostate oncologist?

You are perfectly entitled to a second opinion, which could be crucial in ensuring that you receive the advice most appropriate to you. Further, the NHS Improvement Plan (available on the NHS website), published when John Reid was Secretary, says: "By 2008, patients referred by their GP (General Practitioner) will be able to choose any provider that is able to meet NHS standards and to deliver care at NHS tariffs."

This means you can choose a treatment, and equally importantly, a practitioner who has a record of many successful operations. It also means that any Trust cannot insist that the second opinion or the subsequent treatment be carried out within that Trust. I suggest that you prepare yourself now for a decision, should your condition develop.

Sent from a long stone's throw from Winchester Cathedral



NDA FOR RADIUM-223

(Continued from page 1)

Radium-223 dichloride (radium-223), formerly referred to as radium-223 chloride, is an investigational alpha particle emitting pharmaceutical in development for CRPC patients with bone metastases. A majority of men with CRPC have radiological evidence of bone metastases. Bone metastases from prostate cancer typically target the lumbar spine, vertebrae and pelvis. In fact, bone metastases are the main cause of morbidity and death in patients with CRPC.

The submission was based on data from the ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) trial, a Phase III, randomized, double-blind, placebo-controlled international study of radium-223 with best supportive care (BSC) vs. placebo with BSC in symptomatic CRPC patients with bone metastases. The trial enrolled 921 patients in more than 100 centers in 19 countries. The study treatment consisted of up to six intravenous administrations of radium-223 or placebo each separated by an interval of four weeks.

The primary endpoint of the study was overall survival. Secondary endpoints included time to occurrence of skeletal-related events (SRE), time to total alkaline phosphatase (ALP) and PSA progression, total ALP response and normalization, safety, and quality of life.

In September 2009, Bayer signed an agreement with Algeta ASA (Oslo, Norway) for the development and commercialization of radium-223. Under the terms of the agreement, Bayer will develop, apply for health authority approvals worldwide, and commercialize radium-223 globally. Algeta will co-promote radium-223 with Bayer in the US.

Radium-223 is an investigational agent and is not approved by the FDA, the European Medicines Agency (EMA), or other health authorities.

For more information, please contact Rose Talarico at Bayer HealthCare Pharmaceuticals at (973) 305-5302 or email rose.talarico@bayer.com.

Bayer Healthcare News Release
14 December 2012

ANTIOXIDANTS THE ENEMY IN CANCER TREATMENT, NOBEL WINNER WATSON SAYS

Antioxidants may undermine metastatic cancer treatment and even contribute to its development, according to a hypothesis laid out by James D. Watson, PhD, who shared the 1962 Nobel Prize in Physiology or Medicine for the discovery of the double-helix structure of DNA. Antioxidants neutralize DNA- and RNA-damaging reactive oxygen species (ROS) that would otherwise trigger apoptosis (programmed cell death), Watson explained in an article published online in *Open Biology*.

Although that balance is normally helpful, the vast majority of cancer treatments – radiotherapy, most chemotherapy, and some targeted therapies – rely directly or indirectly on ROS to block key steps in the cell cycle and thus kill cancer cells. "Unless we can find ways of reducing antioxidant levels, late-stage cancer 10 years from now will be as incurable as it is today," Watson said in a statement, calling this among his most important work since the double helix discovery.

Watson cited experiments with the chemotherapy drug paclitaxel (Taxol®) showing that its effectiveness was higher against cell lines with lower antioxidant capacity and also pointed to a variety of genetic factors pointing to connections between ROS and apoptosis. For example, apoptosis can be turned on by the p53 transcription factor, which boosts synthesis of genes that generate ROS.

"The fact that cancer cells largely driven by RAS and Myc are among the most difficult to treat may thus often be due to their high levels of reactive ROS-destroying antioxidants," Watson wrote. "The fact that late-stage cancers frequently have multiple copies of *RAS* and *MYC* strongly hints that their general incurability more than occasionally arises from high antioxidant levels," he added.

WenYong Chen, PhD, a cancer genetics researcher at City of Hope in Duarte, CA, agreed. "This describes a very important sea change about what we think about cancer therapy," he said, predicting it would fuel research over the next decade.

"We must focus much, much more on the

(Continued on page 6)

ASK DOCTOR SNUFFY MYERS

Editors' 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.

I know Dr. Myers is an advocate of Color-Doppler Ultrasound imaging (CD-TRUS), especially as used in the practice of Dr. Duke Bahn in Ventura, California. My question is – why is CD-TRUS not more widely available in the United States? There are apparently only a few other centers besides Dr. Bahn's Prostate Institute of America where this technique is routinely available. Considering the large advantage of CD-TRUS over regular TRUS imaging it begs the question of why the medical community has not embraced and sought to promote the use of this superior imaging modality.

Of course, I cannot really know the answer to this question. So, I will give you my best guess. I would start by noting that the only physicians I have seen use this tool are trained radiologists. Now radiologists are, by definition, trained to read images. Urologists are not trained to read images with anything like the same rigor. I think performing and reading color Doppler ultrasound is not a trivial thing to do. I think it is best in the hands of someone who's training and major interests are focused on imaging.

I would also note that MRI is advancing rapidly and can compete well with color Doppler ultrasound in the evaluation of the prostate gland. I would also note that reading the MRI images also is best done by someone with rigorous training and interest in radiology. Increasingly, I see routine TRUS being replaced by more advanced, clearly superior imaging technology done in the hands of people with the skill to use that technology and that is the radiologist not the urologist.

RISK OF ANTIOXIDANTS

(Continued from page 5)

wide range of metabolic and oxidative vulnerabilities that arise as consequences of the uncontrolled growth and proliferation capacities of cancer cells," he wrote. Under his hypothesis, ROS are what directly induce apoptosis in most cells.

Although no trials of antiantioxidant strategies have indicated more than a modest effect, there do appear to be some potential candidates. The oxidative phosphorylation inhibitor 3-bromopyruvate has been shown in an animal model to kill hepatocellular carcinoma cells more than 10 times faster than the more resilient normal liver cells "and so has the capacity to truly cure, at least in rats, an otherwise highly incurable cancer," Watson noted.

However, Richard Schilsky, MD, of the University of Chicago Comprehensive Cancer Center and incoming chief medical officer of ASCO commented that there's less immediate impact for clinical practice. "The one practical implication is that patients with cancer getting treatment with chemotherapy or radiation or some of the newer antiangiogenic agents probably should not be taking antioxidant therapies, like vitamins, and certainly not without discussion with their oncologist," he cautioned.

Supplements are popular among cancer patients but none have been proven to help, so it's reasonable to suggest holding off, Schilsky explained. On the other hand, patients don't need to avoid antioxidant-containing fruits and vegetables as part of a healthy diet, he noted.

MedPage Today, 8 January 2013

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

"Metformin is on a roll, so is it time to discuss this dirt cheap drug with your doctor regardless of your prostate cancer situation? Affirmative!"

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

Editors' 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: A new study from Sloan-Kettering suggests that diabetic men taking the generic drug metformin that also received radiation therapy had a reduced risk in the development of hormone refractory prostate cancer (HRPC), dying from prostate cancer and probably dying from any cause compared to men not on metformin.[1] Whether or not this drug will benefit diabetic and non-diabetic individuals is receiving research now but come on folks it is time to talk about this cheap drug with your doctor because it helps some folks lose weight.

You know the Moyad philosophy thus far (it ain't tough to figure out… just to do)-"if it is heart healthy then it is prostate healthy and if it is dirt cheap then even better!" I have talked about my excitement for cholesterol lowering drugs and/or aspirin to fight prostate cancer for over a decade and over the past few years I have talked a little about metformin so let's review shall we? Metformin is the only drug to prove that it reduces the risk of type II diabetes, treats type II diabetes, probably reduces the risk of weight gain when on hormonal therapy for prostate cancer, is very cheap and has a ridiculously low risk of side effects. Now, there is all this new data to suggest that it reduces the risk of more cancers than I can name in a column (over 40 clinical trials are going on with it right now). Can all this be true? Or is this one of those over-hyped situations kind of like a Notre Dame football team? Well, let me put it this way, metformin is more popular than an Alabama Football team in Alabama right now and by controlling blood sugar, insulin and reducing growth factors there is a lot of excitement for individuals to try this drug right now against prostate cancer. This new study from Sloan-Kettering is not proof but it adds to the excitement to the point where I believe it is now time for any patient with prostate cancer to ask your doctor about the positives and negatives of taking it now, or in the future regardless of your situation. Look, this drug could turn out to be a bust but if all it does is help you to lose some weight then great! By the way, the median BMI of the men in the Sloan Kettering study was 27 (overweight), which means men/all of us need help for weight loss and a potential benefit against prostate cancer along with conventional treatment and I am beginning to believe that metformin might be something where in the worst case scenario it is not such a bad scenario at all! Oh and Happy Valentines Day and remember "a happy wife = a happy life" and any man, say Mark Moyad for example that receives a new big screen TV as a surprise on Valentine's Day from his significant other (say for example, his wife or from Tom Kirk) will always be grateful!

Reference:

1. Spratt DE, Zhang C, Zumsteg ZS, Pei X, Zhang Z, Zelefsky MJ. Metformin and prostate cancer: Reduced development of castration-resistant disease and prostate cancer mortality. Eur Urol, 14 December 2012; Epub ahead of print.

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

Editor: www.prostatevideos.com

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a1p1c1 Physicians from Johns Hopkins hospital have recently updated the results of the well-known Partin tables that provide an estimate of a man having localized disease, tumor outside the gland, into the seminal vesicles and into the lymph nodes based on the Gleason score, the PSA and the digital rectal exam. This has been an excellent tool for helping to counsel men about different therapies.

However, a major weakness of this predictive tool remains, which is its inability to predict the outcome of men followed for 10 and 15 years after undergoing surgery. For example, another article in this issue of the *HotSheet*, provide data offering greater support for surgery in men with Gleason 8 cancers. But we really do not know how often the cancer recurred, required additional therapy or still resulted in a man's death. That information is available from another predictor called the Kattan nomogram. Still, the updated data will be a useful tool.

The Bottom Line: The more information men have about the risk from the cancer, the easier they may be able to participate in deciding if surgery is right for them.

a2p1c2 Men with bone metastases are likely to have another option for helping improve their survival. Radium-223 was tested in a randomized study and showed an improvement in survival. This occurred without major morbidity so it is highly likely that the FDA will give them approval. When that occurs, there will be four options for men failing hormone therapy; Provenge, abiraterone and then radium 223. Studies may be needed to figure out the best sequence of these options.

The Bottom Line: Radium-223 is likely to become available and offer another way to help men suffering from bone metastases.

a3p1c3 The article by Cooperberg and co-workers raises many interesting issues. The authors attempted to compare cost and outcomes of the different therapies for prostate cancer. Unfortunately, there are many unresolved issues about their analysis, primarily the lack of randomized studies upon which results can be compared. The only two randomized studies done compared watchful waiting to radical prostatectomy and those results have been discussed before.

Furthermore, discussing five-year survival rates also is rather unimportant for this disease. Unless we get randomized studies comparing surgery to other treatments, the relative benefit of the options will remain very uncertain.

As for cost, I would question why that really matters. Patients are not concerned about cost when choosing their therapy, as evidenced by the growing volume of men getting proton therapy or IMRT + brachytherapy without evidence this form of therapy conveys advantages over less expensive therapies.

A radical idea would be for Medicare to pay for the least expensive therapy that is considered reasonable and let patients decide if they want to pay the extra amount for more expensive therapies that have not been proven to be better.

The Bottom Line: We will continue to debate the merits of different treatment options without really knowing the truth unless randomized studies are somehow mandated.

a4p2c2 Using genetic markers to decide on prostate biopsy is making progress, based on the study cited in this issue of the *HotSheet*. For those readers that are not familiar with AUC analyses, the closer the value gets to 1.0, the more accurate is the predictive tool. In this medical study, although the genetic markers did increase the AUC significantly from 0.62 to 0.66 it has a long way to go before it will be useful on a case-by-case analysis (AUC ~ 0.8-0.9).

The Bottom Line: Genetic markers may one day provide helpful information for deciding on whether to do a prostate biopsy but it is not yet ready for clinical use.

a5p2c3 An increasing number of reports are evaluating MRI to improve the diagnostic value of ultrasound-guided prostate biopsies. Some have shown an improvement in detection as found in the report by Marks who combined MR and ultrasound. Some caution is needed in interpreting the results. Although a higher percentage of targeted biopsies showed cancer compared to random biopsies, several questions need to be answered.

First, in terms of counseling patients, does it really matter of cancer is found on 2 cores vs 3? The way the results are presented does not tell us in how many men cancer was detected or not. The other issue is how often the MRI is giving false positive results. Using this method for men undergoing their first biopsy could prove to be extremely expensive and may further increase the detection of non-life threatening cancers.

The Bottom Line: More work is needed to determine if MRI should become part of routine prostate biopsies.

a6p3c1 Docetaxel chemotherapy was the first treatment showing a survival benefit for men failing hormone therapy. Unfortunately, most men never receive the drug primarily because of side effects. The randomized study by Kellokumpu-Lehtinen and co-workers looked at the impact of modifying the dose and giving it every two weeks instead of every three. The preliminary results are very encouraging with a better time to treatment failure with fewer major side effects. These results need to be further studied for survival and if the findings persist could provide additional benefit for men with progressive disease.

The Bottom Line: Modifying the interval between doses of docetaxel may offer better efficacy with lower morbidity for patients but additional studies will be needed.

MRI-TARGETED PROSTATE CANCER BIOPSIES *(Continued from page 2)*

In the UCLA study, researchers actively monitored 171 men with slow-growing prostate cancers or those who had received negative biopsies but maintained persistently high PSA levels, suggesting that a tumor might be present.

The participants first had an MRI to visualize their prostate. That image was sent to a device, called Artemis that fuses the MRI pictures with real-time, 3D-US. This process allows a urologist to see lesions visible on MRI while performing a 3D-US-guided biopsy.

According to the study, which was published online December 10th in *The Journal of Urology*, prostate cancer was found in 53 percent of the men involved in the study. Marks and his colleagues also found that 38 percent of the cancers found using targeted biopsy were aggressive tumors – meaning they were more likely to spread and require treatment.

"With the Artemis, we have a virtual map of the suspicious areas placed directly onto the ultrasound image during the biopsy," noted Marks. "When you can see a lesion, you've got a major advantage of knowing what's really going on in the prostate. The results have been very dramatic, and the rate of cancer detection in these targeted biopsies is very high. We're finding a lot of tumors that hadn't been found before using conventional biopsies."

Dr. Louis Potters, chair of radiation medicine at North Shore-LIJ Health System in New Hyde Park, NY said that the UCLA data matches those from his own institution "that reports improved cancer detection of this technique" vs. traditional biopsy. "More importantly, the lesions seen on the MRI with a corresponding positive biopsy are associated with a higher grade cancer and increased amount of cancer sampled," he said.

Dr. Bromberg agreed and noted that "adding the MRI to the ultrasound seems to allow preferential detection of the more life-threatening type of cancer [high-grade], which could reduce the chances that a man would undergo unnecessary treatment," he said.

As for cost, "the overall added cost of the MRI may be offset by a reduced number of biopsy procedures," he added.

HealthDay News, 10 December 2012

2– VS 3-WEEKLY DOCETAXEL

(Continued from page 3)

Findings: 177 men were randomly assigned to the 2-weekly group and 184 to the 3-weekly group. 170 men in the 2-weekly group and 176 in the 3-weekly group were included in the analysis. 2-weekly administration was associated with significantly longer TTTF than was 3-weekly administration (5·6 months, 95% CI 5·0–6·2 vs 4·9 months, 4·5–5·4; hazard ratio 1·3, 95% CI 1·1–1·6, p=0·014). Grade 3–4 adverse events occurred more frequently in the 3-weekly than in the 2-weekly group, including neutropenia (93 [53%] vs 61 [36%]), leucopenia (51 [29%] vs 22 [13%]), and febrile neutropenia (25 [14%] vs six [4%]). Neutropenic infections were reported more frequently in men who received docetaxel every 3 weeks (43 [24%] vs 11 [6%], p=0·002).

Interpretation:

Administration of docetaxel every 2 weeks seems to be well tolerated in men with advanced CRPC and could be a useful option when 3-weekly single-dose administration is unlikely to be tolerated.

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